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Celiac disease in children

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Celiac disease in children

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Editorial: Celiac disease in children

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KEYWORDS

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Editorial on the Research Topic
Celiac disease in children

The aim of this Research Topic was to gather original research articles, case reports, and review articles focusing on various aspects of pediatric celiac disease (CD) in 2025 and contribute to the existing literature. This editorial reviewed 17 articles, 11 of which were accepted for publication by the reviewers and Editors in the Research Topic "*Celiac Disease In Children*". The articles cover topics such as the prevalence of acute reactions to inadvertent gluten contamination, molar incisor hypomineralization, serum levels of vitamin D and calcium-phosphorus, allergic and immunological evaluations, clinical manifestations, a non-biopsy strategy in children with CD, celiac disease screening and depression, and anxiety in adolescents with CD.

Celiac disease is an immune-mediated enteropathy triggered by dietary gluten consumption in genetically predisposed individuals. It is marked by the presence of specific antibodies and variable degrees of small intestinal mucosal damage (1). In addition to genetic susceptibility and gluten exposure, the pathogenesis of CD autoimmunity is considered to be multifactorial, including impaired intestinal barrier function, a gluten-induced proinflammatory innate immune response, and an inappropriate adaptive immune response (1, 2). Intestinal fatty acid binding protein (i-FABP) and fecal zonulin (FZ) are crucial for preserving intestinal physiological functions and may indicate enterocyte damage (Geller et al.). A relationship has been shown between the clinical manifestations of CD and the levels of FZ and i-FABP (Geller et al.). The authors stated that increased FZ and i-FABP values can serve as markers of increased intestinal barrier permeability and damage, opening up new possibilities for understanding the restoration processes of the small intestinal mucosa.

Due to increased physician awareness and the extensive use of highly sensitive and specific diagnostic tests for CD, its prevalence rate has dramatically increased over the past three decades (1). Approximately 95% of cases of CD remain undiagnosed despite increased awareness and the availability of trustworthy testing techniques (1, Naredi Scherman et al.).

The clinical presentation of CD varies considerably, and there has been a notable change in how CD presents itself over the last three decades. Infants typically exhibit

different symptoms than older children. Infants may present with malabsorptive symptoms, including diarrhea, anorexia, abdominal distension, and failure to thrive. Young children may present with any of the above symptoms and/ or abdominal pain and iron deficiency anemia, which are the most common presenting symptoms in this age group. While the symptoms of older children are either limited or atypical, some develop non-specific gastrointestinal symptoms, such as constipation, along with extraintestinal symptoms and signs such as short stature, iron deficiency, and delayed puberty. In older children and adults common presentations include infertility, dermatitis herpetiformis, osteoporosis, enamel defects, and neurological manifestations such as ataxia, anxiety, and recurrent headaches (1, 3). Many children are diagnosed without exhibiting symptoms due to the screening of family members with CD, or the screening of patients with associated autoimmune or genetic diseases.

Consistent with the literature, the most prevalent symptoms among children with CD include abdominal pain, diarrhea, and failure to thrive, all of which were found to be common in a recent study conducted in Lebanon (1, 4, Andari et al.). In addition to having considerably lower vitamin D levels and higher tissue transglutaminase levels, children recently identified as having CD and who were found to be incompatible with a gluten-free diet were also observed to be more likely to have molar-incisor hypomineralization (Tok et al.). Approximately 75% of patients with CD are found to have osteopenia, and up to 30% exhibit osteoporosis, as a result of inadequate absorption of calcium and vitamin D consequent to the mucosal damage (1, 5).

Adequate exposure to sunlight is known to increase vitamin D levels. However, Kamilova et al. found that a high prevalence of vitamin D deficiency is also seen in children with CD living in regions with increased sunlight exposure.

Individuals with autoimmune thyroid disorders, selective immunoglobulin A (IgA) deficiency, type 1 diabetes mellitus, or psoriasis, along with those with genetic syndromes such as Turner syndrome, Down syndrome, or Williams syndrome, are recognized as being at increased risk of developing the disease (1, Lattuada et al.). Patients with these conditions should always be evaluated for CD because of these known correlations.

Children with CD may potentially have immunologic abnormalities and allergic disorders. Beyond the well-known correlation with selective IgA deficiency, a recent study demonstrated a notable prevalence of immunologic abnormalities (e.g., partial IgM deficiency, unclassified hypogammaglobulinemia, etc.) and allergic diseases (e.g., aeroallergen sensitivity, allergic rhinitis, allergic conjunctivitis, food allergy, and asthma) in children with CD (Demirtaş Güner and Baskın).

The 2020 ESPGHAN guidelines recommend that CD be diagnosed without an intestinal biopsy under certain conditions (6). According to a recent study from Romania, serology-based diagnosis results in less compliance with follow-up, more dietary violations, and shorter mucosal healing than in patients with biopsy-proven CD (Enache et al.). Additionally, the authors suggested that management should be improved, paying particular attention to individuals who were diagnosed with the non-biopsy method according to the new ESPGHAN guidelines (Enache et al.).

A wide range of neurological symptoms, such as anxiety, ataxia, and headaches, in addition to body image dissatisfaction, may occur in patients with CD, especially adolescents (Daldaban Sarıca et al.). It is critical to recognize mood disorder and body image dissatisfaction symptoms early in order to improve the general well-being of adolescents with CD and provide appropriate patient management. Periodic follow-up is necessary to identify mood-related symptoms and assess the teenagers' body acceptance.

The wide spectrum of clinical manifestations makes CD challenging to identify, often leading to significant delays in diagnosis. According to reports, the delay in diagnosing CD may range from months to over a decade (1, 7, Naredi Scherman et al.). It is crucial to diagnose CD early in order to avoid long-term consequences. The sole curative option is a lifelong gluten-free diet (GFD).

Despite good adherence to a GFD, a recent study showed nutritional inadequacies in children with CD (Ekşi et al.). A nutritional assessment should be performed at each visit. Any identified deficiencies, such as those involving vitamin D, folate, B vitamins, iron, calcium, or zinc should be addressed.

Accidental gluten ingestion is a significant issue troubling patients and physicians alike. It has been reported that one-third of children with CD on a GFD suffer from acute gastrointestinal symptoms such as vomiting and nausea as a result of accidental gluten ingestion (Pjetraj et al.). To enhance quality of life by preventing accidental exposure to gluten in individuals with CD, it is critical to educate, monitor and regulate accidental gluten consumption.

We hope that you will enjoy reading this special issue with its new studies on pediatric CD. We believe that these articles, which were evaluated through a thorough peer review and deemed appropriate for publication by the editors, contribute significantly to the existing literature on celiac disease.

Author contributions

YS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing, Resources, Visualization. NU: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Data curation, Supervision, Visualization, Validation. MK: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing, Validation. ES: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing, Validation.

Conflict of interest

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Clinical presentations and outcomes of celiac disease in children and adolescents at a tertiary care center in Lebanon

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Introduction: Studies on the clinical presentation of celiac disease and its impact on the growth of children in Lebanon are limited. The aim of this 10-year-retrospective study was to describe the common clinical presentations, diagnostic modalities, and the effect of the gluten-free- diet (GFD) on the growth of children and adolescents with celiac disease.
Methods: This was a retrospective chart review of subjects aged 6 months to 18 years who visited the Pediatric Gastroenterology clinic at the American University of Beirut Medical Center (AUBMC) between January 1, 2013, and June 30, 2023, and who were diagnosed with celiac disease based on serological markers and/or changes on histology of the small intestinal mucosal biopsies for those who underwent upper endoscopy, or HLA typing expressing the HLA-DQ2 or DQ8 gene for few subjects.
Results: The study included 90 patients with celiac disease, of whom 64 were newly diagnosed during the study period. The mean age at diagnosis of celiac disease was 6.93 years. Females represented 60% of the pediatric subjects with celiac disease. The most common symptoms reported were abdominal pain (51.1%), weight loss or failure to thrive (45.6%), and diarrhea (24.4%). There was a significant increase in the mean weight-for-age *Z*-score (WAZ) and mean body mass index (BMI)-for-age *Z*-score (BMIZ) 12 months following initiation of GFD; however, the change in height-for-age *Z*-score (HAZ) at 12 months was not statistically significant. Half of the subjects were in remission at the last clinic follow-up.
Conclusion: The most common symptoms that children with celiac disease in this cohort presented with are diarrhea, abdominal pain and failure to thrive. In this cohort, there was a significant increase in the weight parameters with no significant change in the height at 12 months after initiation of the GFD. The recognition of early manifestations, early diagnosis and strict adherence to the diet are of paramount importance to prevent long term complications.

KEYWORDS

celiac disease, gluten-free diet, growth, Mediterranean diet, children

1 Introduction

The effect of pediatric gastrointestinal autoimmune diseases including celiac disease on nutrition and growth in children and adolescents can be devastating (1). Growth failure is related to poor appetite, abdominal symptoms, malabsorption, in addition to genetic factors. Celiac disease was found to be the leading cause for short stature, surpassing even growth hormone deficiency (2). There are only few studies assessing the growth trajectory of affected children longitudinally. A study by Kahrs et al. found that children diagnosed with celiac disease tend to be significantly shorter at 12 months of age as compared to controls (3). Another study from the Netherlands showed a decrease in the overall growth trajectory from 6 months to 6 years of age in patients with celiac disease (4).

The gluten-free- diet GFD is currently the only available treatment for patients with celiac disease along with necessary nutritional supplementation such as vitamin D, calcium and iron (5). Following a gluten-free-diet, by avoiding gluten-containing grains, wheat, rye and barley, typically promotes catch-up growth and normalization of weight and leads to clinical remission and normalization of serological markers and histological findings (5–9). In addition, GFD was associated with improvements in serum vitamin D and iron levels as demonstrated in previous studies, and this was attributed to enhanced intestinal absorption (10). However, adherence to the GFD, in the developing world, is challenging mainly in the pediatric and adolescent population due to several barriers, including limited gluten-free options, high costs, poor palatability of the alternatives, insufficient awareness about the importance of the diet, and conflicts between children and their caregivers regarding food choices (5).

There are limited studies on the clinical presentation of celiac disease and its effect on growth of children in the Middle East and North African (MENA) region. This 10-year-retrospective study, aimed to describe the common clinical presentations, diagnostic modalities, and the effect of the gluten-free-diet on the growth of children and adolescents with celiac disease followed at the American University of Beirut Medical Center, a tertiary care center in Lebanon.

2 Materials and methods

2.1 Study design

We conducted a retrospective chart review of pediatric subjects diagnosed with celiac disease who were followed at the Pediatric Gastroenterology clinic at the American University of Beirut Medical Center (AUBMC) between January 1, 2013, and June 30, 2023.

All subjects were identified retrospectively, and their charts were reviewed through medical records by looking at the following ICD-9 and ICD-10 code for clinic visits for "celiac disease". The study was approved by the institutional review board (IRB) at AUBMC (IRB approval number: BIO-2023-0174).

2.2 Inclusion and exclusion criteria

The subjects included in the study were patients aged 6 months to 18 years diagnosed with celiac disease based on: 1- serological markers including anti-tissue transglutaminase antibody (tTGA) IgG and IgA and anti-endomysial antibody (EMA) IgA (EMA-IgA), and/or; 2- changes on histology of the small intestinal mucosal biopsies with villous atrophy for patients who underwent upper endoscopy, or; 3- HLA typing expressing the HLA-DQ2 or DQ8 gene for patients who refused endoscopy. The EMA is done as a qualitative measure, whereas the tTGA provides quantitative values (for tTGA IgG negative is less than 10 U/ml, and for tTGA IgA negative is less than 4 U/ml). Total blood IgA levels were measured to rule out IgA deficiency. All initial tests were performed while patients were on a gluten-containing diet.

For subjects who did not undergo upper endoscopy and biopsy, the new ESPGHAN guidelines were used for the diagnosis of pediatric celiac disease, where a no-biopsy approach can be followed in patients with tTGA IgA levels ≥10 times the upper limit (11).

Subjects with an unconfirmed diagnosis of celiac disease, those who were lost to follow up and subjects in whom the diagnosis of celiac disease was refuted, were excluded from the study.

2.3 Data collection and study variables

Data extracted from medical records included age, gender, clinical presentation, anthropometric measurements, laboratory results such as serological markers, hemoglobin, iron and serum 25-hydroxyvitamin D levels, small intestinal biopsy results, and HLA typing, when available.

The measurements of weight and length/height recorded in the charts of the included subjects were taken by a trained pediatric nurse. The weight of children below the age of two years and below the weight of 20 Kilograms (kg) was measured using a regularly calibrated infant scale with only a clean diaper on. The length of these children was measured in the supine position using a rigid pediatric length measuring board with a range from 0 to 100 cm. Children above the age of two years were weighed barefoot standing on a regularly calibrated scale. Their height was measured standing on a stadiometer with a measuring range of 85–200 cm. The body mass index (BMI) was calculated as the weight in kg divided by height in meters (m) squared.

The anthropometric parameters were expressed as *Z*-scores relative to the National Center for Health Statistics standards using the Baylor College of Medicine calculator [weight-for-age *Z*-score (WAZ), height-for-age *Z*-score (HAZ), and BMI-for-age *Z*-score (BMIZ)] (12).

2.4 Definitions

Stunting was defined as HAZ less than 2 standard deviations relative to the normal standards; while wasting or undernutrition

was defined as BMIZ less than 2 standard deviations relative to the normal standards. Underweight was defined as WAZ less than 2 standard deviations relative to the normal standards (13, 14).

Remission was defined as symptoms' resolution, and normalization of celiac disease serology after following a GFD. Improved but not in remission was defined as subjects who showed clinical and/or serological improvement but had not yet reached full remission. Relapse was defined as recurrence of symptoms or the reappearance of positive antibody results after clinical and serological normalization.

2.5 Statistical analysis

All statistical analysis were performed using the Statistical Package for the Social Sciences program [SPSS, version 23.0 for Windows (IBM, Armonk, NY)]. Simple descriptive statistics were used to describe the subjects' demographics and characteristics, and were represented as frequency and percentages. Continuous variables were reported as mean and range.

The change in growth parameters and hemoglobin, iron and vitamin D values was calculated at 6 and 12 months with the statistical significance determined using the paired *t*-test. A *p*-value less than 0.05 was considered statistically significant.

3 Results

We identified 137 subjects with a diagnosis of "celiac disease", out of which 47 were excluded due to the following reasons: unconfirmed diagnosis, patient lost to follow-up, or the diagnosis of celiac disease was refuted. Therefore, 90 subjects met the inclusion criteria and were reviewed and included in the statistical analysis. Out of the 90 included subjects, 64 were newly diagnosed and thus included in the analysis of the growth parameters and laboratory value temporal changes. The remaining 26 subjects were diagnosed prior to the first presentation and were already maintained on GFD. These subjects were included in the analysis of the baseline clinical characteristics, pathology results and final outcomes (Figure 1).

3.1 Baseline characteristics and clinical presentation

The mean age at first presentation to the Pediatric Gastroenterology Clinic of the 90 subjects was 8.28 years (range 1.1–17.9 years) while the mean age at diagnosis was 6.93 years (range 1.2–16.25 years). The average duration of follow-up was 1.37 years (range 0–9.8 years); therefore, the last follow up results retrieved were taken at 1-year following the initial presentation.

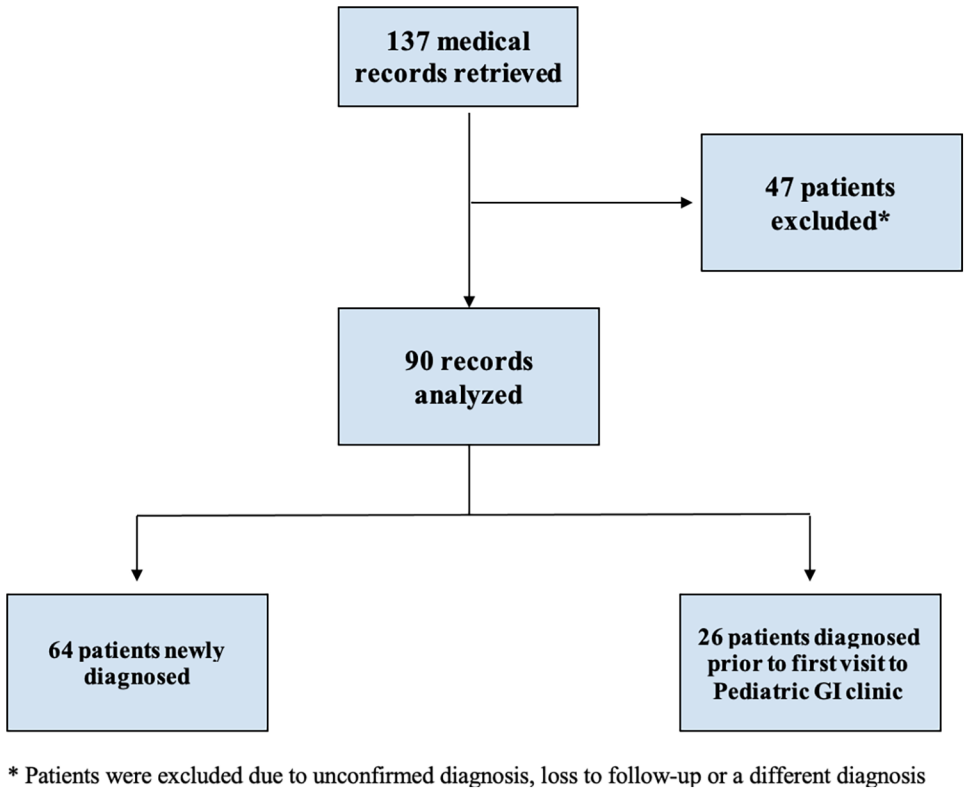

FIGURE 1
Flowchart of identification and inclusion criteria.

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Table 1 represents the demographic and baseline characteristics of the subjects. Among the 90 included subjects, 54 (60%) were females. The majority of the subjects did not have any underlying comorbidities; however, 17.8% had a past medical history of autoimmune diseases such as type 1 diabetes mellitus. In addition, 10% of the subjects had associated gastrointestinal (GI) diseases which included eosinophilic esophagitis or inflammatory bowel disease (IBD). Regarding the family history, 10% of the subjects had a positive family history of autoimmune diseases including type 1 diabetes mellitus or rheumatoid arthritis, and 17.8% of subjects had a family history of GI diseases including colon cancer or IBD. Family history of celiac disease was present in 11.1% of subjects (Table 1).

At the first development of symptoms, subjects often presented with more than one symptom. The most common clinical symptom reported was abdominal pain in 46 subjects (51.1%), followed by weight loss or failure to thrive in 41 (45.6%) subjects, and diarrhea in 22 (24.4%) subjects. There were 12 (13.3%) subjects who had other disorders that warranted screening for celiac disease. These included prior diagnosis of type 1 diabetes mellitus, abdominal distention, recurrent infections, or hematochezia. Out of the 90 subjects, 12.2% required a hospital visit and/or admission due to abdominal pain and diarrhea prior to presentation (Table 1).

TABLE 1 Baseline characteristics and clinical presentation of the study population.

	Frequency, *n* (%) *N* = 90
Gender	
Female	54 (60.0)
Past medical history	
Autoimmune diseases[a]	16 (17.8)
Gastrointestinal diseases[b]	9 (10.0)
None	65 (72.2)
Positive family history	
Autoimmune diseases[c]	9 (10.0)
Gastrointestinal diseases[d]	16 (17.8)
Celiac disease	10 (11.1)
No	65 (72.2)
Clinical Presentation	
Abdominal Pain	46 (51.1)
Diarrhea	22 (24.4)
Constipation	11 (12.2)
Weight loss Failure to thrive	41 (45.6)
Extraintestinal symptoms[e]	14 (15.6)
Loss of Appetite	13 (14.4)
Recurrent oral ulcers	4 (4.4)
Fatigue	13 (14.4)
Other clinical presentation[f]	12 (13.3)
Needed hospital admission at presentation	11 (12.2)

[a]Autoimmune diseases such as type 1 diabetes mellitus.
[b]Gastrointestinal diseases included eosinophilic esophagitis or inflammatory bowel disease (IBD).
[c]Autoimmune diseases such as type 1 diabetes mellitus or rheumatoid arthritis.
[d]Gastrointestinal diseases include colon cancer, Inflammatory Bowel Disease (IBD) or celiac disease.
[e]Extraintestinal symptoms: joint pain or skin rash.
[f]Other clinical presentation: Abdominal distension, recurrent infections, hematochezia, type 1 diabetes mellitus.

3.2 Anthropometric parameters

Anthropometric indices during follow up are detailed in Figure 2. At the time of first presentation, stunting was identified in 9 (14.1%) subjects, underweight in 11 (17.2%) subjects, and wasting in 4 (6.5%) subjects, with no significant change in these percentages, at 6 months and 12 months after the start of the GFD (p-value > 0.05).

There was no significant change of the WAZ 6 months after the start of the GFD, while there was a significant increase of 0.344 in the mean WAZ at 12 months following the start of the GFD (p-value = 0.022). Similarly, there was no significant change of BMIZ at 6 months, but there was a significant increase of 0.253 at 12 months (p-value = 0.047). In contrast, there was no significant change in the HAZ at either 6- and 12-months follow-up (p-value 0.0721 and 0.085, respectively) (Figure 2).

3.3 Laboratory evaluation

At baseline, the mean hemoglobin level was 12.58 ± 1.34 g/L, with 36.5% of subjects having a hemoglobin level less than 12 g/L. The mean serum iron level was 63.10 ± 44.70 mcg/dl (normal: 37–160 mcg/dl), and the mean serum vitamin D level was 26.32 ± 15.53 ng/ml (adequate: > 20 ng/ml).

Among the 48 subjects tested for EMA-IgA at baseline, 44 subjects (91.7%) had positive serology. At 6 and 12 months after starting GFD, 11 out of 16 subjects (68.8%) and 12 out of 19 subjects (63.2%), respectively, continued to test positive for EMA-IgA.

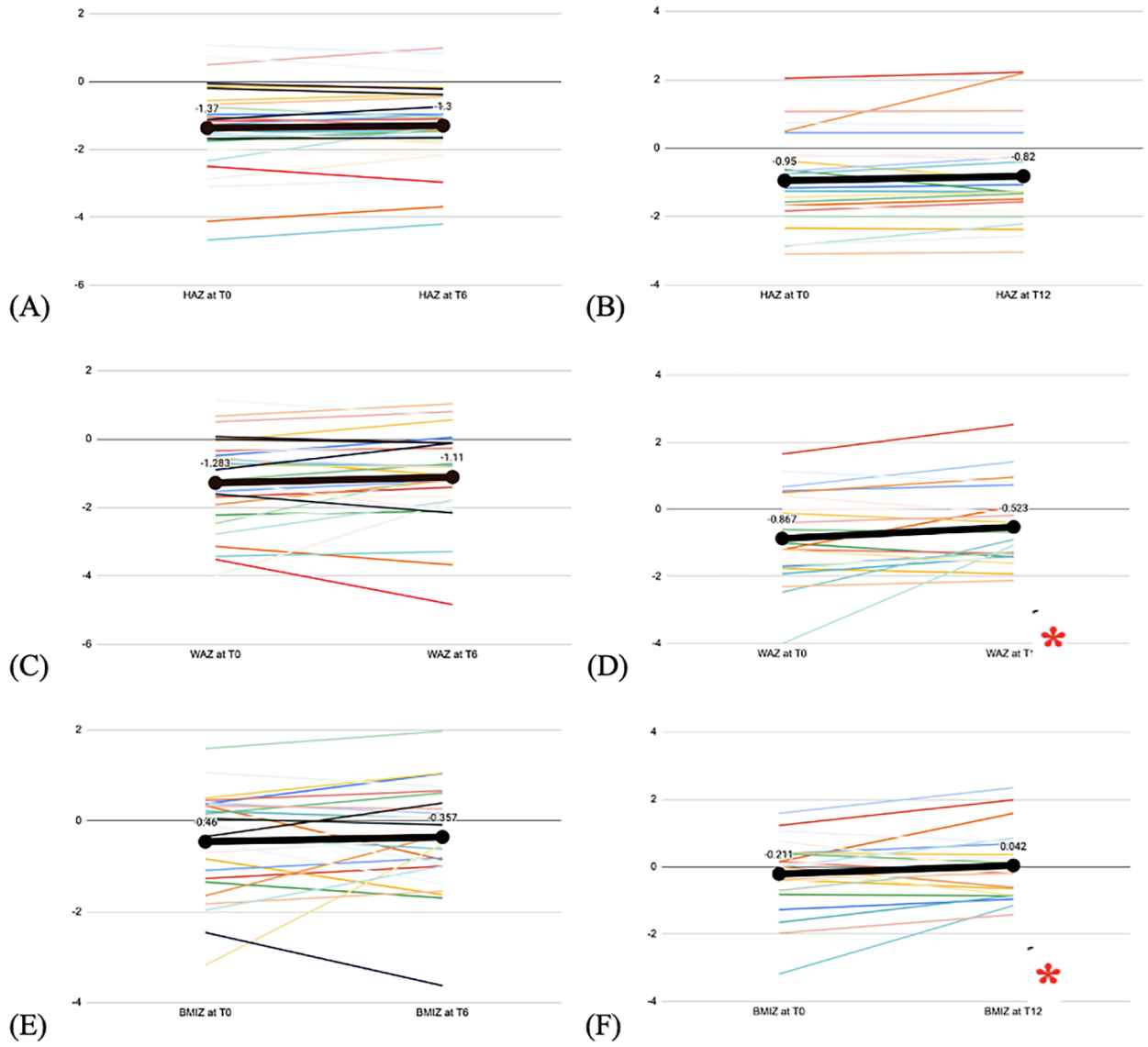
At presentation, 70.5% of the 61 subjects who were tested for tTGA-IgA had levels greater than 100 U/ml. This percentage decreased to 16% and 4.6%, at 6 and 12 months, respectively, following the initiation of GFD (Table 2).

To note that the EMA is done by indirect immunofluorescence assay (IFA) by Euroimmun as a qualitative measure, whereas the tTGA provides quantitative values (for tTGA IgG negative is less than 10 U/ml, and for tTGA IgA negative is less than 4 U/ml). tTGA IgG and IgA are an enzyme-linked immunosorbent assay (ELISA) based; automated, *in vitro* test performed on Alegria® from Orgentec (ORG 240A-24, ORG 240G-24).

Moreover, eight subjects had HLA typing (specifically HLA DQ2 and DQ8) performed showing positive results.

3.4 Pathology

Out of the 90 subjects with celiac disease, 51 subjects underwent upper gastrointestinal endoscopy with duodenal biopsies. The remaining 39 subjects did not undergo the procedure due to lack of financial coverage, fear of endoscopy and sedation, or loss to follow up. Among the 51 subjects who had biopsies, 49 (96%) subjects showed villous atrophy on



**Statistically significant difference from baseline with p-value less than 0.05*

HAZ: Height-for-age Z-score, WAZ: Weight-for-age Z-score, BMIZ: BMI-for-age Z-score, GFD: Gluten-free diet, T0: baseline, T6: 6 months after starting GFD, T12: 12 months after starting GFD

Mean HAZ, WAZ, and BMIZ at baseline (T0), 6 months after starting GFD (T6) (A, C, E, respectively), and 12 months after starting GFD (T12) (B, D, F, respectively) (shown in bolded line) with individual patient's HAZ, WAZ, and BMIZ curves at baseline, 6 months after starting GFD, and 12 months after starting GFD.

FIGURE 2
The mean height, weight and BMI Z-scores, at baseline and follow-up ($N = 64$).

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TABLE 2 Laboratory values and serology markers at baseline (T0), 6 months after starting the GFD (T6) and 12 months after starting the GFD (T12).

Laboratory values	T0, mean	T6, mean	T12, mean
Hemoglobin (g/L); normal: ≥ 12	*N* = 41 12.58	*N* = 23 12.97	*N* = 19 12.81
Iron (mcg/dl); normal: 37–160	*N* = 30 63.10	*N* = 19 80.46	*N* = 14 66.39
Vitamin D (ng/ml); normal: > 20	*N* = 27 26.32	*N* = 20 24.13	*N* = 18 23.45
Serology Markers	**T0, *n* (%)**	**T6, *n* (%)**	**T12, *n* (%)**
Endomysial IgA	*N* = 48	*N* = 16	*N* = 19
Positive	44 (91.7)	11 (68.8)	12 (63.2)
Negative	4 (8.3)	5 (31.2)	7 (36.8)
Anti-transglutaminase IgA (U/ml)	*N* = 61	*N* = 25	*N* = 22
<4	6 (9.8)	9 (36.0)	14 (63.6)
4–100	12 (19.7)	12 (48.0)	7 (31.8)
>100	43 (70.5)	4 (16.0)	1 (4.6)
Anti-transglutaminase IgG (U/ml)	*N* = 31	*N* = 20	*N* = 17
<10	13 (41.9)	14 (70.0)	13 (76.5)
10–100	14 (45.2)	6 (30.0)	4 (23.5)
>100	4 (12.9)	0 (0.0)	0 (0.0)

pathology results. Of those with villous atrophy, 49.0% had partial villous atrophy, 30.6% had subtotal villous atrophy, and 20.4% had total villous atrophy.

3.5 Treatment and outcomes

All subjects had consultation with a certified pediatric dietitian who thoroughly discussed the GFD with both the subjects and caregivers and provided individualized diet plans taking into consideration the Mediterranean diet followed in Lebanon.

At their last follow up visit (range 0–9.8 years), half of the subjects were in remission while 19 (21.1%) subjects had an improvement in their symptoms and serological values. Relapse, defined as re-development of symptoms or positive antibody results after clinical and serological normalization, occurred in 5 (5.6%) subjects relapsed. Three subjects were not adherent to a strict GFD which resulted in no changes in their clinical symptoms and/or serological tests. Loss to follow up was documented in 20% of subjects (Figure 3).

4 Discussion

In this cohort, there was a greater percentage of females (60%) as compared to males that were diagnosed with celiac disease, which concurs with the evidence that celiac disease is twice as frequent in females than males (15). The mean age at diagnosis of celiac disease was 8.28 years in our cohort which is similar to studies from Oman and Finland in which the mean age at diagnosis was 7 years and 7.2 years respectively (16, 17). In our group, the mean years of follow-up was 1.37 years with a range of 0–9.8 years. We postulate that there are several potential factors for the lack of follow up in our setting including the COVID-19 pandemic, the economic crisis, and the armed conflicts in Lebanon.

The most common symptoms reported by these 90 subjects were abdominal pain (51.1%), weight loss or failure to thrive (42.2%), and diarrhea (23.3%). Previous studies linked the symptoms of celiac disease to growth failure due to abdominal pain and malabsorption (2). A study done in Morocco showed that the main consultation reason was diarrhea (46%) and growth delay (32.4%) (18). To note that in our cohort, the majority of the subjects were symptomatic at the time of first presentation which is unlike other studies where children are asymptomatic at the time of diagnosis (19). This may be due to limited resources and specialists in the field leading to overlooked diagnoses until a later stage.

Screening for celiac disease usually starts with serological testing with EMA IgA and IgG, tTGA IgA and IgG, antigliadin antibodies IgA and IgG, and a new generation of antigliadin antibodies to deamidated synthetic gliadin peptides (20). These tests have a very high sensitivity and specificity for the disease (21–23). In our center, the most common tests used are the EMA-IgA and tTGA IgA and IgG. Previously, the gold standard for the diagnosis of celiac disease was known to be small intestinal biopsy (21, 22, 24, 25). However, in line with the new ESPGHAN guidelines for the diagnosis of pediatric celiac disease, a no-biopsy approach can be followed given that the tTGA IgA levels are ≥10 times the upper limit, and there is a shared decision with the caregivers and/or patients (11). Of the 90 subjects in the cohort, only 51 had an endoscopy done, and 49 of those showed villous atrophy on pathology. From the 39 subjects who did not undergo upper endoscopy and duodenal biopsies, 8 subjects had HLA typing. For the rest of the subjects, the diagnosis was established based on the clinical manifestations and the serologic tests. Gidrewicz et al. studied the duration to normalization of serologies and found that approximately 75% of patients with celiac disease strictly adherent to GFD still had abnormal serologies one year later (23). This is similar to our cohort with 63.2% of patients still testing positive for EMA-IgA.

At the time of diagnosis, 14.1% of subjects were stunted, 17.2% were underweight, and 6.5% were wasted. To note that the percentage of children in Lebanon under the age of 5 who were stunted in 2020 was 10.4%, and in the region was 26.2% (26). A study done by Aggarwal et al. showed that patients with celiac disease in India do not necessarily have short stature (27). However, a study done in Pakistan showed that 38% were severely undernourished and 8% were severely stunted with 79% having short stature (28). In a study done in Saudi Arabia, 85% of the patients with celiac disease were stunted with the mean HAZ and the mean WAZ at diagnosis being −3, −2.8 respectively (29). Our cohort had less underweight and wasted patients which may be due to the Mediterranean diet followed in Lebanon.

The prevalence of iron deficiency anemia (IDA) ranges from 2.3 to 33% in children with celiac disease (10). In our cohort, 26.7% of subjects who had iron studies at baseline were iron

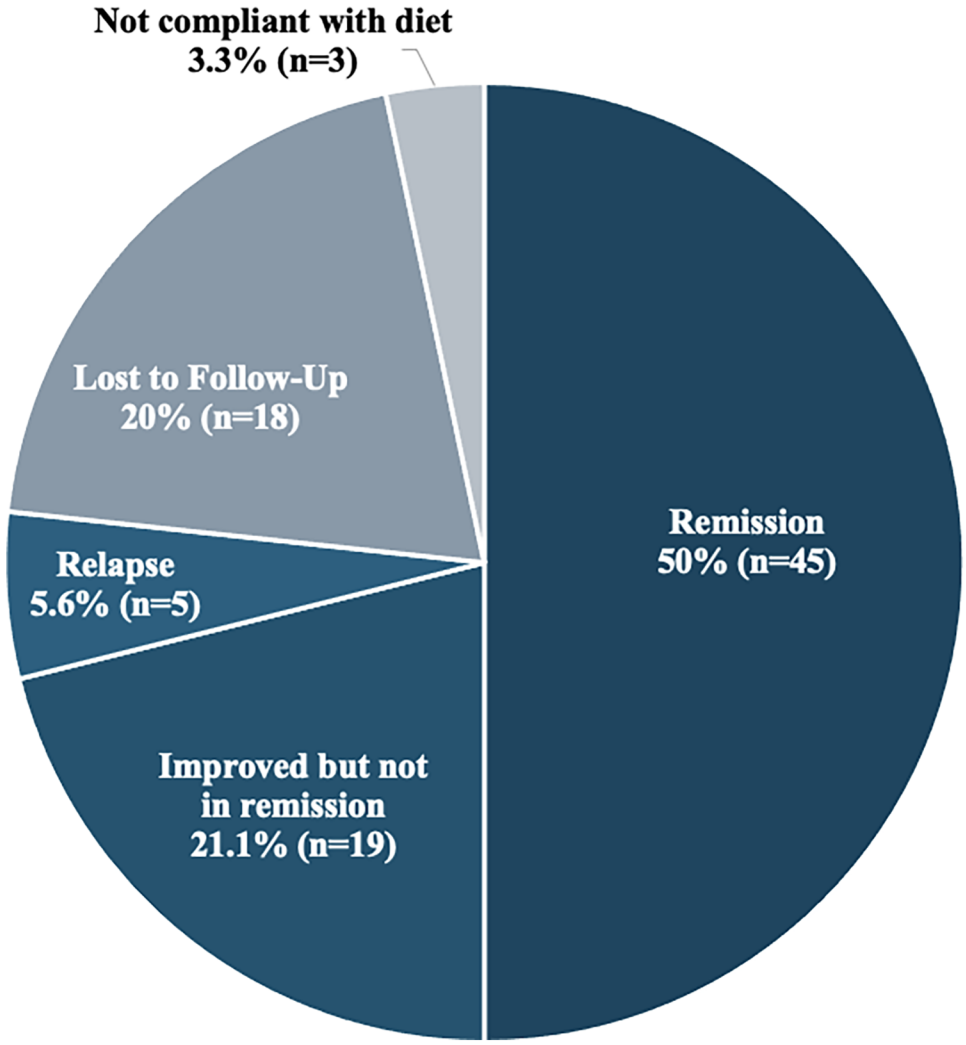

FIGURE 3
Outcomes at last follow-up ($N = 90$).

deficient. Furthermore, the mean serum vitamin D level in the cohort was in the lower range of desirable. This is in contrast to the literature showing that patients with untreated celiac disease tend to have lower serum vitamin D levels as compared to healthy controls without celiac disease (30). Our cohort's value could be attributed to the low number of subjects who had serum vitamin D levels tested ($n = 27$).

There was a significant increase in the mean WAZ and mean BMIZ (p-value = 0.022 and 0.047), and no significant change in the mean HAZ at 12 months after initiation of GFD. A controlled study done in Qatar comparing the effect of the GFD on linear growth in patients with celiac disease showed no significant change in the mean HAZ at the 12-month follow-up. However, the children in the controlled study's cohort were still increasing in height, but at a slower pace (31). It was shown that at 6–12 months after starting the GFD, children with celiac disease tend to achieve a near-normal growth curve for weight, and at 2–3 years after starting the GFD, they tend to achieve a normal growth curve for height (32, 33). This may explain the results in our cohort that showed a significant improvement in WAZ, but not in HAZ indicating that height catch-up might need longer than one year after GFD to occur. Furthermore, a systematic review and meta-analysis done by Xin et al. showed that the GFD has a significant and beneficial effect on weight of patients with celiac disease (34). Another retrospective study comparing patients with celiac disease in Italy and the United States of America (USA) showed that the catch-up growth in children in Italy was slower as compared to those in the USA (35). This was linked to the differences in the lifestyle and culture, which could be applied to the Lebanese population as well since there are limited gluten-free resources and the Mediterranean diet includes several foods containing gluten (35). To date, there are no studies that evaluated the effect of the gluten-free Mediterranean diet on growth in children, which could be an area of exploration in future studies.

At the time of the last follow-up visit, 50% of the subjects were in remission, whereas 21.1% were improving clinically and serologically but were still not in remission. The reason for poor

compliance is not completely clear, but lack of awareness about celiac disease manifestations, lack of GFD knowledge or even lack of benefit from the diet have been described as contributing factors (36). Lebanon has limited gluten-free options available and accessible. The Mediterranean diet is rich in grain and wheat which contain gluten making it challenging to follow a strict GFD. In addition, the mean age at diagnosis is between 7 and 8 years of age, which may be a difficult age to convince the child to follow a strict diet. In the pediatric population, compliance to the GFD is 52–95 percent with very minimal adherence to permanent GFD as shown in a study done in North India (9).

4.1 Limitations

Although our study is the first to describe the clinical presentations and outcomes of celiac disease in children and adolescents in Lebanon; it is important to note certain limitations. The retrospective design limited our capacity to gather accurate and complete data and did not allow us to have appropriate long-term follow up to evaluate compliance with the GFD. In addition, the study included a small sample size from one tertiary care center in Lebanon which may affect its generalizability and lead to referral bias.

5 Conclusion

The most common symptoms that children with celiac disease in this cohort presented with are diarrhea, abdominal pain and failure to thrive. In a resource-constrained country like Lebanon, the diagnosis and management remain challenging in view of the high cost of procedures and the scarcity of affordable gluten-free products. Therefore, opting for more cost-friendly diagnostic parameters such as celiac serologies in specific cases instead of endoscopy may be a feasible alternative as shown in this study and supported by the ESPHGAN guidelines. Celiac disease in children affects negatively growth and development which are expected to improve after initiation of GFD. In this cohort, there was a significant increase in the WAZ and BMIZ and no significant change of HAZ at 12 months after initiation of the GFD. The recognition of early manifestations, early diagnosis and strict adherence to the diet are of paramount importance to prevent long term complications.

Since the Lebanese population follows the Mediterranean diet, we believe that our paper will add to the current literature available and hopefully open discussions for further research on the topic of linking different types of diets to the outcome of patients with celiac disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by American University of Beirut - Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Patients were not contacted to provide any further information related to the research topic.

Author contributions

DA: Data curation, Formal Analysis, Investigation, Writing – original draft, Writing – review & editing. RH-W: Writing – original draft, Writing – review & editing. SK: Formal Analysis, Writing – original draft, Writing – review & editing. NY: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing.

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Impact of ESPGHAN no-biopsy strategy on the outcome of celiac disease treatment in children

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Aim: The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) allows a no-biopsy diagnostic of celiac disease under certain conditions. We assessed the impact of the diagnostic algorithm on the patient's long-term outcome by comparing the serology-based diagnosed patients to biopsy-proven ones.
Methods: We reviewed the charts of children presenting with antitransglutaminase IgA titers above ten times upper limit of normal and consecutively diagnosed with celiac disease between 2010 and 2014, a time-period overlapping with ESPGHAN diagnostic guideline change in 2012. Outcome measures for no-biopsy vs. biopsy-proven diagnosed patients were clinical and laboratory findings, compliance to gluten-free diet and to regular visits after one, two and 8–10 years of follow-up.
Results: Clinical and laboratory, i.e., serum chemistry and autoantibody outcome measures on gluten-free diet clearly showed worse patient healing in the 33 serology-based diagnosed children compared to the 30 biopsy-proven ones. The attendance of the follow-up visits was also higher in the biopsy group.
Conclusions: Our results indicate that dietary transgressions are common in childhood celiac disease resulting in slow healing. Therefore, there is a need of improvement of the management, with special attention regarding the ESPGHAN no-biopsy criteria diagnosed patients. Our study also indicates that novel treatments adjunctive to diet are warranted in children.

KEYWORDS

childhood celiac disease, serology-based diagnosis, gluten-free diet, transgressions, long-term outcome, biopsy-proven diagnosis

1 Introduction

Celiac disease (CD) is a systemic autoimmune disorder, which gradually develops as a response to gluten intake in genetically predisposed individuals. Once diagnosed, the only available treatment is a strict life-long gluten-free diet (GFD), a major change in the life of the children and their families.

As patients may seem adherent to the dietary restriction, transgressions can occur at any time, even after years of treatment. Further, inadvertent gluten ingestion is common even when following a strict GFD (1). Therefore, regular follow-up of these children is critical (2). One of the main characteristics of CD is the production of specific gluten-dependent transglutaminase 2 (TG2-IgA) and endomysial (EmA) autoantibodies (3, 4). The serum

identifications of the TG2-IgA and EmA are important steps of the CD diagnostic and follow-up algorithms. Starting 2012, the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendations has removed from the CD diagnostic strategy the requirement for a small-bowel biopsy, the historical gold standard (5). This change was based on retrospective studies showing that high autoantibody titers are indicative for a severe duodenal mucosal lesion (6, 7). Further, large multicentric prospective studies confirmed these findings showing that up to 50% of the children clinically suspected for CD would not need the intestinal biopsy to complete the diagnosis (8–10). Therefore, clinical diagnosis of CD was allowed based on serology alone, in children having serum TG2-IgA titers higher than 10 times the upper limit of normal of the laboratory kit used (TG2-IgA>10xULN) provided that EmA were also positive from a different blood sample (11). A recent meta-analysis showed that the no-biopsy criteria have high positive predictive value when compared with the small bowel biopsy reference standard (12). Quantitative measurements of TG2-IgA are further recommended during follow-up visits with the expectation of full normalization by 24 months in most of the children (11).

In the present study we sought to assess the impact of the change of CD diagnostic strategies on the patient's long-term outcome regarding clinical and laboratory features, dynamics of CD serum antibody titers and adherence to follow-up appointed visits by comparing serology-based to biopsy-proven diagnosed patients.

2 Methods

2.1 Patients and study design

The study includes retrospectively collected data from the medical charts of consecutive children who were diagnosed and followed for CD at the National Institute for Mother and Child Health, Bucharest, between 2010 and 2014. This 4-year period overlapped with the 2012 guideline change of diagnostic algorithm in pediatric CD, from duodenal biopsy-proven to allowing serology-based diagnostics. All CD diagnoses were established according to valid diagnostic criteria at the time of diagnosis (5, 13). After applying our inclusion criteria, i.e., a firm, either serology-based or biopsy-proven diagnosis at the age of <16 years and having an initial serum TG2-IgA titer >10xULN, the children were divided into two study groups, the serology-based group and the biopsy-proven group. The serology-based diagnosed group patients had also a confirmatory EmA positivity and demonstrated the mandatory CD genetic risc alleles, human leukocytes antigens DQ2 and/or DQ8 (5).

2.2 Data collection

Clinical data were collected according to a standardized medical chart and compared between the two groups. This included, when available, duration of symptoms before the diagnosis, dietary adherence and time-length between the diagnosis and start of GFD. The family history of CD and the presence of CD associated conditions (type 1 diabetes, autoimmune thyroid disease) were recorded. The clinical and laboratory data again were collected at baseline at CD diagnosis and follow-up visits, after both 1 year and 2 years of GFD. Additionally, data were collected from everyone at their last follow-up visit in our unit. Weight and height measurements were expressed as body mass index (BMI) calculated as weight/height^2 (kg/m^2) adjusted for age and gender. Symptoms were divided into gastrointestinal and extraintestinal. The gastrointestinal symptoms were further divided in diarrhea, abdominal pain, constipation, vomiting and flatulence problems. Data on asymptomatic children diagnosed by screening among risk groups were collected. Further, laboratory values of serum autoantibodies and of blood biological parameters comprising hemoglobin [Hb, lower reference values (rfv) being 11 g/dl–13 g/dl according to age and gender], mean erythrocyte volume (MCV, rfv 73–95 fl), alanine aminotransferase (ALT, upper rfv 32 U/L), iron (lower rfv 8 µmol/L), ferritin (lower rfv 20 µg/L), vitamin D (lower rfv 75 nmol/L), and alkaline phosphatase (upper rfv 500 U/L) were also gathered. For the quantitative measurements of the serum TG2-IgA the same enzyme-linked immunosorbent assay kit was used at diagnosis as well as at each follow-up visit. The cut-off for positivity was set at 20 U as recommended by the kit producer (Quanta Lite, Inova Diagnostics, CA, USA). Serum EmA was assessed by indirect immunofluorescence method using the same laboratory kit at diagnosis and each follow-up visit (Nova Lite, Inova Diagnostics). The cut-off for positivity was set at a serum dilution of 1:5. Positive samples were further diluted in 1:50, 1:100, 1:200, 1:500, 1:1,000, 1:2,000 and 1:4,000 to obtain the highest positive titer. All EmA assessments were done by the same observer.

Compliance with regular follow-up visits and adherence to GFD were evaluated at each follow-up visit at 1 and 2 years after starting GFD. The adherence to the diet was assessed with the help of a questionnaire filled in by all the children or caregivers after starting the GFD. It contained 2 simple questions: *1. How long after being diagnosed with CD did you start the GFD?; 2. How frequently do you transgress from your GFD? A. Never, B. Sometimes.*

2.3 Statistical analysis

Statistical analysis was done using SPSS software version 20.00 (Statistical Package for Social Sciences, IBM, US). For the statistical significance of the differences between the groups the T test was used. Statistical significance was defined by p-value <0.05. Results are expressed as average ± standard deviation or median (range, quartiles) as appropriate.

3 Results

3.1 Baseline characteristics of patients in the diagnostic groups

The baseline characteristics for the two study groups of children are presented in Table 1. Altogether 63 out of the 82

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TABLE 1 Baseline characteristics of the 63 children with high serum antibody titres at diagnosis (TG2-IgA>10xULN).

Characteristics of the patients	Serology-based diagnosis $n = 33$	Biopsy-proven diagnosis $n = 30$	p-value
Age, median, (range) yrs	3.33 (1.1 to 14.5)	4.87 (1.2 to 15.9)	0.819
Girls, %	63.6	63.3	0.980
Celiac disease in family, %	6.1	16.7	0.187
Celiac disease associated conditions, %	3	20	–
BMI Z-score median (quartiles)	−1.51 (−2.7 to −0.2)	−1.5 (−2.92 to −0,15)	0.840
Clinical presentation			
Gastrointestinal, %	72.7	63.3	0.432
Diarrhea, %	39.4	53.3	0.275
Abdominal pain, %	66.7	40.7	0.499
Constipation, %	12.1	0	0.050
Extraintestinal, %	24.2	16.7	0.466
Screen-detected, %	3.0	20.0	0.033
Laboratory results			
EmA, median titre (quartiles)	1:500 (1:100–1:1,000)	1:1,000 (1:200–1:2,000)	0.28
Hb, median (quartiles), g/dl	12.5 (10.9–13.1)	12.2 (10.6–12.9)	0.36
MCV, median (quartiles), fL	77 (73.2–80.5)	79 (73–85)	0.23
Serum iron, median (quartiles), µmol/L	11 (4–16.8)	10.5 (4–13)	0.23
Ferritin, median (quartiles), µg/L	23 (7.9–39)	28 (5–50.5)	0.80
Alkaline phosphatase, median (quartiles), U/L	169 (121.5–211)	256 (238–294)	0.005
ALT, median (quartiles), U/L	34 (22.5–65)	40.5 (28–55.8)	0.67

BMI, body mass index; TG2-IgA, type 2 transglutaminase antibodies IgA; ULN, upper limit of normal; EmA, antiendomysial antibody; Hb, hemoglobin; MCV, median corpuscular volume; ALT, alaninaminotransferase.
Data was available in >90% of the cases.

newly diagnosed children with CD fulfilled our inclusion criteria. Of this, 63.5% were girls with no difference between the serology-based diagnosed children ($n = 33$, median age 3.3 years, range 1.1–14.5) and the biopsy-proved ($n = 30$, median age 4.8 years, range 1.2–15.9) respectively.

All these patients having TG2-IgA >10xULN were also positive for EmA, with similar titers in both groups (Table 1). In the biopsy-proven group, 8/30 children and their parents chose to have a biopsy even though the new criteria would have allowed them to omit it. Altogether 39.7% of the newly diagnosed patients were underweight but no significant difference in growth parameters were found between the two groups, neither in age nor gender proportion. In the biopsy-proven group there was a trend towards higher prevalence of family history and CD associated conditions. Children presented mainly with one or more gastrointestinal symptoms with abdominal pain and diarrhea being the most frequent. CD patients with constipation were all in the serology-diagnosed group. No statistically significant differences in Hb levels, MCV and iron levels were observed. However, alkaline phosphatase was significantly lower at baseline in the serology-based diagnosis group as compared to the biopsy-proven diagnosis group (Table 1).

At the diagnosis of CD, anemia was similarly present in both groups (27.3% among children with serology-based diagnosis and 26.7% among those with biopsy-proven diagnosis). The median duration of symptoms before CD diagnosis tended to be higher in the biopsy-proven group (median 9 months, range 0–84 months) than in the serology-based group (median 4 months, range 0–132 months), $p = 0.370$. This information was available in the charts for 88% of the children. The median time between the diagnosis and the initiation of GFD was slightly higher in the serology-based group (2.3 months) than in the biopsy-proven group (1.6 months), $p = 0.568$.

3.2 One-year follow-up on GFD

Only 57.6% of children from the serology-based group responded to the GFD follow-up visit at one year, as compared to the biopsy-proven group (73.3%) (Figure 1). Most of the patients who regularly attended the follow-up visits were girls, brought up in an urban environment. Median BMI Z-score improved for both groups, in the serology group from baseline median −1.51 to −0.8 ($p = 0.071$) and in the biopsy group the result was better, from median −1.5 to −0.2 ($p = 0.018$) (Table 2). During the first year after the diagnosis,

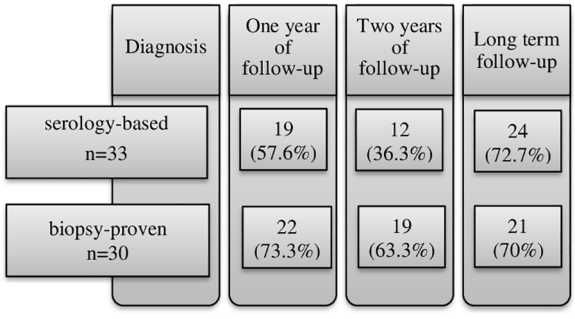

FIGURE 1
Dynamics of follow-up visits of children enrolled in the study.

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TABLE 2 Follow-up characteristics in 41 children after 1 year of gluten-free diet.

Characteristics of the patients	Serology-based diagnosis $n = 19$	Biopsy-proven diagnosis $n = 22$	p-value
Girls, %	78.9	63.6	0.294
Urban, %	68.4	59.9	0.548
BMI Z-score median (quartiles)	−0.8 (−1.9 to 0.1)	−0.2 (−0.97 to 0.9)	0.056
Clinical presentation[a]			
Gastrointestinal, %	36.8	25	0.467
Diarrhea, %	5.3	6.3	0.944
Abdominal pain, %	26.3	18.8	0.818
Constipation, %	10.5	0	0.904
Laboratory data[b]			
TG2-IgA, mean titre (range), U	66.2 (3–200)	65 (7–173)	0.948
EmA, median titre (quartiles)	1:50 (1:5–1:1,000)	1:50 (1:5–1:100)	0.123
Hb, median (quartiles), g/dl	12.0 (11.3–13.2)	12.7 (11.9–13.2)	0.177
MCV, median (quartiles), fL	78 (72–83)	81.5 (75.5–83.25)	0.334
Serum iron, median (quartiles), µmol/L	11 (4.1–17)	8 (5.5–15)	0.874
Ferritin, median (quartiles), µg/L	27.5 (20–33.5)	59 (23–110)	0.040
Alkaline phosphatase, median (quartiles), U/L	252.5 (190–327.5)	295.5 (245.25–344.25)	0.078
ALT, median (quartiles), U/L	31 (20.5–33.5)	37 (29.5–40)	0.034

BMI, body mass index; TG2-IgA, type 2 transglutaminase antibodies IgA; EmA, antiendomysial antibody; Hb, hemoglobin; MCV, median corpuscular volume; ALT, alaninaminotransferase.
[a]Clinical presentation data was available in all children in serology-based group and in 16 children in biopsy-proven group.
[b]Laboratory data was available in >90% of children.

most of the patients from both groups reported improved gastrointestinal symptoms as compared to baseline, being still present in one third of the patients (Table 2). No overt clinical malabsorption syndrome was present anymore and diarrheal symptoms were rare.

Anemia had been assessed in 16/19 children from the serology group and 14/22 children from the biopsy-proven diagnosis. No significant improvement of hemoglobin from baseline was observed in the serology group at one year of GFD, compared to the baseline level ($p = 0.661$). On the contrary, hemoglobin was higher in the biopsy-proven group compared to that from baseline after one year of GFD ($p = 0.055$) There was no statistically significant difference in the hemoglobin levels between the groups. Significantly lower ferritin in the serology group can be noted (Table 2). Alkaline phosphatase and liver enzyme ALT showed higher normal values in the biopsy-proven group after 1 year of GFD.

The TG2-IgA titers had decreased from the baseline values and were similar in both groups (Table 2). However, after one year of GFD 73.7% and 76.2% of patients in the respective groups were still positive for TG2-IgA. As shown in Table 2 the EmA titers had clearly decreased as compared to baseline, but positivity was still seen in 53.9% of patients in the serology-diagnosed group and 40% in the biopsy-diagnosed group (Figure 2b).

Both groups reported occasional transgressions to GFD, 83% in the serology-based and 62% in the biopsy-proven group (Figure 2a).

3.3 Two-year follow-up on GFD

After 2 years of GFD, 12 children (36.3%) from the serology-based group and 19 children (63.3%) from the biopsy-proven group responded positively to the follow-up visit appointment (Figure 1). Similarly to one-year visit, most of the children compliant to the follow-up were females living in urban conditions. The BMI showed deterioration in the serology-based group (median Z-score −1.35) as compared to the initial healing at one year (−0.8) (Tables 2, 3). Median BMI was again significantly higher in the biopsy-proven group (Z-score −0.2, $p = 0.023$) with only 5.3% of these children still being underweight (BMI below percentile 5 for age and gender) as opposed to 27.3% from the serology-based group. The serology-based diagnosis group experienced more frequently gastrointestinal symptoms compared to the biopsy group (58.3% vs. 26.7%). These percentages also include overall gastrointestinal complaints, vomiting and flatulence problems, data not shown in Table 3. No overt malabsorption syndrome or diarrhea was present any more in either group. Anemia was assessed in all 12 children in the serology group and in 12/19 from the biopsy-proven group. In both groups 16.6% still had anemia. In the serology group the hemoglobin levels did not improve significantly from baseline ($p = 0.791$), while for the biopsy-proven group a significant improvement was documented ($p = 0.025$). No significant difference in ferritin levels was noted between the groups and liver enzymes were normal in both groups.

Serum TG2-IgA and EmA titers had decreased during the GFD and there was no difference between the two diagnostic groups (Table 3). Remarkably, after two years on GFD both TG2-IgA and EmA were often still above the cut-off for positivity in both diagnostic groups; positive TG2-IgA in 58.3% patients and positive EmA in 50% patients included in the serology group; 50% and 28.6% respectively, in the biopsy group (Figure 2b). Occasional transgressions were again reported in both groups, with less frequency compared to the previous check-up visit (37% in the serology-group and 18% in the biopsy-group) (Figure 2a).

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TABLE 3 Follow-up characteristics in 31 children after 2 years of gluten-free diet.

Characteristics of the patients	Serology-based diagnosis $n = 12$	Biopsy-proven diagnosis $n = 19$	p-value
Girls, %	75	63.16	0.508
Urban, %	75	78.95	0.806
BMI Z- score median (quartiles)	−1.35 (−3.27 to −0.22)	−0.2 (−2.13 to 0.9)	0.023
Clinical presentation[a]			
Gastrointestinal, %	58.3	26.7	0.103
Diarrhea, %	0	0	–
Abdominal pain, %	8.3	6.6	0.745
Constipation, %	16.7	0	0.069
Laboratory data[b]			
TG2-IgA, mean titre (range), U	39.7 (2–120)	31.1 (6–100)	0.504
EmA, median (quartiles)	1:5 (1:<5–1:50)	1:5 (1:<5–1:50)	0.203
Hb, median (quartiles), g/dl	12.2 (11.6–13.2)	12.9 (12.5–13.1)	0.120
MCV, median (quartiles), fL	79.5 (74.5–81.75)	80 (77–82)	0.389
Serum iron, median (quartiles), µmol/L	12 (6–18)	12 (10.5–16)	0.496
Ferritin, median (quartiles), µg/L	43 (13–58)	47 (19–60.5)	0.653
Alkaline phosphatase, median (quartiles), U/L	207.5 (175.5–349.75)	262 (248–277)	0.920
ALT, median (quartiles), U/L	25 (18–33)	31.5 (25.7–35.25)	0.125

BMI, body mass index; TG2-IgA, type 2 transglutaminase antibodies IgA; EmA, antiendomysial antibody; Hb, hemoglobin; MCV, median corpuscular volume; ALT, alaninaminotransferase.
[a]Clinical presentation data was available in all children in serology-based group and in 15 children in biopsy-proven group.
[b]Laboratory data was available in >90% of children.

3.4 Follow-up after long-term GFD

Altogether 24 children (72.7%) from the serology-based diagnosis group and 21 (70%) from the biopsy-proven diagnosis group responded to the follow-up appointment at median time of 8.7 and 10 years, respectively, after diagnosis (Figure 1). Various symptoms were still reported in both groups (Table 4). In the biopsy-group no diarrhea was reported at two years on follow-up but at long-term diarrhea was again a complaint in two patients. No children had anemia anymore in either group. On long term there were no differences in biological parameters between the two groups. Serum TG2-IgA and EmA antibody titers had clearly decreased but 4 children from the serology group and 8 children from the biopsy group, altogether 27%, were still positive for TG2-IgA (Figure 2b).

The children from the biopsy-proven diagnosis group were compliant with the follow-up program significantly longer than the children diagnosed based solely on serology. In the biopsy group 15/30 (50%) children did not miss any follow-up appointment, having yearly evaluations up to the age of 17, when the transfer to the adult health care system usually begins. The remaining six children responded discontinuously to the follow-up appointments up to their respective last follow-up. The overall age at the latest follow-up evaluation was 15.4 years old

TABLE 4 Last follow-up characteristics in 45 children at median time of 8.7 (serology-based group) and 10 years (biopsy-based group) on gluten-free diet.

Characteristics of the patients	Serology-based diagnosis $n = 24$	Biopsy-proven diagnosis $n = 21$	p-value
Girls, %	79.2	61.9	–
Age, median (quartiles), years	12.8 (10.4–15.6)	15.4 (12.95–17.8)	0.015
Gluten-free diet, median (quartiles), years	8.7 (6.33–9.6)	10 (7.5–12)	0.011
Clinical presentation[a]			
Gastrointestinal, %	19.1	13.6	0.831
Diarrhea, %	4.7	9.5	0.355
Abdominal pain, %	14.3	5.3	0.374
Constipation, %	4.7	0	0.355
Laboratory data[b]			
TG2-IgA, mean titre (range), UEmA	23.8 (4–200)1:<5	20.6 (4–115)1:<5	0.76
Hb, median (quartiles), g/dl	13.1 (12.5–13.8)	13.5 (12.65–14.7)	0.14
MCV, median (quartiles), fL	82.7 (79.5–84.3)	84.8 (80.65–88.45)	0.08
Serum iron, median (quartiles), µmol/L	13 (11–19)	17.5 (10.25–22)	0.37
Ferritin, median (quartiles), µg/L	27 (19–60)	43 (18–70)	0.26
Alkaline phosphatase, median (quartiles), U/L	211 (83–251)	100.5 (62.25–269.75)	0.15
ALT, median (quartiles), U/L	21.5 (16–24)	20 (19–28)	0.46

TG2-IgA, type 2 transglutaminase antibodies IgA; EmA, antiendomysial antibody; Hb, hemoglobin; MCV, median corpuscular volume; ALT, alaninaminotransferase.
[a]Clinical presentation data was available in 21 children in serology-based group and in 19 children in biopsy-proven group.
[b]Laboratory data was available in >90% of children.

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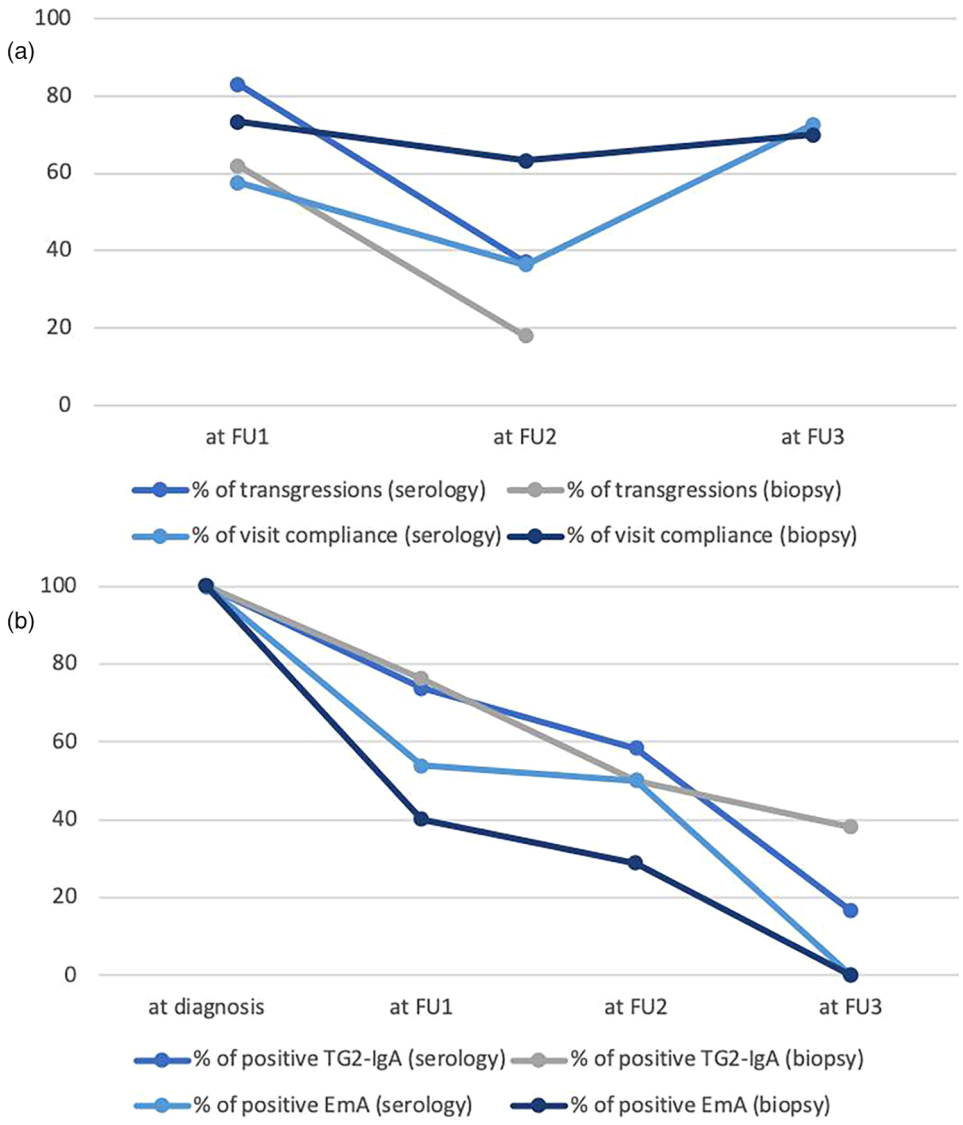

FIGURE 2
(a) Percentage of patients who attended the first (FU1), second (FU2) and third (FU3) follow-up visits and percentage of transgressions at FU1 and FU2 in the serology-based and biopsy-proven groups. (b) Percentage of positive TG2-IgA (>20 U) and EmA (<1:5) in serology-based and biopsy-proven groups at diagnosis and after the first (FU1), second (FU2) and third (FU3) follow-up.

in the biopsy group. Ten children/33 (30%) diagnosed based on the serology positively responded to all yearly follow-up appointments, the rest of them were discontinuously evaluated. The median age of the total group at their latest follow-up was 12.8 years old.

4 Discussion

Our results show that the change of diagnostic strategy from mandatory biopsy-proven to serology-based alone in 2012 (5) did in fact have an impact on patient behavior and different outcome measures both at short and long-term GFD in our present routine clinical diagnostic and follow-up study.

We noticed an overall difference in the responses to the follow-up appointments in our children and families as seen in Figure 1, the children diagnosed by biopsy were more active and responded positively to the follow-up visit appointments after one and two years on GFD. This can be explained by the burdensome longer duration of symptoms between clinical onset and diagnosis in the biopsy-proven patients, also by the greater impact of the more complex approach associated with upper gastrointestinal endoscopy at diagnosis. Further, 8 parents with serology-based diagnosis in their child demanded an endoscopy with biopsies for the diagnosis. Proof of gluten-induced small bowel injury might be a stronger driver for perceiving CD as a lifelong disease which warrants continuous follow-up, compared to serology-based only. It is of note that children diagnosed by biopsy started the diet sooner after the completion of the diagnosis than children diagnosed based on serology alone.

Our results also suggest that screen-detected children, having family members with CD, are more likely to opt for biopsy at

diagnosis. We clearly need to put more effort into how to deliver the message regarding different diagnostic strategies used in CD and into the importance of follow-up in general but especially into our instructions on follow-up to serology-based diagnosed children. When looking at symptoms and signs of CD, gastrointestinal symptoms tended to be more frequent in the serology-based diagnostic group compared to the biopsy-proven one during the GFD. Furthermore, the nutritional status in general was inferior in this group as compared to the biopsy-proven group. In fact, the BMI of the serology group patients had even deteriorated at the two-year follow-up visit, and Hb values showed no improvement. We cannot identify the cause of the differences between the diagnostic groups, we can only assume that those in the biopsy group paid more attention to the children's daily nutrition, also that they potentially had less transgressions in their GFD.

When evaluating again the results of gluten-dependent celiac-type autoantibodies, TG2-IgA and EmA-IgA, and finding the high percentages of positivity on follow-up, it seems clear that the diet was all but gluten-free after one and two years of treatment. We can conclude that we did not fulfill the ESPGHAN expectation of full normalization of antibodies by 24 months in most of the children (11). However, it is known that the time required for negative seroconversion is longer for children with high titers at diagnosis and that normalization can take even longer than the expected time-length of 18–24 months of dietary elimination of gluten (14–16). The strength of our study is again the use of the same reagent kits through the time-points of diagnosis and follow-up visits.

Nevertheless, the proportion of children with persistent positive titers (51.6% for TG2-IgA and 37% for EmA) after 2 years of GFD is clearly higher than that reported in studies from other centers (14, 16–18). As mentioned, undetected transgressions but also suboptimal adherence to the diet as well as the lower accessibility to the specific gluten-free products may all together be behind the present results (1, 19). In fact, we still observed positivity for TG2-IgA in one third of the patients tested after following 8–10 years of GFD. It is of note that poor adherence to the GFD was reported with higher frequency in the group diagnosed solely by serology. This result supports earlier published assessment on the low accuracy of self-declared (by the children of their families) level of adherence and the need of dietary assessment by a health professional (20, 21). The limitation of our present study is that we lack detailed dietary assessment, this has not been done in our real-life routine clinical follow-up. Further studies are warranted using validated questionnaires to address dietary adherence. We note that half of the children declaring occasional transgressions had normal TG2-IgA titers. A promising biomarker for objective assessment of GFD adherence is the measurement of stool and urine excretion of gluten immunogenic peptides indicating continuous ingestion of gluten-containing food (22). This agrees with the meta-analysis results of Silvester et al. in 2017 (23) where it was shown that occasional transgressions are not detected by serological assessments.

The review article by Besser and Khosla in 2023 (24) presents the current understanding of CD pathogenesis and how this knowledge is being harnessed for therapeutic design and development. In adults, proof-of-concept studies for the use of several novel investigational medical products, future drug candidates using the gluten challenge design, have been presented. Today, all companies striving to develop novel treatments are trying to develop the drug for the real-life situation targeting patients already on GFD, those who still experience gluten-triggered symptoms and/or with duodenal mucosal inflammation and morphological injury. Towards this background, we feel our clinical study gives strong indication for the need of novel treatments in children suffering from CD, first as an adjunctive therapy to GFD. Nonetheless, further research needs to focus on the selection of the children which would benefit from a potential novel treatment and how this would integrate into standard care of dietary treatment. However, it should be noticed that we did not perform re-endoscopies and duodenal biopsies on our patients, but our clinical follow-up study results indicate mucosal injury to be present in our children. In a similar study, Leonard et al. 2017 (25) showed persistent enteropathy despite maintaining a GFD to be present in 20% of the children. They noticed again that neither the presence of symptoms nor positive serology were predictive of a patient's histology at the time of repeat biopsy. The authors used a qualitative Marsh grouping instrument to assess mucosal injury, known to be heavily observer dependent, as was the case in our large ESPGHAN multicenter study (9). When we again used standard operating procedures for morphometry, i.e., quantitative measurements of duodenal morphology and inflammation, baseline histology in therapeutic trials in adults revealed villus atrophy in most patients with CD who appear well controlled on GFD, i.e., symptom free and negative for TG2-IgA (26, 27). Also in children quantitative biopsy reading is essential (28). The present study findings clearly indicate that children on long-term GFD should be revisited as to their duodenal mucosal status by using quantitative morphometric tools. On long term gluten-induced small intestinal mucosal inflammation and morphological injury may cause complications to the celiac sufferers. Real-life GFD does not seem to be gluten-free in our country but neither in the USA, potentially globally (1, 25). Adjunctive therapies to GFD are warranted also in children.

A limitation of our study is the retrospective nature of it, resulting in many children and their families not complying with the invitations to the follow-up visit. On the other hand, we used this as an outcome measure in routine clinics as a strength and noticed that especially serology-based diagnosed patients need extra support and explanations as to their need of GFD and follow-up. Similarly, other studies have reported the lack of follow-up to be 14%–57% (15, 29–31), but we feel the no-biopsy diagnosed patients need our focus at present. No-biopsy strategy has been today adopted by the health-care, both in children and adults (32). Our findings indicate that in clinical practice of celiac disease management in children improvement should be focused on the follow-up of the patients. Potential interventions in order to improve compliance in these patients include regular nutritional and also possibly psychological assessments to address the potential contributing factors to their loss of adherence to the GFD and follow-up. Earlier and more frequent follow-up controls during the first two years on GFD might also improve

compliance. We tried to minimize potential biases by exclusively selecting patients diagnosed according to the current at date ESPGHAN criteria, including demonstrating the presence of the CD genetic risk alleles in the serology-based group. Another limitation of the present study is represented by the small number of participants, studies on larger samples are therefore needed in order to further compare the impact of the two diagnostic strategies on the outcome of childhood CD.

In conclusion, our results indicate that serology-based diagnosis leads to slower mucosal healing, higher dietary transgressions, and lower follow-up compliance compared to biopsy-proven cases. There is a need for improvement of the management, with special attention regarding ESPGHAN no-biopsy diagnosed patients. Further long-term outcome studies are warranted to establish the best follow-up system for childhood CD. Overall, also in children, novel treatments adjunctive to GFD are needed.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Data is not publicly available due to privacy and ethical reasons. Requests to access these datasets should be directed to Alina Popp, alina.popp@tuni.fi.

Ethics statement

The studies involving humans were approved by Ethical Committee of National Institute for Mother and Child Health. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

IE: Data curation, Formal analysis, Methodology, Writing – original draft. MJ: Conceptualization, Methodology, Supervision, Writing – review & editing. AP: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. DVB: Formal analysis, Methodology, Validation, Writing – review & editing. FG: Formal analysis, Writing – review & editing, Methodology. D-MM: Writing – review & editing, Data curation, Formal analysis. AP: Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Publisher's note

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Celiac disease screening in children: evaluating the evidence, benefits, and challenges

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Comprehensive screening of the general population is the only approach capable of identifying the majority of cases with celiac disease. In 2023, the Italian Parliament enacted a law to implement nationwide screening for celiac disease and type 1 diabetes. However, critical decisions regarding the target population, optimal timing, and screening methods remain unresolved. Previous observational studies on birth cohorts of children with genetic risk for these conditions have demonstrated that the incidence peaks early in life and is influenced by HLA risk genotypes. This mini-review explores different aspects of screening for celiac disease, presenting the advantages and challenges of identifying children before onset of symptoms. In addition, we summarize the current knowledge and gaps in understanding related to screening programs for celiac disease in children and adolescents and discuss health benefits, psychosocial aspects and cost-effectiveness, and their potential implications for future public health strategies.

KEYWORDS

celiac disease, screening, children, transglutaminase antibody, HLA, quality of life, costeffectiveness, population

1 Introduction

Advancements in technology have significantly improved the feasibility of mass screening for immune-mediated diseases. Celiac disease is a chronic autoimmune disorder that targets the mucosa of the small intestine in genetically predisposed individuals carrying the human leukocyte antigen (HLA) risk genotypes DQ2 and/or DQ8. Its pathogenesis is strongly associated with elevated levels of tissue transglutaminase (tTG) autoantibodies (1, 2), detectable in the blood long before the clinical onset of the disease (3) and thereby making it a valuable marker for screening (4).

The primary rationale for screening for celiac disease is early detection and treatment with gluten-free diet (GFD), which may prevent long-term complications. According to the World Health Organization (WHO), the ten criteria established by Wilson and Jungner must be considered when evaluating a condition for screening (5). Celiac disease meets several of these criteria: it is an important health problem with a latent or early symptomatic stage, there is an appropriate test available, and an accepted treatment for affected individuals. However, certain criteria remain subject to debate. Particularly, the progression from latent to clinically manifest disease is not yet fully understood, consensus is lacking regarding the criteria for determining which individuals should receive treatment, and the cost-effectiveness of systematic screening relative to overall healthcare costs remains uncertain. Despite ongoing debate regarding whether celiac disease meets the criteria for general population screening (6–9), Italy

has taken a pioneering step by approving a law to implement nationwide screening for celiac disease and type 1 diabetes in children aged 1–17 years (10).

Celiac disease has been described as a clinical "chameleon" due to its wide range of presentations, varying from severe malabsorption to nearly asymptomatic cases (11, 12). In children, gastrointestinal symptoms and malabsorption are more common, whereas adults often present with extraintestinal manifestations (13). This complexity often results in diagnostic delays spanning months to years (14–18), yet most individuals remain undiagnosed unless active screening is performed (19). The key questions that arise are whether children should be screened for celiac disease and what the potential benefits and drawbacks of such an approach might be?

2 To screen or not to screen?

2.1 What are the health benefits of screening?

Celiac disease is among the most prevalent autoimmune conditions in children, with a global prevalence of approximately 1% (20). However, recent screening studies in children and adolescents suggest a higher prevalence of up to 3% in certain populations (21–23). Despite increased awareness and improved detection, a significant proportion of cases remain undiagnosed without mass screening; a recent study found that 60% of cases went undetected in the absence of systematic screening (23).

The clinical manifestations of celiac disease exhibit a remarkable variation. While some patients present with classic symptoms of malabsorption, including diarrhea, steatorrhea, weight loss, and growth retardation, others develop more non-specific gastrointestinal symptoms, such as abdominal pain and constipation (24), or extraintestinal symptoms or signs such as iron deficiency, short stature, delayed puberty, osteoporosis, infertility, dermatitis herpetiformis, enamel defects, neurological issues (e.g., gluten ataxia, peripheral neuropathy), or psychiatric symptoms (12, 25). Celiac disease is also associated with several other conditions such as selective immunoglobulin A (IgA) deficiency, type 1 diabetes, autoimmune thyroid disease and psoriasis, as well as chromosomal abnormalities such as Down, Turner, and William syndromes (25, 26). Given these known associations, celiac disease should always be considered in patients with these conditions.

The wide spectrum makes celiac disease challenging to diagnose, often leading to significant delay in diagnosis. The delay can range from months to over a decade (14–18) and patients are frequently misdiagnosed with alternative diagnoses such as anemia, irritable bowel syndrome, or stress-related disorders, before celiac disease is identified (14). In children, the diagnostic delay tends to be shorter than in adults. One study reported a median delay of five months (17), while another documented a broader range of 2–109 months (27). Prolonged delay in diagnosis is associated with more severe disease at presentation, including higher tTG autoantibody levels, more advanced villous atrophy, persistent symptoms, and reduced quality of life (18, 28). Interestingly, approximately one-fifth of children with screening-detected celiac disease had sought medical care for symptoms prior to screening, but the possibility of celiac disease had not been considered (29).

A controversial issue in screening is whether children identified as asymptomatic benefit from a diagnosis. In an Italian school-based screening program, as many as two-thirds of the children diagnosed with celiac disease were reportedly asymptomatic (30). However, studies have shown that many "asymptomatic" individuals have subtle symptoms or laboratory abnormalities that improve on a GFD (8). Furthermore, screening-detected and clinically detected children do not differ in regards of autoantibody titers, histological damage, or response to GFD (31). It has also been shown that screening-detected children exhibit systemic inflammation at diagnosis which resolves with dietary intervention, indicating that also these children benefit from treatment (32).

Previously undetected anemia, low ferritin, and other micronutrient deficiencies that improve after starting a GFD have been observed in screening-detected children (33, 34). Poor growth and reduced body mass index (BMI) are also common (33, 35). Dietary intervention leads to significant improvement (33), emphasizing the importance of early detection to prevent long-term irreversible effects on stature.

Another critical consideration is bone health. Malabsorption of calcium and vitamin D can result in osteopenia, osteoporosis, and increased fracture risk (12, 36, 37). Childhood and adolescence are pivotal periods for bone accretion and the peak bone mass reached in young adulthood is predictive for the risk of osteoporosis later in life (38). Early diagnosis and adherence to a GFD during these critical periods have been shown to normalize bone mineral density and improve the overall outcomes of bone health (27, 32, 39), which is not seen to the same extent in individuals diagnosed as adults (40).

In a long-term perspective, early diagnosis and adherence to a GFD during critical developmental periods not only optimize growth and bone health outcomes but also mitigate the risk of severe complications, including certain malignancies. Celiac disease has been associated with an increased risk of enteropathy-associated T-cell lymphoma (EATL) and intestinal adenocarcinomas, and although these malignancies are rare, it underlines the importance of early diagnosis and adherence to a GFD to reduce cancer risk (41, 42).

These findings highlight the potential benefits of screening programs for celiac disease. Early diagnosis can reduce nutrient deficiencies, improve growth, enhance bone health, and potentially prevent severe complications such as malignancies. But do the benefits of widespread screening outweigh the associated challenges and costs?

2.2 Which individuals should be targeted for screening?

Symptomatic screening for celiac disease involves individuals seeking medical care for classical symptoms such as chronic diarrhea, abdominal pain, or failure to thrive. These symptoms are common in the general pediatric population, and most

children presenting with such complaints do not have celiac disease. Studies have shown that symptom-based screening is a poor discriminator of celiac disease, as there is no significant difference in symptom prevalence between children who test positive or negative through screening (23, 43, 44).

Expanding screening to include individuals with extraintestinal manifestations, abnormal laboratory findings, or those belonging to risk groups significantly increases diagnostic yield. Individuals at increased risk of developing celiac disease are first-degree relatives, patients with other autoimmune diseases, such as type 1 diabetes or autoimmune thyroid disease, patients with IgA deficiency or psoriasis, or patients with genetic syndromes, such as Down, Turner, or William syndromes. An active case-finding approach is endorsed by both the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (1, 26) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) (45), which recommend a low threshold for testing individuals within these identified risk groups. However, despite these guidelines, it is estimated that active case-finding would only identify around 40% of cases of celiac disease (43). Although the pooled prevalence of celiac disease among first-degree relatives to affected individuals has been shown to be as high as 7.5% (46), approximately 80%–90% of children with celiac disease autoimmunity or celiac disease detected through mass screening did not have a first-degree relative with the condition (44, 47).

Increased awareness among healthcare providers and the public about the diverse manifestations and related conditions of celiac disease could enhance case detection through active case-finding, but this strategy would still miss most of affected individuals. Comprehensive screening of the general population is the only approach capable of identifying the majority of cases, and in recent years several mass screening programs for celiac disease have been initiated around the world (23, 44, 47). Nevertheless, Italy remains the only country where nationwide screening for celiac disease and type 1 diabetes has been legislatively approved (10).

2.3 What are the optimal methods for screening?

In population-wide screening programs, screening tests must exhibit high sensitivity and specificity, as most individuals screened will have a low pre-test probability of disease. Celiac disease screening commonly includes analyzing disease-specific autoantibodies, with IgA endomysial antibodies (EMA) and IgA-tTG showing the highest sensitivity and specificity (11). Due to higher cost, time consuming procedures, and interobserver variability for EMA, IgA-tTG has become the preferred first-line screening method for celiac disease (1, 2, 45). Other autoantibodies, such as antigliadin antibodies (AGA) and deamidated gliadin peptide (DGP) antibodies, are also markers for celiac disease but their lower sensitivity and specificity compared to EMA and IgA-tTG make them unsuitable as first-line screening tests (1, 2, 45). In addition to IgA-tTG, it is generally recommended to take the cost for assessing total IgA in serum in order not to miss celiac disease in individuals with selective IgA deficiency.

An alternative to mass screening with autoantibodies as first-line analysis, is to identify children with increased genetic risk and target screening to these individuals. Celiac disease is strongly associated with HLA genotypes DQ2 and DQ8, and cases in individuals lacking these heterodimers are extremely rare (48). Pre-screening for HLA genotypes effectively excludes individuals without genetic risk from further testing, reducing the number of individuals requiring autoantibody testing. This approach has been implemented in several screening studies, including the multinational TEDDY study (49), the American DAISY study (50), the Swedish CiPiS study (51), and a recent large-scale Italian school-based screening (23). In the Swedish CiPiS study, 3.5% of children carrying HLA risk genotypes DQ2 and/or DQ8 had celiac disease, compared to no cases in the control group lacking any of these HLA risk genotypes (51). Given the shared HLA risk genotypes for celiac disease and type 1 diabetes (52), a joint screening initiative for both conditions could be a practical and cost-efficient alternative. With new technologies for autoantibody detection it is now possible to analyze multiple autoantibodies in a very small volume of blood (53, 54) and combining pre-screening for HLA risk genotypes and subsequent autoantibody testing may improve the efficiency of screening efforts.

2.4 When is the optimal time-point to screen?

The timing of screening for celiac disease is important to maximize detection, prevent complications, and avoid unnecessary interventions. Evidence suggests that a significant proportion of cases develop autoantibodies before three years of age (52) making this an important starting point for screening. However, studies have demonstrated that seroconversion can occur well beyond the early years, with new cases emerging up to adolescence (55, 56). Repeated testing every 3–6 years during childhood and adolescence strikes a balance between detecting late-onset cases and minimizing the burden on healthcare resources and families. For children in risk groups, more frequent testing (e.g., every 2–3 years) may be warranted, especially if symptoms or laboratory abnormalities are present. Early adolescence represents a second key time-point period for screening since a delayed diagnosis during late adolescence can lead to more severe complications, including delayed puberty, reduced bone mineral density, and psychological distress. Conversely, children with no identified risk factors and consistently negative IgA-tTG results might require less frequent or no follow-up.

2.5 Psychosocial aspects of screening

Even though early detection and treatment of celiac disease can lead to numerous health benefits, adopting a lifelong GFD can pose

significant psychosocial challenges, especially for children and adolescents who perceive themselves as asymptomatic. The restrictive nature of a GFD can affect social interactions, particularly in settings where food plays a central role, such as school events, social gatherings, and traveling. These restrictions may lead to feelings of exclusion, embarrassment, or stigma potentially impacting social functioning and overall quality of life (57). For symptomatic individuals, both clinically and screening-detected, quality of life tends to be lower prior to diagnosis but improves after the initiation of a GFD (15, 29). However, in asymptomatic individuals quality of life is comparable to that of healthy peers, both before and after diagnosis (29), indicating that a screening-detected diagnosis does not have a negative impact on quality of life in this group. Furthermore, long-term follow-up of individuals diagnosed in childhood suggest no significant differences in quality of life in adulthood between screening-detected and clinically detected patients (58, 59). Furthermore, despite the potential challenges associated with dietary management, approximately 90% of children and caregivers express satisfaction with participating in screening programs and the subsequent diagnosis of celiac disease (60, 61).

2.6 Is screening a cost-effective approach?

The economic burden of celiac disease extends far beyond the costs of maintaining a GFD; it includes healthcare expenses related to diagnostic investigations, follow-up visits, management of complications and associated conditions, and societal costs such as reduced productivity due to work limitations (62). The costs associated with celiac disease vary across different countries, which complicates the estimations of generalizable cost-effectiveness analyses.

A commonly used measure to evaluate the cost-effectiveness of celiac disease screening programs is to estimate the cost per quality-adjusted life year (QALY) gained. A threshold of $50,000 per QALY gained has been widely accepted as the benchmark for cost-effectiveness (63). However, it has been proposed that this threshold may vary based on a country's health expenditure per capita and the life expectancy of the population, with thresholds ranging from less than $100 in low income countries to nearly $100,000 in high income countries (64).

Both the cost-effectiveness of active case-finding in individuals with higher risk of celiac disease, and mass screening in the general pediatric population has been evaluated. A British study found that the cost per QALY for screening newly diagnosed patients with type 1 diabetes ranged from £12,000 to £20,000 (65). A recent Dutch study estimated the QALY gain for active case-finding in a hypothetical cohort of 3-year-old's using point-of-care (POC) tests in children with at least one symptom suggestive of celiac disease (66). This strategy was associated with an additional 4.33 QALYs at a cost of €15,585 compared to current care. This study also assessed the cost-effectiveness of mass screening in the same hypothetical cohort of 3-year-old's, which resulted in an additional 7.46 QALYs at a cost of €28,635 compared to current care (66). A Swedish study based on data from a program involving 12-year-old schoolchildren found a cost of €40,105 per gained QALY (67). These studies indicate that screening for celiac disease is cost-effective, as costs were below the commonly accepted threshold of $50,000 per QALY gained.

However, for screening to be deemed cost-effective, two essential prerequisites must be fulfilled. First, early detection and treatment with GFD must significantly reduce the risk of associated conditions and complications such as osteoporosis and malignancies. Second, screening-detected individuals, including asymptomatic cases, must adhere to the GFD for any health benefits to occur. Concerns have been raised about whether asymptomatic, screening-detected individuals would be sufficiently motivated to comply with the restrictive diet. Some reports have indicated poor adherence rates following mass screening (68, 69), but many studies show that adherence rates in screening-detected children and adults range from 70% to 100% (8, 59), comparable to rates observed in clinically detected patients (31). Importantly, early diagnosis during childhood appears to facilitate long-term adherence to the GFD (29).

It is crucial to recognize that analyses of cost-effectiveness frequently depend on assumptions regarding mortality, morbidity, and adherence to a GFD, and that even minor changes in these assumptions can substantially impact the results of the cost-effectiveness evaluation (6).

3 Discussion

Celiac disease meets several of the WHO criteria for public screening (5). Firstly, it affects both children and adults worldwide, with a substantial burden of undiagnosed cases. Secondly, individuals with latent or early symptomatic celiac disease can be identified through reliable autoantibody testing. Thirdly, tests for celiac disease-specific autoantibodies, particularly IgA-tTG, are sensitive, specific, and widely accepted by the population. Finally, treatment with GFD improves symptoms and prevents complications, enhancing quality of life in symptomatic individuals and without deteriorating quality of life in asymptomatic individuals. Despite these factors, several challenges remain before screening for celiac disease can be recommended in the public.

A key question is if screening for celiac disease is cost-effective. Based on available evidence, celiac disease screening programs can be cost-effective, particularly in high-prevalence populations if complications are effectively mitigated and quality of life improved through early detection and treatment. Ensuring adherence to the GFD among screening-detected individuals is essential to maximize the benefit of screening. Further research into optimizing screening strategies and enhancing adherence support will be critical for improving cost-effectiveness and health outcomes.

Moreover, the long-term benefits of diagnosing asymptomatic individuals remain uncertain. As a result, the U.S. Preventive Services Task Force (USPSTF) has determined that there is insufficient evidence to assess the balance of benefits and harms of screening for celiac disease in asymptomatic individuals. This conclusion applies to both mass screening and screening of high-risk groups (7, 70).

Furthermore, the potential psychological impact of false-positive results must be carefully considered, and additional complexity lies in managing individuals with potential celiac disease, i.e., those who test positive for autoantibodies but exhibit normal intestinal mucosa (11). Approximately one-third of such individuals progress to clinical celiac disease, while another third experience normalization of IgA-tTG levels over time (71). There is a potential risk that a positive test result without a diagnosis can increase individuals' anxiety. However, providing information about risk for disease may also raise awareness of symptoms, potentially leading to earlier diagnosis. To date, there is limited evidence regarding whether individuals with potential celiac disease face an increased risk of long-term complications compared to healthy individuals.

While celiac disease fulfills many of the WHO criteria for screening, uncertainties regarding cost-effectiveness, long-term benefits, and the management of potential celiac disease present significant challenges. Addressing these gaps will require efforts from researchers, policymakers, and healthcare providers to ensure that screening programs are both effective and sustainable. Until then, the ten criteria for mass-screening for celiac disease cannot be considered met.

In the future, the WHO may play and important role by enhancing global awareness of celiac disease screening in children by developing evidence-based guidelines, advocating for policy integration, and supporting healthcare provider training. Additionally, WHO can promote research, facilitate data sharing, and incorporate screening into existing child health programs to improve early diagnosis and patient outcomes worldwide.

4 Summary

Celiac disease meets many of the WHO criteria for public health screening, including high prevalence, availability of a suitable diagnostic test, and the existence of an effective treatment. Early detection through screening could potentially improve health outcomes by preventing complications like growth retardation, osteoporosis, and gastrointestinal malignancies. However, the current evidence is not conclusive regarding the overall benefit of mass screening. More research is needed to evaluate the long-term benefits of early detection, especially in asymptomatic individuals and those with potential celiac disease, optimize screening strategies, and assess the cost-effectiveness of screening programs. Until further evidence becomes available, clinicians should have a low threshold for testing for celiac disease in individuals with gastrointestinal symptoms, extraintestinal manifestations or laboratory finding associated with celiac disease, and screening strategies should focus on high-risk groups, such as first-degree relatives of patients with celiac disease and those with related autoimmune conditions.

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Allergic and immunologic evaluation of children with celiac disease

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Introduction: Celiac disease (CD) and allergic diseases are immune-mediated disorders with overlapping clinical and immunologic features. The association between CD and selective immunoglobulin (Ig) A deficiency (sIgAD) is well-established, but limited data exist on the relationship between CD, other antibody deficiencies, and allergic diseases in children. This study aimed to evaluate the prevalence of allergic manifestations and immunologic abnormalities in children with CD.

Methods: This prospective study included children with biopsy-confirmed CD, followed at a gastroenterology clinic from August 2022 to February 2023. Participants underwent comprehensive immunologic and allergic evaluation, including serum immunoglobulin levels, vaccine antibody responses, lymphocyte subgroup analysis, and allergy testing as clinically indicated.

Results: The cohort included 76 patients with a median age of 11 years and a median age at CD diagnosis of 5.8 years. Allergic manifestations included aeroallergen sensitivity (22.4%), allergic rhinitis (15.8%), allergic conjunctivitis (13.2%), food allergy (5.3%), and asthma and eczema (3.9% each). Immunologic evaluations revealed normal profiles in 69.7% of patients, while abnormalities included partial IgM deficiency (6.6%), unclassified hypogammaglobulinemia (5.3%), sIgAD (2.6%), and transient hypogammaglobulinemia of infancy (2.6%). Elevated IgE levels were observed in 13.2% of patients.

Conclusion: This study highlighted a significant prevalence of allergic diseases and immunologic abnormalities in children with CD, extending beyond the commonly recognized association with sIgAD. These findings underscore the importance of comprehensive immunologic and allergic evaluation in children with CD.

KEYWORDS

allergy, antibody deficiency, celiac disease, children, immunodeficiency, immune dysregulation

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by dietary gluten in genetically predisposed individuals. It affects 0.7%–1.4% of the population worldwide, with a higher prevalence in pediatric populations compared to adults (1).

The cornerstone of CD diagnosis relies on tissue transglutaminase immunoglobulin (Ig) A (TGA-IgA) testing, typically accompanied by total IgA measurement to identify selective IgA deficiency (sIgAD). This practice emerged from the well-documented association between CD and sIgAD, which occurs more frequently in patients with CD

than in the general population (2–4). As a result, TGA-IgA levels may be low in patients with CD who also have sIgAD, which can complicate diagnosis. In cases of sIgAD, alternative testing using IgG-based assays becomes essential for accurate diagnosis. It is recommended to check for deamidated gliadin peptide IgG, tissue transglutaminase IgG, or anti-endomysial IgG in children with low total IgA levels (2).

Consequently, pediatric gastroenterologists routinely measure total IgA levels alongside TGA-IgA during screening or in suspected CD cases. However, other immunoglobulin levels are often overlooked, potentially leaving immunodeficiencies undiagnosed. For instance, common variable immunodeficiency (CVID) can present with gastrointestinal manifestations mimicking CD, including villous atrophy. Without comprehensive immunoglobulin evaluation, such cases might be misdiagnosed as seronegative CD (5, 6).

Beyond immunodeficiencies, recent evidence suggests that allergic conditions, including atopic dermatitis, allergic rhinitis, asthma, and food allergies, have an increased prevalence in patients with CD. This association suggests shared immune dysregulation mechanisms in CD and allergic diseases (7–10).

There is growing interest in understanding the potential relationships between CD, immunodeficiencies, and allergic diseases. While early identification of coexisting conditions can guide comprehensive management strategies, further studies are needed to clarify these associations (5, 9, 11).

This study aimed to characterize the immunologic and allergic profiles of children with CD, with particular attention to immunoglobulin levels, allergic sensitization, and immunodeficiencies beyond sIgAD.

Materials and methods

Study design and population

This prospective cohort study was conducted at the pediatric gastroenterology clinic of Van Training and Research Hospital between August 21, 2022, and February 21, 2023. Children with biopsy-confirmed CD, diagnosed according to the Marsh-Oberhuber classification criteria, were enrolled.

Inclusion criteria were as follows: (a) Children aged 2–18 years. (b) Biopsy-confirmed CD diagnosis. (c) Informed consent obtained from parents/guardians.

Exclusion criteria were as follows: (a) Patients undergoing immunosuppressive therapy. (b) Patients with incomplete clinical or laboratory data. (c) Presence of other chronic diseases affecting immune function (e.g., primary immunodeficiencies). (d) Inability to complete study procedures.

Clinical and laboratory evaluation

Patients were referred to the pediatric allergy and immunology clinic for a comprehensive evaluation as part of the study protocol. Serum immunoglobulin levels (IgA, IgM, IgG, IgE) were measured using turbidimetric methods, with age-specific reference ranges applied. For patients with low immunoglobulin levels, a second measurement was performed at least one month later to confirm the diagnosis before classification. Patients with persistently low or abnormal immunoglobulin levels underwent further immunologic evaluation, including lymphocyte subset analysis (CD3+, CD4+, CD8+, CD19+, and CD16+/56+) (12). Vaccine antibody responses (anti-HBs and anti-rubella IgG) were assessed to evaluate immune function.

Patients were evaluated for gastrointestinal and allergic symptoms, including dysphagia and food impaction. However, routine endoscopic screening for eosinophilic esophagitis (EoE) was not performed.

Allergy testing included skin prick tests (SPTs) for common aeroallergens (e.g., pollen, house dust mites, grass pollens, molds, animal dander) and food allergens (e.g., milk, eggs, wheat). SPTs were performed using standardized allergen extracts, and a wheal diameter ≥3 mm greater than that of the negative control was considered positive. Respiratory function testing was performed for patients with respiratory symptoms.

Statistical analysis

Data were analyzed using SPSS for Windows, version 22.0. Continuous variables were expressed as medians with interquartile ranges (IQR), and categorical variables as counts and percentages. The normality of continuous variables was assessed using the Shapiro–Wilk test. Based on this assessment, appropriate statistical methods were applied: normally distributed data were analyzed using the Student's *t*-test, while non-normally distributed data were analyzed using the Mann–Whitney *U*-test. A p-value < 0.05 was considered statistically significant.

The study was approved by the Institutional Review Board of Van Training and Research Hospital (decision number: 2023/13–06), and written informed consent was obtained from all participants' parents.

Results

Demographic and clinical characteristics

The study included 76 children diagnosed with CD [52 females (68.4%), 24 males (31.6%)], with a median age of 11 years (IQR 7.2–14.3) and a median age at diagnosis of 5.8 years (IQR 3.8–9.8). Parental consanguinity was present in 24 patients (31.6%), and 13 patients (17.1%) reported family history of atopy. During the study, 27 patients (35.5%) had negative TGA-IgA results, indicating that these patients had been adhering to a gluten-free diet (GFD), leading to serological normalization. In 28 patients (36.8%), TGA-IgA was positive but less than 10 times the upper limit of normal (ULN). In 19 patients (25%), TGA-IgA was greater than 10 times the ULN (≥200 RU/ml). Tissue transglutaminase IgA levels were missing in two patients.

None of the patients had symptoms suggestive of EoE, such as dysphagia or food impaction. Therefore, no additional endoscopic evaluation for EoE was performed. However, asymptomatic cases of EoE may have gone undetected.

Allergic manifestations

Allergic diseases were prevalent among the patients. Allergic rhinitis was diagnosed in 15.8% of the cohort, while allergic conjunctivitis was observed in 13.2%. Food allergy or a history of food allergy was present in 5.3% of the patients, and asthma and eczema were diagnosed in 3.9% of the patients each. These findings are summarized in Table 1. Of the four patients with food allergy, one was allergic to milk, eggs, walnuts, and sesame; another had a history of egg and lamb allergy; a third had a history of milk and egg allergy; and the last patient had a history of peanut allergy.

Immunological findings

None of the patients had neutropenia or lymphopenia. Normal immunoglobulin levels and antibody responses were observed in 69.7% of the patients, while immunological abnormalities were identified in 30.3%. The most common abnormality was partial IgM deficiency, followed by unclassified hypogammaglobulinemia, sIgA deficiency, and a preliminary diagnosis of transient hypogammaglobulinemia of infancy. The latter was diagnosed in two patients (aged 2 and 4 years) based on low IgG levels, normal vaccine responses, absence of growth failure, and no evidence of T-cell defects, according to the clinical criteria of the European Society for Immunodeficiencies (ESID) Registry (13). None of the patients had a history of frequent infections. Elevated total IgE levels were observed in 13.2% of the patients.

Further details on the distribution of immunological abnormalities are summarized in Figure 1.

The four patients with unclassified hypogammaglobulinemia underwent immunologic evaluation with simultaneous measurement of TGA-IgA levels at a median of 5.6 years after CD diagnosis. Two of these patients had negative TGA-IgA levels and were adherent to a GFD, while the other two had persistently elevated TGA-IgA levels due to nonadherence. Similarly, among patients with partial IgM deficiency, three had elevated TGA-IgA levels due to nonadherence to a GFD.

TABLE 1 Prevalence of allergic diseases accompanying celiac disease.

Allergic disease	n (%)
Allergic rhinitis	12 (15.8%)
Allergic conjunctivitis	10 (13.2%)
Food allergy	4 (5.3%)
Asthma	3 (3.9%)
Eczema	3 (3.9%)

Discussion

Our study highlights the association between CD, allergic diseases, and immunologic abnormalities in children. We identified allergic diseases such as allergic rhinitis, allergic conjunctivitis, food allergy, asthma, along with immunologic abnormalities including partial IgM deficiency, unclassified hypogammaglobulinemia, sIgAD, and a preliminary diagnosis of transient hypogammaglobulinemia of infancy. Importantly, these immunologic abnormalities extend beyond the commonly recognized sIgAD associated with CD, suggesting a broader spectrum of immune dysregulation may coexist with CD and contribute to immune dysfunction.

The link between CD and allergic diseases has been increasingly recognized, with studies suggesting that children with allergic rhinitis, allergic conjunctivitis, asthma, and atopic eczema have a higher risk of developing CD compared to the general population. One study demonstrated adjusted incidence rate ratios of 1.39 for allergic rhinitis/conjunctivitis, 1.44 for atopic eczema, and 1.41 for asthma in adults, highlighting the importance of considering CD screening in patients presenting with allergic symptoms (14). Our findings are consistent with previous studies and further support the clinical association between CD and allergic diseases. In our cohort, 22.4% of patients exhibited aeroallergen sensitivity, 15.8% had allergic rhinitis, 13.2% had allergic conjunctivitis, 3.9% had asthma, and 3.9% had eczema. Additionally, elevated IgE levels were observed in 13.2% of our patients, particularly among those with allergic conditions such as eczema and asthma, supporting the hypothesis of immune dysregulation in CD. A study involving 2,297 individuals found a higher prevalence of IgE sensitization to specific allergens such as wheat, house dust mites, and food allergens in patients with CD (9).

IgE-mediated food hypersensitivity is relatively common among children with CD. One study reported that 50% of children with CD had a positive SPT for at least one food allergen, with peanuts being the most commonly identified sensitization (8). In our cohort, food allergy was documented in 5.3% of patients, with allergen profiles indicating sensitivity to milk, egg, nuts, sesame, and meat (lamb).

The relationship between CD and severe food allergy, defined as high IgE levels combined with a history of severe allergic reactions, has been investigated. One study found that children with severe food allergy had a higher prevalence of CD compared to those with mild allergy or the general population, particularly in the presence of elevated IgE levels (15). Although severe food allergy was not identified in our study, the elevated IgE levels in patients with allergic diseases underscores the complex interplay between CD and allergic sensitization. These findings highlight the importance of screening for CD in children with allergic profiles, even in the absence of severe food allergies. Similarly, screening for allergies in children diagnosed with CD is essential to ensure comprehensive management and address any coexisting allergic conditions.

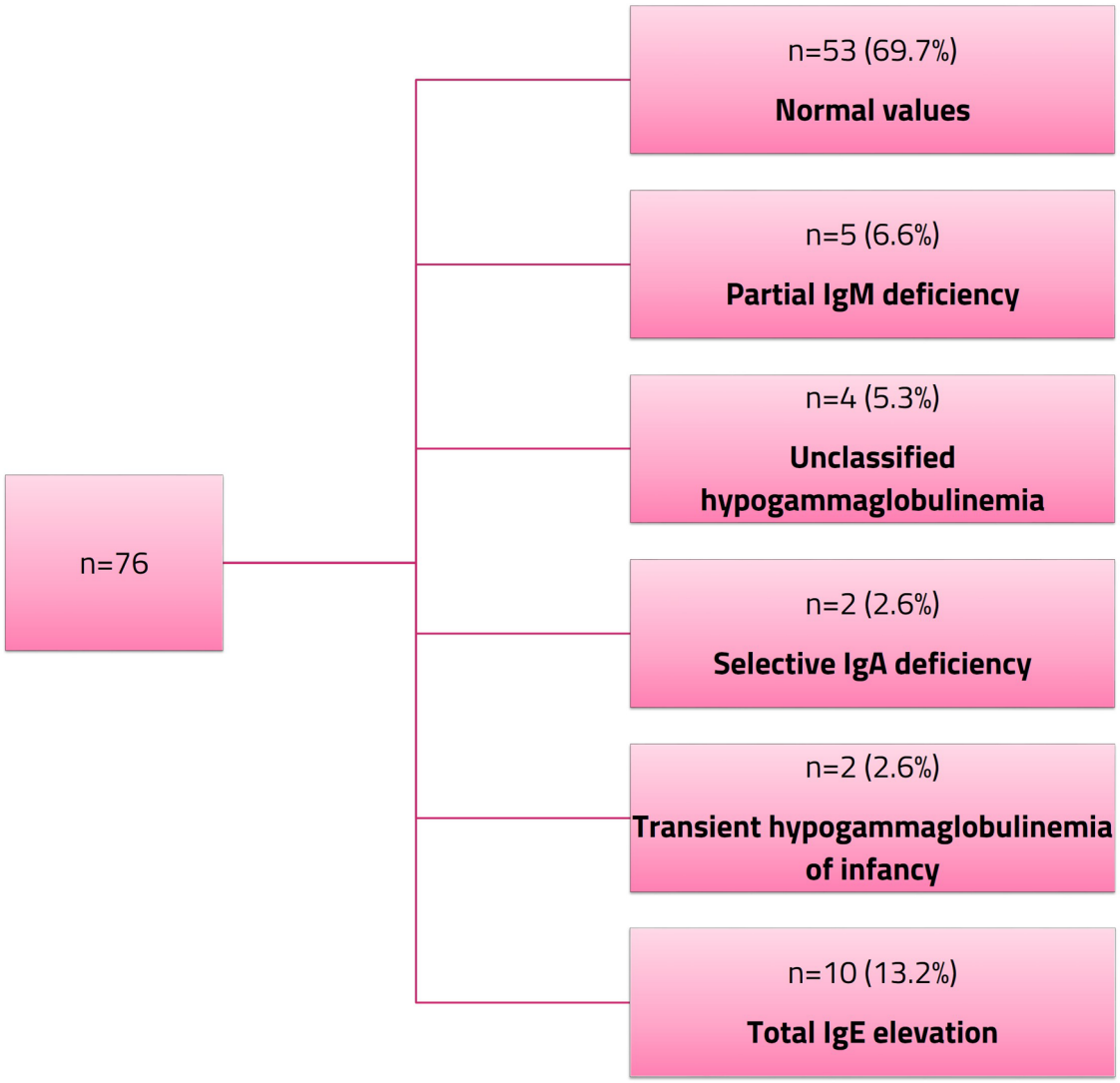

FIGURE 1
Immunological abnormalities in pediatric celiac disease.

Increased intestinal permeability in CD, which may increase antigen exposure and promote subsequent allergic sensitization, has been proposed as a potential mechanism underlying the overlap between celiac disease and allergic diseases (9, 15). Additionally, mast cells have been implicated in CD pathogenesis, suggesting another potential mechanism that warrants further investigation (16). Although our study did not directly evaluate these mechanisms, future research is needed to better understand the immunologic interplay between CD and allergic diseases.

It is important to note that immunodeficiencies such as CVID, sIgAD, and IgM deficiencies can present with gastrointestinal symptoms that mimic those of CD, thereby complicating its diagnosis. When coexisting with CD, these immunodeficiencies may lead to false-negative serological results due to insufficient immunoglobulin production (5). This underscores the need for pediatric gastroenterologists to extend their immunological assessments beyond IgA levels, particularly in patients with refractory symptoms despite adherence to a GFD.

Adherence to a GFD is crucial for intestinal mucosal healing, which facilitates the normalization of immunoglobulin levels by improving nutrient absorption and supporting immune function (17, 18). However, persistent immunoglobulin abnormalities despite strict GFD adherence may indicate the presence of primary immunodeficiencies, such as selective IgM deficiency (sIgMD), which require ongoing monitoring and treatment (19).

In our study, partial IgM deficiency and unclassified hypogammaglobulinemia were identified in 11.8% of patients, suggesting a potential role in immune dysregulation in CD. Notably, these abnormalities were observed in both

GFD-adherent and non-adherent patients, suggesting that immune dysfunction in CD may not be solely attributed to gluten exposure or intestinal inflammation but may also involve an underlying immunologic component. Non-adherent patients with persistently elevated TGA-IgA levels may develop secondary hypogammaglobulinemia due to ongoing intestinal inflammation. However, the persistence of immunoglobulin deficiencies despite strict dietary adherence suggests an underlying primary immunodeficiency, warranting further investigation. Regular monitoring of dietary adherence is essential in patients with CD, particularly those with coexisting immunologic abnormalities, as continued gluten exposure may exacerbate both gastrointestinal symptoms and immune dysfunction.

Even with strict adherence to a GFD, some patients with CD may continue to experience gastrointestinal symptoms due to coexisting food allergies. For instance, a case report described a 13.5-year-old girl with persistent symptoms despite strict GFD adherence who was diagnosed with a non-IgE-mediated soy allergy that resolved following soy elimination (20). This case highlights the need to consider additional food allergies in children with CD who have refractory symptoms. In our cohort, 5.3% of patients had documented food allergies, emphasizing the necessity of comprehensive allergen screening and management to optimize outcomes.

This study had several strengths that enhance the validity and reliability of our findings. First, its prospective design enabled systematic and standardized data collection. Second, the inclusion of only biopsy-confirmed CD cases ensured diagnostic accuracy. Third, the comprehensive immunological evaluation, including the assessment of all immunoglobulin classes and vaccine responses, provides novel insights beyond the typical focus on IgA levels. Additionally, the use of both clinical assessments and objective testing for allergic conditions strengthens the reliability of our findings.

Despite some limitations, including being conducted at a single center with a relatively small sample size, our results may have limited generalizability to the broader pediatric CD population. Moreover, the absence of a control group restricted our ability to compare the prevalence of immunologic and allergic abnormalities with the general population. Additionally, due to the short study duration, we were unable to reassess immunoglobulin levels after TGA-IgA normalization in some patients, leaving uncertainty about whether these abnormalities resolve with strict dietary adherence.

In conclusion, our findings suggested that CD may be part of a broader spectrum of immune dysregulation, encompassing allergic and immunologic components. The overlap between CD, allergic diseases, and immunologic abnormalities highlighted the importance of comprehensive immunological and allergic evaluations in children with CD, ensuring early detection and management to optimize care and improve outcomes.

Our study underscored the need for an integrated, multidisciplinary approach to managing children with CD, addressing the complex interplay of immune dysregulation and allergic manifestations associated with this condition.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Van Training and Research Hospital (2023/13-06). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. KB: Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

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Markers of enterocyte damage in celiac disease in children: is there an association with the clinical manifestations of the disease?

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Actuality: The state of the intestinal barrier has crucial importance in the pathogenesis of celiac disease (CD). Fecal zonulin (FZ) and intestinal fatty acid binding protein (i-FABP) are important components in maintaining physiological processes in the intestine and potential biomarkers of enterocyte damage.
Aim of study: To evaluate FZ and i-FABP levels as markers of small intestine injury in children with CD, depending on the clinical forms and histomorphological changes in the small intestinal mucosa.
Materials and methods: In 2021–2023 yy, a single-center observational study was conducted among children with newly diagnosed CD.The level of FZ in stool and I-FABP in serum were determined using the Immundiagnostik ELISA kits (Germany).
Results: Study included 75 patients,control group was 37 healthy children. The intestinal form of the CD was established in 51 (68.0%) patients,the remaining 24 (32.0%) children have CD with extraintestinal manifestations. Among children with classical CD, the mean values of FZ were 157.9 $\pm$ 29.8 ng/ml ($p < 0.02$ with control), in second group the mean values of FZ were 136.7 $\pm$ 17.0 ng/ml, ($p < 0.05$ with the control), and a statistically significant difference between the groups was $p < 0.02$. The i-FABP values in the first group were 2476.9 $\pm$ 297.4 pg/ml ($p < 0.05$ with control),and in the second –2061.47 $\pm$ 291.5 pg/ml. In the group of children with intestinal manifestations of CD, a weak positive correlation relationship was found between FZ and stool frequency ($r = 0.35$). In the second group: weak inverse correlations were between FZ and weight, and height ($r = -0.37$ and $r = -0.36$ respectively). I-FABP values in the first group moderately correlated with stool frequency ($r = 0.53$). In the group with extraintestinal manifestations, a moderate negative relationship was found between the i-FABP2 level and BMI ($r = -0.53$) and a moderate positive relationship between the i-FABP level and antibodies to tissue transglutaminase IgA ($r = 0.58$) and a weak positive correlation with histological assessment according to Marsh criteria ($r = 0.34$).
Conclusions: Our study demonstrated a relationship between the clinical manifestations of CD and the levels of FZ and i-FABP. The increase in the values also can serve as marker of increased permeability and damage of the intestinal barrier, which will open up new possibilities for understanding the processes of restoration of the small intestinal mucosa.

KEYWORDS

celiac disease, children, fecal zonulin, intestinal fatty-acid-binding protein, enterocyte damage

1 Introduction

Celiac disease (CD) is a chronic enteropathy caused by an immune-mediated reaction to gluten that occurs in genetically predisposed people and can manifest itself at any stage of life, from early childhood to old age (1). The prevalence of CD in the world is estimated at 1.4% according to serology and 0.7% according to biopsy data, mainly among the Caucasian population (2, 3).

Intestinal villous atrophy in CD leads to malabsorption and improper digestion of nutrients, resulting in symptoms such as diarrhea, abdominal pain, weight loss, and steatorrhea. The intestinal form of CD is most common in the pediatric population and in children under 3 years of age when gluten-containing foods are introduced into the diet (4), while older children and adults are more likely to have extraintestinal signs (4, 5).

Intestinal permeability (IP) plays a decisive role in the pathogenesis of CD. The mucous membrane of the gastrointestinal tract acts as a highly specialized barrier separating the internal environment from the external, which is necessary to maintain the homeostasis of the body and prevent the entry of harmful substances and microorganisms into the circulatory system (6). Zonulin, a human protein weighing 47 kDa, plays an important role in modulating the permeability of tight junctions of the small intestine, which is fundamental for maintaining physiological processes in the intestine (7) and has become a potential non-invasive biomarker for the study of intestinal permeability. Tight junctions in CD are disrupted, allowing undigested gluten peptides to pass through the epithelial barrier, triggering an immune response involving both the adaptive and innate immune systems (8). Study by Fasano et al. (9) showed that zonulin expression in intestinal tissues increased during the acute phase of CD, a clinical condition, in which tight junctions opened and permeability increased. In most studies, zonulin is determined in two biological substances (blood and feces) (10–13). It is assumed that determination of zonulin levels in feces may be a more sensitive and specific method for assessing intestinal permeability, since it reflects protein secretion directly from the site of epithelial damage (14, 15). There are only a few studies in the literature on the determination of fecal zonulin in children with CD; we found only one study by Gallego et al, who found that the concentration of zonulin in feces was higher in children with active CD compared to healthy people and those who followed a gluten-free diet (GFD) (16).

Serum cytosolic intestinal Fatty-Acid-Binding Protein (i-FABP), which is a small 5 kDa protein that accounts for 1%–2% of the total cytosolic protein in enterocytes, is also a non-invasive marker of enterocyte injury (17). The tissue specificity of i-FABP, as well as its ability to be mea-sured in readily available noninvasive samples (e.g., urine), make it an attractive biomarker of upper GI tissue injury/damage. Previous studies have shown that patients with IBD and CD have significantly higher circulating serum i-FABP concentrations compared to healthy individuals, but the evidence has not always been specifically (18–28).

In several studies, it has been noted that the level of i-FABP in blood plasma in patients with CD is higher than in healthy people at diagnosis compared to healthy people, which indicates damage to the small intestinal mucosa (20, 21, 24, 26, 29–32). In CD in adults, it has been found that i-FABP are involved as mediators of inflammatory processes in the tissues where they are represented, and changes in the enterocytes of the epithelium disrupt the absorption of nutrients, which can lead to changes in intracellular lipid transport, protein expression (33).

Thus, a review of the literature on the concentration of zonulin and i-FABP demonstrated the limitations of studies on these indicators in children with CD depending on the clinical forms and histomorphological changes in the small intestinal mucosa.

The aim of our study was to evaluate fecal zonulin and i-FABP indicators as markers of small intestine injury in children with CD, depending on the clinical forms and histomorphological changes in the small intestinal mucosa for future assessment of their potential diagnostic and prognostic value.

2 Methods

2.1 Study subjects and grouping

In 2021–2023 yy., at the Gastroenterology Department of Republican Specialized Scientific-Practical Medical Center of Pediatrics (RSSPMCP), Tashkent, Uzbekistan a single-center prospective study was conducted.

Inclusion Criteria: children newly diagnosed CD aged 1 to 16 years and healthy children of the same age.

Exclusion Criteria: previously diagnosed with CD; exclusion of gluten from the diet at the time of selection for the study; refusal to sign informed consent to participate in the study.

The study did not include patients with comorbid conditions such as Down syndrome, Hoshimoto's thyroiditis.

Controls were recruited from the community and included healthy volunteers with no known history of gastrointestinal diseases or symptoms per Rome IV and eating gluten without restriction.

Limitations of the study: a small group of patients and a lack of studies in dynamics on the background of a gluten-free diet.

2.2 General clinical data collection

General clinical examination of patients included anamnesis, objective examination, instrumental and laboratory research methods. Objective examination was conducted according to the standard scheme. At the same time, attention was paid to the general condition, the presence of specific complaints, the time of onset of symptoms of the disease, the state of internal organs and systems, changes in the nature of the stool were taken into account. The assessment of the physical development of children was carried out according to reference tables of anthropometric indicators proposed by experts of the World Health Organization, using the WHO Anthro, WHO AnthroPlus programs (34).

2.3 Laboratory analysis

2.3.1 Confirmation of diagnosis

To confirm the diagnosis of CD, 2020 ESPGHAN criteria were used: the first stage was the determination of antibodies to tissue transglutaminase IgA and total IgA, IgG, IgM [Orgentec Diagnostika GmbH Enzyme-Linked Immunosorbent Assay (ELISA) kit for quantitative determination in human serum, Cat. No. 416-5400A]. If the values of antibodies to tissue transglutaminase IgA increased above 100 U/ml, the patient moved on to the next stage, at which, due to the absence of endomysial antibodies in the Republic of Uzbekistan, all serologically positive patients underwent to upper gastrointestinal endoscopy and duodenal biopsy (by Pentax EG2930 K endoscope after overnight fasting). With parental consent, 51 patients underwent biopsy of the post-bulbar portion of the duodenum (4 biopsies). The biopsy samples were included in neutral buffered formalin and processed according to standard procedures, in order to be evaluated by two experienced pathologists who graded the histologic findings according to the modified Marsh criteria (35).

According to indications, examination was performed for the presence of specific heterodimers DQ2 and DQ8 ($n = 24$).

2.3.2 Fecal zonulin detection methods

To assess the function of tight junctions of the small intestine, the level of fecal zonulin was determined using the IMMUNDIAGNOSTIK enzyme-linked immunosorbent assay kit (Germany, Cat. No. K 5600). The fecal extract in frozen form was stored at −20°C. The analysis is based on the competitive ELISA method, the study was carried out in duplicates with the construction of an analytical curve.

2.3.3 Intestinal fatty acid-binding protein detection methods

To assess the presence of enterocyte damage, the level of intestinal fatty acid-binding protein in blood serum or plasma was determined using the IMMUNDIAGNOSTIK ELISA kit (Germany, Cat. No. K 6809).

2.4 Ethical statement

Approved by the Ethics Council of the Republican Specialized Scientific and Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan IP-2021-1223. Informed written consent was acquired from their parents or guardians and the research was conducted in compliance with the World Medical Association Declaration of Helsinki.

2.5 Statistical analysis

The sample size was not calculated preliminarily, a continuous study of children who came to our center with the first established CD was carried out. Studies were carried out with the written consent of their parents.

Missing data were handled using the Complete Case Analysis method, in which rows/columns containing gaps were excluded from the data set. Statistical analysis was performed using GraphPad Prism (version 9.3.1, 2021). Using statistical functions with calculation for quantitative values of the arithmetic mean (M), standard deviation (SD), median (Me), quartiles (Q1; Q3), Student's criterion (t), Mann–Whitney criterion. The normality of the distribution of quantitative variables was checked using the Kolmogorov–Smirnov method. The following indicators had a normal distribution in a group 1: weight, hemoglobin, total protein, i-FABP; in group 2: age, weight, height, age of introduction of gluten-containing products, stool frequency, age of first symptoms, tTG-IgA, hemoglobin, total protein, i-FABP.

For measuring the strength and direction of the relationship between two variables Pearson's correlation coefficient was used.

Categorical variables were expressed as absolute and relative values. 95% CI for the proportion was calculated using the Wald normal approximation method.

The differences were considered statistically significant at $p < 0.05$, the calculation was made by the two-sided p-value.

3 Results

3.1 Demographic and clinical characteristics

Study was conducted in 75 children. Girls were more prevalent than boys, when distributing by gender—58.6% (44). The median age was 3 years 3 months [1; 15.5 years]. Controls were 37 children from 1 to 16 years old, whose average age was 4.5 ± 1.8 years.

Intestinal or classical form of the disease was in 51 (68.0%) patients (group 1), the remaining 24 (32.0%) children were diagnosed with CD with extraintestinal manifestations (group 2). Girls prevailed in both groups. The average age between the groups did not have a statistically significant difference, however, in the group of patients with extraintestinal manifestations, there was a later introduction of gluten-containing products into the diet 12.7 ± 3.7 and 7.5 ± 5.1 months, respectively ($p < 0.001$). The time of appearance of the first complaints in both groups coincided, on average, 2.5 years, however, due to the non-specificity of symptoms and the complexity of diagnosis, the age of diagnosis of CD with extraintestinal symptoms was several times higher 65.6 ± 48.3 and 38.2 ± 28.6 months, respectively ($p < 0.005$).

The leading clinical symptoms in the group of patients with typical manifestations were abdominal distention (48–94.1%), abdominal pain (24–47.0%), vomiting (25–49.0%), diarrhea (51–100.0%) with a stool frequency of 4.5 ± 1.8 times, lag in weight (30–58.8%) and height (38–74.5%) of moderate and severe degree. Of the extraintestinal symptoms in this group, a quarter had pain in the bones and joints, caries, and every fifth person had headaches (Table 1).

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TABLE 1 Comparative clinical and laboratory characteristics of patients with CD.

Characteristic	CD with intestinal manifestations (n = 51)	CD with extraintestinal manifestations (n = 24)	Control group (n = 37)	p-value
Age, Me (Q1–Q3), months	40 (28;79)	50 (32;100)	72 (42;102)	*$p > 0.05$ **$p < 0.001$ ***$p > 0.05$
Number of boys/girls abs. (%)	20/31 (39,2/60,8)	11/13 (45,8/54,2)	30/7 (81,1/18,9)	*$p > 0.05$ **$p < 0.01$ ***$p < 0.001$
Age of introduction of gluten-containing products, Me (Q1–Q3), months	6,5 (6;10)	10 (8:14)	8 (7;10)	*$p < 0.001$ **$p > 0.05$ ***$p > 0.05$
Age of appearance of the first signs, Me (Q1–Q3), months	24 (14;36)	24 (14,5;42)	–	*$p > 0.05$
Age of diagnosis, Me (Q1–Q3), months	36 (26;77)	45 (41,5;94,5)	–	*$p < 0.005$
Gastrointestinal symptoms				
Abdominal distention	48 (94,1%)	10 (41,6%)	–	*$p < 0.001$
Abdominal pain	24 (47,0%)	8 (33,3%)	–	*$p > 0.05$
Stool frequency, times	4 (3;5)	1 (1;2)	1 (1;2)	*$p < 0.001$ **$p < 0.001$ ***$p > 0.05$
Constipation	–	6 (25,0%)	–	–
Vomiting	25 (49,0%)	–	–	–
Extraintestinal symptoms				
Recurrent stomatitis	8 (15,6%)	10 (41,6%)	–	*$p < 0.02$
Bone pain	13 (25,5%)	11 (45,8%)	–	*$p < 0.02$
Caries	13 (25,5%)	10 (41,6%)	–	*$p < 0.02$
Headaches	10 (19,6%)	9 (37,5%)	–	*$p > 0.05$
Anemia	9/17,6%	12/50,0%	–	*$p < 0.01$
Hair loss	–	6/25,0%	–	–
Anthropometric indicators				
Height (z-score)	−2.57 (−3.28; −1.82)	−1.605 (−2.73; −1.15)	0,31 (0,11;0,52)	*$p < 0.02$ **$p < 0.001$ ***$p < 0.001$
Weight (z-score)	−2.125 (−3.05; −1.58)	−1.85 (−3.13; −0.645)	0,54 (0,24;0,83)	*$p < 0.02$ **$p < 0.001$ ***$p < 0.001$
BMI (z-score)	−0.92 (−2.02; 0.19)	−0.985 (−1.94; 0.27)	0,49 (0,3;1,0)	*$p > 0.05$ **$p < 0.001$ ***$p < 0.001$
Laboratory indicators				
Hemoglobin, g/L	105 (87;115)	112.5 (97;122)	118.6 (115;125)	*$p > 0.05$ **$p < 0.001$ ***$p > 0.05$
Total protein, g/L	56 (49;63)	62 (57;65)	72 (68; 76)	*$p > 0.05$ **$p < 0.001$ ***$p < 0.001$
Leukocytes 10^9	8.05 (6.37;11.22)	8.075 (6.525; 11.215)	7.0 (4.35;10.87)	*$p > 0.05$ **$p > 0.05$ ***$p > 0.05$
tTG-IgA, Me (Q1–Q3), (U/ml)	174 (118;400)	166.9 (110;370,9)	5.2 (4.3;8.7)	*$p > 0.05$ **$p < 0.001$ ***$p < 0.001$
tTG-IgG, Me (Q1–Q3), (U/ml)	53 (11; 126.2)	23.3 (5.57; 93.8)	3.8 (2.6;4.8)	*$p < 0.02$ **$p < 0.001$ ***$p < 0.001$
Histological picture according to Marsh	n = 40	n = 11		
Marsh I infiltrative	0	0	–	*$p > 0.05$
Marsh II Hyperplastic	2/5,0%	7/63,6%	–	*$p < 0.001$
Marsh III Destructive:	38/95,0%	4/36,4%	–	*$p < 0.002$
Marsh IIIa	12/31,5%	3/75%	–	*$p < 0.02$
Marsh IIIb	20/52.6%	1/25%	–	*$p > 0.05$
Marsh IIIc	6/15,9%	–	–	–

(*Continued*)

TABLE 1 Continued

Characteristic	CD with intestinal manifestations ($n = 51$)	CD with extraintestinal manifestations ($n = 24$)	Control group ($n = 37$)	p-value
HLA typing	$n = 11$	$n = 13$		
HLA-DQ2.5	7/63,6%	5/38,4%	–	*$p > 0.05$
HLA-DQ2.2	2/18,2%	5/38,4%	–	*$p > 0.05$
HLA-DQ7.5	2/18,2%	3/23,2%	–	*$p > 0.05$

*p-validity between groups of patients with CD with intestinal manifestations and CD with extraintestinal manifestations.
**p-validity between groups of patients with CD with intestinal manifestations and control group.
***p-validity between groups of patients with CD with extraintestinal manifestations and control group. Counts (%), medians (Me, interquartile range) are presented appropriate.
CD, celiac disease; Me, median; tTG-IgA, tissue transglutaminase IgA; tTG-IgG, tissue transglutaminase IgG; BMI, body mass index; HLA, human leukocyte antigen system.

Whereas children from the group 2 did not have any significant complaints from the gastrointestinal tract. These patients were referred to a gastroenterologist mainly to assess the condition associated with low height (12–50.0%) and/or weight delay (13–54.2%), as well as frequent stomatitis (10–41.6%), caries (10–41.6%), hair loss (6–25.0%), refractory anemia (12–50,0%).

Analysis of anthropometric data by (z-score) showed that, on average, growth deficiency in the group 1 was −2.57 (−3.28; −1.82) and −1.605 (−2.73; −1.15), respectively, which was significantly important compared to patients with extraintestinal manifestations of CD ($p < 0.02$). There was also a significant difference between the groups in terms of weight deficit, which was −2.125 (−3.05; −1.58) and −1.85 (−3.13; −0.645), respectively ($p < 0.02$). There was no statistically significant difference in BMI indicators (Table 1).

An increased level of tTG-IgA (>10 U/ml) was found in 48 (94.1%) children with classical CD, the mean value was 230 ± 147.05 U/L. In 3 children, the level of IgA was below the age-related reference range. In the group 2, the mean value of tTG-IgA was 209.1 ± 131.5 U/ml, selective IgA deficiency was also present in 3 patient.

A statistically significant difference was observed between the groups in terms of the level of tTG-IgG, the mean value in the group 1 was 96.2 ± 20.2 U/L, in the group 2 it was 1.8 times less —53.7 ± 19.8 U/ml, $p < 0.02$ (Table 1).

With parental consent, 51 patients underwent biopsy of the post-bulbar portion of the duodenum (4 biopsies). In the assessment of morphological changes, stage I, infiltrative, was absent, stage II (hyperplastic) was observed in 9 (17.6%) children. In 42 (82.3%) children, stage III (destructive) changes in the mucous membrane of the small intestine were noted, which corresponded to the clinical picture of the disease.

For patients with CD with extraintestinal manifestations, hyperplastic changes in the small intestinal mucosa Marsh II were more characteristic compared to the group 1 (63.6% and 5.0%, respectively, $p < 0.001$). Among children with classical CD, the destructive picture according to Marsh IIIb prevailed (20–52.6%), in the group 2—Marsh IIIa in 75%, $p < 0.02$ (Table 1).

12 patients (50.0%) were carriers of HLA-DQ2.5, encoded by the genes DQA1_05 (alpha- chain) and DQB1_02 (beta- chain), 7 (29.1%) were carriers of HLA-DQ2.2, encoded by the genes HLA-DQ2.2 (DQA1 * 02/DQB1 * 02) and 5 (20.8%)—DQ7.5, encoded by the genes (DQA1 * 05, DQB1 * 03: 01). DQ 8 was not detected in any case.

3.2 Fecal zonulin levels depending on the form of celiac disease

The mean value of fecal zonulin in patients with CD was 150.5 ± 35,8 ng/ml, which was 2 times higher than the control value 90,3 ± 15,2 ng/ml ($p < 0.01$) (Figure 1).

If we consider the groups separately, among children with classical CD, fecal zonulin was increased in 41.2% (mean value for the group 157.9 ± 29.8 ng/ml ($p < 0.02$ relative to the control), among patients with extraintestinal symptoms in half of patients (mean value for the group 136.7 ± 17.0 ng/ml).

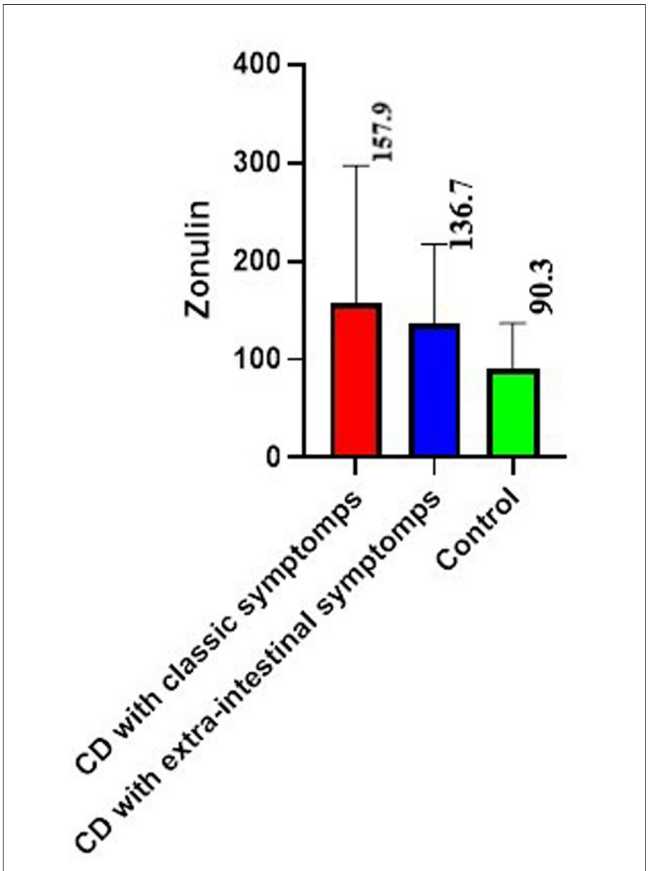

FIGURE 1
Fecal zonulin level in patients with celiac disease (CD), ng/ml (mean with SD).

10.3389/fped.2025.1566149

3.3 i-FABP levels depending on the form of celiac disease

The results of measuring the activity of i-FABP in children with CD demonstrated a significant increase in its values compared to the control. The mean i-FABP value in patients was 2293.5 ± 1075.8 pg/ml, which was almost 1.8 times higher than the control value 1090.4 ± 325.8 pg/ml ($p < 0{,}0001$) (Figure 2).

In the group of patients with classical CD, as well as among children with CD with extraintestinal manifestations, this indicator was increased in half of patients. The mean value in groups was 2476.9 ± 297.4 pg/ml ($p < 0.001$ compared to the control) and 2061.47 ± 291.5 pg/ml ($p < 0.01$ compared to the control, respectively).

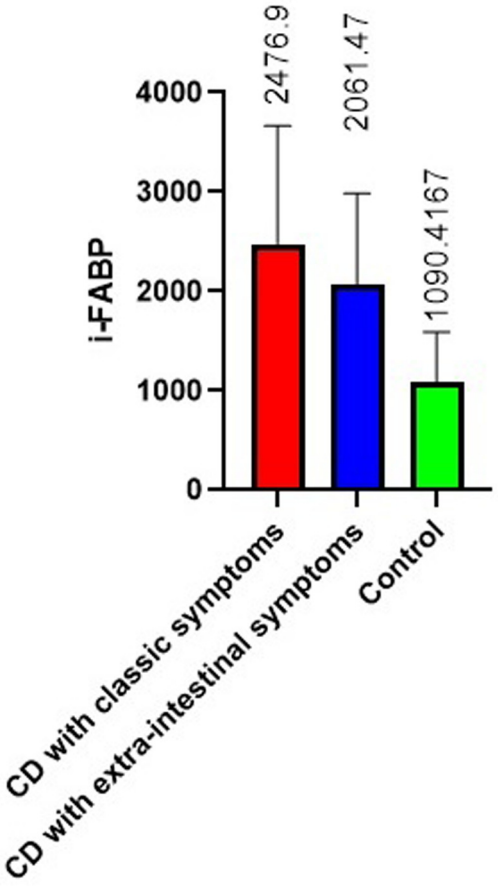

FIGURE 2
i-FABP level in celiac disease, pg/ml (mean with SD).

3.4 Correlation analysis of clinical and laboratory findings and fecal zonulin/I-FABP

Evaluation of the correlations in the group 1 shows a weak positive relationship was found between the level of zonulin and stool frequency ($r = 0.35$, $p < 0.02$), as well as a weak positive relationship with the level of tissue transglutaminase IgA ($r = 0.36$) (Table 2).

More correlation relationships were found in the group 2: a weak inverse correlation relationship between zonulin and weight and height ($r = -0.37$ and $r = -0.36$, $p < 0.02$), a weak positive relationship between zonulin level and antibodies to tissue transglutaminase IgG ($r = 0.35$, $p < 0.02$), a weak negative relationship with protein level ($r = -0.34$, $p < 0.02$), and a weak inverse correlation relationship between zonulin and the time of diagnosis ($r = -0{,}30$, $p < 0.02$).

When assessing the correlation with i-FABP in the group 1, there was a moderate positive relationship with the stool frequency ($r = 0.53$, $p < 0.02$), a weak positive relationship with the number of leukocytes ($r = 0.41$, $p < 0.02$), and a weak negative relationship was also found between the level of i-FABP and anthropometric indicators (weight, height, BMI)—$r = -0.40$, $r = -0.36$, $r = -0.40$ ($p < 0.02$), respectively. There were also weak

TABLE 2 Correlations of clinical and laboratory findings and fecal zonulin/I-FABP in classical CD and CD with extraintestinal manifestations.

Indicator	Fecal zonulin		i-FABP	
	Classic CD	CD with extraintestinal manifestations	Classic CD	CD with extraintestinal manifestations
Stool frequency	0,35	–	0,53	–
tTG-IgA	0,36	–	–	0,58
tTG-IgG	–	0.35	–	–
The number of leukocytes in the blood	0,31	–	0,41	0,52
Weight	–	−0,37	−0,40	−0,34
Height	–	−0,36	−0,36	−0,34
BMI	–	–	−0,40	−0,53
Time of appearance of the first symptoms	–	–	–	−0,37
Time of diagnosis	–	−0,30	−0,28	−0,35
Protein level	–	−0,34	−0,38	–
Histological picture according to Marsh	-	–	–	0,34

CD, celiac disease; I-FABP, intestinal fatty acid binding protein; tTG-IgA, tissue transglutaminase IgA; tTG-IgG, tissue transglutaminase IgG; BMI, body mass index.

negative associations between the level of i-FABP and the time of diagnosis, as well as the level of the protein $r = -0.28$ ($p < 0.02$) and $r = -0.38$ ($p < 0.02$), respectively.

In the group 2, a moderate positive relationship was recorded between the level of i-FABP and antibodies to tissue transglutaminase IgA ($r = 0.58$, $p < 0.02$), as well as with the level of leukocytes ($r = 0.52$, $p < 0.02$), a weak negative relationship between the level of i-FABP and such anthropometric indicators as weight and height: $r = -0.34$ ($p < 0.02$), $r = -0.34$ ($p < 0.02$), respectively, there was a moderate negative relationship with BMI $r = -0.53$ ($p < 0.02$). Weak negative relationships were established between the level of i-FABP and the time of appearance of the first signs, as well as the establishment of the diagnosis: $r = -0.37$ ($p < 0.02$), $r = -0.35$ ($p < 0.02$), respectively. In contrast to the group 1, there was also a weak positive relationship of i-FABP with morphological changes according to Marsh ($r = 0{,}34$, $p < 0.02$).

4 Discussion

This study is the second study to establish fecal zonulin values in the pediatric population up to 16 years of age. The mean fecal zonulin value among healthy children in our study was significantly lower than the data of Gallego et al. (16) and the values presented by Łoniewska et al. (36), who conducted a single study analyzing fecal zonulin in healthy people during the first 2 years of life and observed an increase in fecal levels from birth to 2 years.

iFABP values in plasma of healthy children in our study were 1.3 times higher than the values in Logan et al. study (37), close to the data of Bottasso Arias et al. (28).

In the group of patients with CD, children with the intestinal form of the disease predominated, whose clinical picture was accompanied by severe protein-energy deficiency and pronounced atrophy of the small intestinal mucosa during morphological examination: atrophy of stage 3, according to Marsh, was found in 95% of children, while in patients with CD with extraintestinal manifestations, stage 2, according to Marsh, was detected 1.5 times less often, despite the later diagnosis.

As can be seen from our results, in half of the patients with CD, the level of fecal zonulin was three times higher than the control values. There were differences in fecal zonulin values among children with CD depending on the variant of the disease. Higher numbers were established in children with the classical form of CD. The same pattern is described by Gallego et al. (16). The authors also note a decrease in fecal zonulin levels in children with CD against the background of GFD, and a dependence of its indicators on the duration of the diet is noted.

Statistically significant differences in zonulin values between patients with CD and the control group emphasize the pronounced intestinal permeability in the active phase of the disease, which is consistent with the data of other researchers (16, 33, 38).

The data are worthy of attention (39) that children with CD showed a significant increase in zonulin levels during 18.3 months (range 6–78 months) preceding the development of the disease. The obtained data suggest that fecal zonulin can be used as a biomarker for preclinical screening of CD.

Statistically significant differences in i-FABP values between patients with CD and the control group highlight the presence of severe enterocyte damage.

As it has been noted in several studies, the level of i-FABP in blood plasma in patients with CD is higher than in healthy people at diagnosis, which indicates damage to the mucosa (20, 21, 24, 26, 29–32). Moreover, it has been suggested that patients who meet the four criteria for diagnosing CD (clinical presentation, tTG-IgA levels above 10 U/ml and IgA-EMA positivity, HLA-DQ2 and/or DQ8 genotype), together with increased serum i-FABP levels, may be diagnosed without a biopsy (24). In addition, i-FABP levels may be useful for disease monitoring from the onset of GFD treatment, as they correlate with intestinal injury and repair (24).

Retrospective studies have shown a significant correlation between serum i-FABP levels in pediatric patients with CD and Marsh histological values at the time of diagnosis (21). In our studies, we found only a weak association between i-FABP values and histological mucosal lesions in children with extraintestinal manifestations of CD.

Similar results were obtained by Israeli scientists (40). In the group of patients with CD, there was a higher level of I-FABP upon confirmation of CD compared to the control group (median 641.7 pg/ml vs. 334 pg/ml; $p < 0.05$). I-FABP levels differed significantly between patients whose tTG-IgA level was 3–10 times the upper limit of normal (ULN) compared to patients with values >10 times ULN (median 432.2 pg/ml vs. 796.2 pg/ml; $p < 0.05$). In patients with CD, a significant decrease in the median i-FABP level was observed after 6 months of GFD.

The analysis of correlational relationships in our study demonstrated the most significant relationship between i-FABP indicators and stool frequency in the classic form of the disease, and an inverse relationship with BMI and values of antibodies to tissue transglutaminase in CD with extraintestinal manifestations. Fecal zonulin values had a weak association with antibodies to tissue transglutaminase and stool frequency in the classic form of the disease and an inverse relationship with the weight and height of children with extraintestinal manifestations.

5 Conclusions

Thus, our study demonstrated a relationship between the clinical manifestations of CD and the levels of fecal zonulin and i-FABP in the blood plasma of children with CD. The growth of fecal zonulin and i-FABP demonstrates a certain relationship between the severity of clinical manifestations and the increase in the values of non-invasive markers of small intestinal damage, also they can serve as markers of permeability and damage of intestinal barrier in CD, which will open up new possibilities for understanding the processes of restoration of

the small intestinal mucosa to improve the prognosis (outcome) of the disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Republican Scientific Medical Center of Pediatrics, approval no. IP-2023-153, 23 April 2023. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The studies were conducted in accordance with the local legislation and institutional requirements.

Author contributions

SG: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. ZU: Methodology, Project administration, Supervision, Validation, Writing – review & editing. NA: Formal analysis, Investigation, Visualization, Writing – original draft. KU: Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. AK: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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A comparison of growth and dietary adequacy of children with celiac disease on a gluten-free diet with their healthy-peers at a tertiary care center in Turkey

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Introduction: Celiac disease (CD) is a chronic autoimmune disorder that requires strict adherence to a gluten-free diet (GFD) initiated after diagnosis. This limited diet may lead to nutritional deficiencies. The aim of this study was to evaluate nutritional intake and dietary adequacy of children with CD having good adherence to a GFD compared with their healthy peers and to assess the contribution of commercial gluten-free products on the daily energy and macronutrient intakes.
Methods: This cross-sectional case-control study included children with CD (age range, 2–18 years) and age- and sex-matched healthy controls. Demographic characteristics, anthropometric measurements and food consumption (3-day food record) were recorded. The groups were compared for dietary compositions, dietary adequacy, and anthropometric parameters.
Results: The study compared 51 patients with 54 controls. The patients had significantly lower height-for-age Z-scores and body mass index-for-age Z-scores ($p < 0.05$). The dietary daily energy, protein, fat and fiber intakes were significantly lower in the patients than in the healthy controls ($p < 0.05$). The mean nutrient adequacy ratio (NAR) for protein, thiamine, calcium, magnesium, iron, zinc and fiber was significantly lower in the patients for both sexes ($p < 0.05$ for all) and the mean NAR for vitamin A and folate was lower in the patients in females ($p < 0.05$ for all). The mean nutrient adequacy ratio (MAR) of protein, thiamine, calcium, magnesium, iron, zinc and fiber was lower in the patients than in the controls ($p < 0.05$ for all).
Conclusion: A comprehensive dietary assessment for patients with CD may enhance their adaptation to healthy nutrition and facilitate their optimal growth.

KEYWORDS

celiac disease, gluten-free diet, dietary assessment, nutrient intake, anthropometry

Introduction

Celiac disease (CD) is an immune-mediated enteropathy triggered by gluten ingestion in genetically predisposed individuals (1, 2). The prevalence of celiac disease is estimated at approximately 1% in the general population (3). Damage to the mucosa of the small intestine causes malabsorption resulting in nutritional deficiencies (4). A gluten-free diet (GFD) is the sole treatment available for CD (5). The GFD excludes wheat, barley, rye,

and their derivatives, including starch, flour, bread, and pasta etc. Adherence to a GFD enables healing of small bowel mucosal damage and restores normal absorption of nutrients within 6 months to 1 year (6). This facilitates the amelioration of clinical symptoms, normalization of laboratory and histological findings, and improvement of disease prognosis (7).

The nutritional adequacy of a GFD after the diagnosis of CD and its effects on the anthropometric parameters of patients with CD have become a compelling issue (8, 9). While some studies have reported positive effects of GFD such as facilitating loss of body fat, attaining a fat-free body mass, providing underweight and overweight patients and accelerating linear growth, other studies have reported negative effects on the body composition and anthropometric parameters of children with CD such as weight gain and obesity (8, 10–13). Elimination of gluten for the production of commercially available gluten-free products (GFPs) leads to alterations in the macro- and micronutrient compositions of foods (7). GFPs tend to contain higher amounts of carbohydrates, fats to improve their palatability and lower amounts of protein, fiber, folate, iron, and vitamin B (thiamine, riboflavin, and niacin) (14, 15). Thus, despite being associated with better outcomes, a GFD may cause unbalanced distributions of carbohydrates, fats, and proteins and inadequate intake of micronutrients (16).

It is crucial to prioritize early adaptation to a strict GFD to enhance the overall health of individuals with CD and promote their healthy growth and development. Hence,the purpose of the present study was threefold: (1) to assess the nutritional intake—including both macro- and micronutrients—and identify possible deficiencies in children with CD who demonstrate good adherence to a GFD, in comparison with healthy peers; (2) to examine gender differences in dietary adequacy and nutritional intake; and (3) to evaluate the impact of a GFD on growth parameters and determine the contribution of commercial gluten-free products (GFPs) to total daily energy and macronutrient intake.

Materials and methods

Study design and population

This cross-sectional, case-control study was conducted on children with CD and age- and sex-matched healthy controls in a tertiary hospital in Turkey. Patients were recruited from January 2016 to November 2018 in the Paediatric Gastroenterology Outpatient Clinic. Children aged between 2 and 18 years with a confirmed diagnosis of CD, based on the criteria of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) were included (17). Only patients who had been on a GFD for at least one year and showed good dietary adherence, confirmed by negative tissue transglutaminase antibody (tTg-IgA) levels and regular follow-up with a dietitian, were enrolled. Exclusion criteria were the presence of a chronic illness such as type 1 diabetes mellitus, hypothyroidism, and IgA deficiency that accompanies CD, receiving enteral or parenteral nutrition, or having any diet restriction other than a GFD. An age- and sex-matched healthy control group was formed from children who were examined for dyspepsia and admitted to the Outpatient Clinic of Pediatrics. Inclusion criteria for the control group were not having a chronic illness, not receiving enteral or parenteral nutrition, and not having special diet restrictions.

Assessment of dietary adherence

Tissue transglutaminase IgA (tTg-IgA) antibodies were detected using enzyme- linked immunosorbent assay (ELISA) according to the instructions of the manufacturers (Euroimmun, Zedira, Organtech, Germany). For tTg-IgA, the results were considered as normal for <7, an equivocal range for 7–10 and positive for >10 U/ml.

Tissue transglutaminase IgA antibody level was taken into account in the evaluation of dietary compliance; patients with normal tTg-IgA levels (<10 U/ml) were considered as "good adherence to diet" (17). Patients who stated that they consumed gluten-containing products with variable frequency (occasionally) and/or whose tTg-IgA levels were found to be above normal (≥10 U/ml) were excluded from the study.

Dietary assessment

The participants' dietary assessment was based on a 3-day food record, consisting of two weekdays and one weekend day, completed retrospectively. The dietician explained the children and their families how to fill in the food consumption record. A "Food and Meal Photo Catalog: Measurements and Quantities" was used to determine the quantities and sizes of consumed food and beverages (18). The amounts of the meals' nutrients per portion consumed by each participant were calculated with the help of the "Standardized Food Recipes" book (19). The dietary energy and nutrients were assessed using the "Nutrition Information Systems Package Program" (BeBiS, Ebispro for Windows, Germany; Turkish Version/BebiS 8.2; 2019, İstanbul), a software database that contains food composition tables for all foods (20). BebiS Program is a particular program that has been used for Nutrition and Dietetics for 22 years in Turkey. The program was developed according to the professional standards of academicians and dieticians, ensuring its reliability and validity. It has thousands of food databases based on references to the World Health Organization, Dietary Guidelines for Turkey, and other scientific sources.

Nutrient adequacy analysis

The recommended daily allowance (RDA) values according to age and sex were used for the assessment of energy and nutrient intake. The nutrient adequacy ratio (NAR) was calculated for 11 nutrients (protein, vitamins A, E and C, thiamine, folate, calcium, magnesium, iron, zinc, and fiber) using the dietary reference intake (DRI) recommended percentages with the following formula: NAR (%) = (nutrient intake of an individual/DRI of the

nutrient) × 100 (21). The mean adequacy ratio (MAR, %) was calculated by dividing the sum of each NAR by the number of nutrients with the following formula: MAR (%) = sum of NAR (%) for each nutrient/number of nutrients. For both NAR and MAR a value of 100% is the ideal since it means that the intake is the same as the requirement (22). Daily energy and macronutrient intakes from GFPs in patients with CD were also evaluated using the information on the labels of the GFPs.

Anthropometric measurements

Body weight and height measurements of the patients and controls were performed by the same dietitian. Body weight was measured with the subjects wearing minimal clothing to the nearest 0.1 kg using a digital scale. Length measurement was performed with the subjects without shoes to the nearest 0.1 cm using a stadiometer. The BMI was calculated as body weight (in kg) divided by the square of height (in m^2) and expressed as kg/m^2. Height-for-age Z-score (HAZ), weight-for-age Z-score (WAZ), and BMI-for-age Z-score (BAZ) were calculated according to the standards defined by the World Health Organization (WHO) (23).

Statistical analysis

Data analysis was performed using the IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to report frequencies, percentages, and either means ± standard deviation (SD) or medians (minimum and maximum) for continuous variables, depending on data normality as assessed by the Kolmogorov–Smirnov test. According to the normality test, age, anthropometric measurements and indices, along with energy and MAR values showed normal distribution. Normally distributed variables were analyzed using the independent samples *t*-test, while non-normally distributed variables were analyzed using the Mann–Whitney *U*-test, where appropriate. A *P* value of <0.05 was considered to be statistically significant.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Gazi University, Ankara, Turkey (approval number: 25901600-598; date: 14.12.2015). Informed consent was obtained from the legal guardians of all participating children, and assent was obtained from each subject.

Results

Demographic and clinical characteristics

The study included 51 children with CD and 54 healthy controls. The mean age of 51 celiac patients (34 female, 66.7%) and 54 controls (28 female, 51.9%) was 10.2 ± 3.79 years and 11.0 ± 3.81 years, respectively. The patients and controls did not significantly differ regarding age ($p = 0.89$) and sex ($p = 0.123$). The median age at diagnosis was 8 (1–12.5) years for males and 4.7 (1.5–14) years for females in the patient group. The median duration of GFD was 31.8 (15–83) months in the patient group.

Anthropometric measurements

The mean body weight, BMI, HAZ, and BAZ values significantly differed between the patients and controls ($p < 0.05$ for all; Table 1); the children with CD had significantly lower HAZ and BAZ values (Table 1). The mean body weight, BMI, WAZ, HAZ and BAZ values of the males with CD and the mean BAZ value of the females with CD were significantly lower as compared with their healthy control group (Table 1).

Energy and macronutrient intake

The daily energy and macronutrient intakes in the patients and controls according to sex are presented in Table 2. Accordingly, the mean daily dietary energy, protein, fat and fiber intakes and the percentage of energy obtained from protein were lower in the patients than in the controls for both sexes ($p < 0.05$ for all). The mean daily carbohydrate intakes were lower (only significant for females) but the percentage of energy obtained from carbohydrates was higher (although not significant) in patients with CD than in the controls for both sexes. The mean daily fat intake was significantly lower in the patients than in the controls for both males ($p = 0.006$) and females ($p = 0.001$); however, the percentage of energy obtained from fats was similar in the patients and controls for both sexes. The percentages of total energy obtained from saturated fatty acids, monounsaturated fatty acids (MUFAs), and polyunsaturated fatty acids (PUFAs) did not significantly differ between the patients and controls for both sexes ($p > 0.05$ for all). The mean daily cholesterol intake was significantly lower in patients with CD than in the controls for both sexes ($p < 0.05$ for all).

Micronutrient intake

The median daily micronutrient intakes in patients and controls according to sex are presented in Table 3. Accordingly, the median daily intakes of thiamine and riboflavin were significantly lower in patients with CD compared to controls for both sexes ($p < 0.05$ for all). Among females, the median daily intakes of vitamins A, B6 and C, niacin and folate were also significantly lower in the patient group than in the controls ($p < 0.05$ for all). Furthermore, both male and female patients exhibited significantly lower median intakes of calcium, magnesium, phosphorus, and selenium ($p < 0.05$ for all), whereas potassium, iron, and zinc intakes were significantly lower only among female patients ($p < 0.05$ for all).

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TABLE 1 Age and anthropometric measurements in children with celiac disease and healthy controls according to sex.

Variable	Study groups, mean ± SD			Male, mean ± SD			Female, mean ± SD		
	Celiac patients *n* = 51	Control group *n* = 54	*P*	Celiac patients *n* = 17	Control group *n* = 26	*P*	Celiac patients *n* = 34	Control group *n* = 28	*P*
Age, years	10.2 ± 3.79	11.0 ± 3.81	0.89	11.6 ± 3.30	11.2 ± 3.11	0.62	10.5 ± 4.23	10.8 ± 4.41	0.76
Height, cm	135.9 ± 18.94	141.9 ± 21.64	0.13	140.6 ± 17.71	144.9 ± 19.4	0.46	133.6 ± 19.36	139.2 ± 23.52	0.31
Body weight, kg	33.2 ± 13.21	41.9 ± 18.27	**0.006**	34.3 ± 12.6	44.4 ± 17.87	0.048	32.7 ± 13.85	39.6 ± 18.65	0.109
BMI, kg/m^2	17.1 ± 3.26	19.5 ± 3.47	**<0.001**	16.7 ± 2.88	20.1 ± 3.32	0.002	17.3 ± 3.45	19.0 ± 3.58	0.067
WAZ	−0.33 ± 1.31	0.19 ± 0.91	0.126	−1.05 ± 0.29	0.42 ± 0.91	0.008	−0.15 ± 1.41	−0.04 ± 0.88	0.805
HAZ	−0.89 ± 1.48	−0.15 ± 0.91	**0.002**	−1.02 ± 1.31	−0.09 ± 0.87	0.008	−0.82 ± 1.57	−0.20 ± 0.97	0.072
BAZ	−0.50 ± 1.38	0.65 ± 0.86	**<0.001**	−0.78 ± 1.28	0.98 ± 0.87	<0.001	−0.36 ± 1.42	0.34 ± 0.74	**0.021**

BMI, body mass index; WAZ, weight-for-age Z-score; HAZ, height-for-age Z-score; BAZ, body mass index-for-age Z-score.
Values with $P < 0.05$ are shown in bold.

TABLE 2 Daily energy and macronutrient intakes in children with celiac disease and healthy controls according to sex.

	Male, Mean ± SD			Female, Mean ± SD		
	Celiac patients *n* = 17	Control group *n* = 26	*P*	Celiac patients *n* = 34	Control group *n* = 28	*P*
Total energy, kcal	1,475.9 ± 524.61	1,889.7 ± 461.92	**0.009**	1,356.9 ± 298.98	1,669.9 ± 392.87	**<0.001**
Macronutrients						
Carbohydrate, g	179.3 ± 72.65	208.8 ± 66.96	0.179	161.6 ± 49.67	183.1 ± 51.28	**0.023**
E% carbohydrate	48.8 ± 7.43	45.7 ± 5.80	0.134	47.4 ± 10.11	44.8 ± 5.74	0.318
Protein, g	49.0 ± 18.68	77.0 ± 26.28	**<0.001**	43.1 ± 10.71	67.7 ± 17.51	**<0.001**
Protein, g/kg	1.53 ± 0.62	1.84 ± 0.48	0.074	1.61 ± 0.86	1.99 ± 0.76	0.067
E% Protein	13.7 ± 3.09	16.5 ± 2.93	**0.005**	12.7 ± 3.04	16.6 ± 2.18	**<0.001**
E% fat	37.6 ± 6.16	37.8 ± 5.64	0.905	37.5 ± 7.74	38.7 ± 5.51	0.667
Saturated fatty acids, g	21.7 ± 8.76	27.5 ± 9.08	**0.042**	19.7 ± 6.78	25.7 ± 9.17	**0.002**
E% saturated fatty acids	13.2 ± 2.15	13.3 ± 3.43	0.943	13.1 ± 3.79	13.7 ± 3.22	0.818
MUFAs, g	20.7 ± 7.14	27.1 ± 8.82	**0.015**	19.98 ± 5.09	25.5 ± 7.95	**<0.001**
E% MUFAs	12.8 ± 2.28	13.1 ± 3.47	0.402	13.4 ± 2.80	13.7 ± 2.90	0.586
PUFAs, g	13.5 ± 5.53	16.6 ± 5.69	0.081	13.9 ± 5.25	15.8 ± 4.72	0.110
E% PUFAs	8.7 ± 3.23	7.9 ± 2.06	0.682	9.3 ± 2.68	8.6 ± 2.17	0.133
Cholesterol, mg	234.9 ± 91.50	315.6 ± 131.25	**0.033**	205.3 ± 103.09	293.1 ± 84.51	**0.001**
Fiber, g/1,000 kcal	12.8 ± 5.52	17.7 ± 6.74	**0.017**	10.9 ± 3.36	17.8 ± 6.09	**<0.001**

%E, percentage of total energy; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids.
Values with $P < 0.05$ are shown in bold.

TABLE 3 Daily micronutrient intakes in children with celiac disease and healthy controls according to sex.

Micronutrients	Male, median (IQR)			Female, median (IQR)		
	Celiac patients *n* = 17	Control group *n* = 26	*P*	Celiac patients *n* = 34	Control group *n* = 28	*P*
itamin A, µg	654.8 (957.6)	739.7 (593.7)	0.587	497.1 (339.90)	847.3 (455.9)	**<0.001**
Thiamine, mg	0.58 (0.31)	0.83 (0.34)	**0.002**	0.56 (0.19)	0.86 (0.21)	**<0.001**
Riboflavin, mg	1.13 (0.60)	1.4 (0.73)	**0.005**	0.96 (0.43)	1.39 (0.70)	**<0.001**
Niacin, mg	9.5 (13.82)	12.8 (12.11)	0.419	8.2 (6.75)	12.9 (5.23)	**0.003**
Vitamin E, mg	13.3 (5.28)	15.2 (7.85)	0.853	15.5 (7.23)	13.2 (8.67)	0.115
Vitamin B6, mg	0.90 (0.71)	1.2 (0.55)	0.198	0.84 (0.41)	1.12 (0.34)	**0.002**
Folate, µg	209.0 (99.58)	242.2 (165.98)	0.305	187.2 (75.48)	247.6 (86.30)	**<0.001**
Vitamin B12, µg	3.5 (4.47)	4.9 (3.36)	0.198	3.6 (2.5)	4.97 (3.22)	0.441
Vitamin C, mg	63.7 (76.20)	76.4 (59.83)	0.786	59.7 (37.49)	82.9 (63.88)	**0.002**
Calcium, mg	528.5 (242.34)	717.2 (408.10)	**0.001**	501.1 (183.0)	730.7 (413.57)	**<0.001**
Potassium, mg	1,821.9 (1,312.90)	2,349.0 (836.8)	0.060	1,670.8 (620.8)	2,331.7 (591.2)	**<0.001**
Magnesium, mg	172.1 (87.10)	259.9 (84.2)	**0.001**	161.4 (41.2)	242.3 (74.6)	**<0.001**
Phosphorus, mg	859.6 (400.80)	1,124.5 (491.44)	**0.002**	753.4 (248.48)	1,114.9 (378.78)	**<0.001**
Iron, mg	6.5 (4.51)	9.2 (2.88)	0.069	7.1 (2.66)	9.2 (4.04)	**<0.001**
Zinc, mg	7.3 (5.70)	8.8 (4.21)	0.078	7.1 (2.71)	8.9 (4.0)	**<0.001**
Selenium, µg	1.46 (3.75)	4.8 (5.75)	**0.024**	0.73 (3.95)	3.4 (6.44)	**0.006**

IQR, The interquartile range.
Values with P < 0.05 are shown in bold.

Nutrient adequacy ratio (NAR) and mean adequacy ratio (MAR)

The comparisons of NAR and MAR between the patients and controls according to sex are presented in Table 4. The mean NAR for protein, thiamine, calcium, magnesium, iron, zinc and fiber was significantly lower in the patients for both sexes ($p < 0.05$ for all) and the mean NAR for vitamin A and folate was lower in the patients in females ($p < 0.05$ for all). The MAR of the patients with CD was significantly lower as compared with the controls for both males ($p = 0.004$) and females ($p < 0.001$). Additionally, the MAR values of both patients and controls were lower than the optimal adequacy ratio (a MAR value of 100%) for both sexes.

TABLE 5 Daily total energy and macronutrient intakes from gluten-free products in children with celiac disease according to sex.

Nutrient/ Unit	Children with celiac disease, mean ± SD	
	Male ($n = 17$)	Female ($n = 34$)
Energy, kcal	338.57 ± 215.01	266.89 ± 140.34
Energy, %	21.45 ± 6.38	19.53 ± 8.54
Protein, g	2.29 ± 1.94	1.58 ± 0.79
Protein, %	4.56 ± 2.41	3.77 ± 1.90
Fat, g	2.96 ± 3.33	1.81 ± 1.24
Fat, %	4.35 ± 2.89	3.33 ± 2.57
Carbohydrate, g	74.56 ± 44.55	60.13 ± 32.07
Carbohydrate, %	39.83 ± 8.99	37.20 ± 14.91
Fiber, g	2.74 ± 1.58	2.12 ± 1.22
Fiber, %	21.66 ± 7.70	19.94 ± 10.30

Contribution of gluten-free products (GFPs) to daily intake

Evaluation of daily energy and macronutrient intakes from GFPs in the patients revealed that the GFPs fulfilled an average of 21.45 ± 6.38% of the daily total energy intake of males with CD and an average of 19.53 ± 8.54% daily total energy intake of females with CD (Table 5). The mean percent energy provided by the carbohydrate content of the GFPs was 39.83 ± 8.99% for males with CD and 37.20 ± 14.91% for females with CD.

Discussion

This cross-sectional case-control study is important to evaluate dietary intakes, dietary adequacy, and growth parameters in children with CD as compared with their healthy control peers at our hospital. The study demonstrated that the HAZ and BAZ values and energy and macro- and micronutrient intakes of the patients with CD were lower as compared with their healthy peers. Moreover, the MAR values showed that the diet of both groups was lower than optimal dietary adequacy (MAR < 100%) and the dietary adequacy was poorer in the patients.

In the present study, the mean HAZ and BAZ values of patients with CD were lower when compared with those of healthy controls. The mean BAZ values of females with CD and the mean WAZ, HAZ and BAZ values of males with CD were also significantly lower as compared with their healthy peers. Previous studies evaluating anthropometric parameters of patients with CD on a GFD have reported different outcomes (10, 11, 24). Similar to the results of this study, a study from Sweden found that males with CD had lower body weights (lower z-scores and percentiles) and females with CD had lower height percentiles as compared with controls (1). Another study comparing children with CD and healthy controls demonstrated that patients with CD had lower body weights and BMI z-scores despite their high consumption of calories and fat (25). Although our study had similar anthropometric results to the above-mentioned studies, as compared with their healthy peers, the children with CD were

TABLE 4 Comparisons of the nutrient adequacy ratio (NAR) and mean adequacy ratio (MAR) in patients with celiac disease and healthy controls according to sex.

	Male, mean ± SD			Female, mean ± SD		
	Celiac patients $n = 17$	Control group $n = 26$	P	Celiac patients $n = 34$	Control group $n = 28$	P
NAR, %						
Energy	94.9 ± 32.72	99.4 ± 14.30	0.535	98.7 ± 27.72	109.8 ± 15.96	0.066
Protein	84.7 ± 18.58	99.4 ± 2.26	**<0.001**	89.8 ± 12.84	98.9 ± 5.85	**0.001**
Vitamin A	76.8 ± 23.80	83.1 ± 20.71	0.370	71.9 ± 24.78	94.2 ± 13.94	**<0.001**
Vitamin E	90.0 ± 14.85	89.9 ± 14.24	0.975	93.7 ± 14.82	86.9 ± 19.27	0.126
Thiamine	52.5 ± 16.86	76.6 ± 15.36	**<0.001**	59.4 ± 13.98	86.0 ± 14.85	**<0.001**
Folate	57.4 ± 18.78	66.1 ± 21.43	0.183	53.6 ± 17.85	68.1 ± 15.68	**0.001**
Vitamin C	81.2 ± 22.36	85.1 ± 23.88	0.601	85.0 ± 22.05	93.8 ± 15.62	0.082
Calcium	39.5 ± 15.38	59.5 ± 19.76	**0.001**	37.6 ± 12.92	59.0 ± 21.47	**<0.001**
Magnesium	46.0 ± 16.43	68.7 ± 17.21	**<0.001**	52.1 ± 17.18	77.4 ± 18.68	**<0.001**
Iron	70.1 ± 20.97	86.5 ± 16.61	**0.007**	57.7 ± 22.50	76.7 ± 19.62	**0.001**
Zinc	70.7 ± 23.04	85.1 ± 14.71	**0.016**	76.9 ± 19.31	89.5 ± 16.10	**0.008**
Fiber	42.6 ± 17.62	58.9 ± 18.67	**0.007**	42.5 ± 13.10	67.6 ± 19.33	**<0.001**
MAR, %	64.7 ± 15.51	78.1 ± 12.77	**0.004**	65.5 ± 12.39	81.7 ± 10.91	**<0.001**

NAR, nutrient adequacy ratio; MAR, mean adequacy ratio.
Values with $P < 0.05$ are shown in bold.

observed to have lower intakes of energy, protein, and fat and poorer dietary adequacy, which could be the underlying reason for lower body weight-height percentiles, BMI, and mean HAZ and BAZ values observed in our patients. Different outcomes reported in the literature might be due to differences in the study parameters, such as durations of GFDs during anthropometric evaluations, disease duration, and socioeconomic level. Although having good dietary adherence was one of the inclusion criteria for patients with CD in this study, the patients were unable to achieve a balanced nutrient intake due to GFDs that likely included inappropriate food choices.

The mean daily dietary energy, carbohydrate, protein, fat and fiber intakes were significantly lower in the children with CD than in their healthy control peers. Although not statistically significant, the percentage of energy obtained from carbohydrates was slightly higher in the patients than in the controls; nevertheless, the percentage of energy obtained from carbohydrates was higher than the recommended daily carbohydrate intakes for both groups (21).

The present study revealed that the amount of fat intake was significantly lower in the patients with CD than in the controls for both sexes; however, the percentage of energy obtained from fats was similar for the patients and controls for both sexes and higher than the recommended. Numerous studies have found that the total fat intake of children with CD is significantly higher than healthy controls (1, 25–27). Nowadays, lifestyle changes resulting from economic development and globalization lead children to consume more fast food and unhealthy snacks with high amounts of fat (28). GFPs tend to contain more fat as compared with gluten-containing foods; moreover, carbohydrate restriction in diets of patients with CD may also increase the percentage of energy intake from fat.

The patterns of fatty acid consumption are as important as the total amount of dietary fat (29). In this study, although children with CD had lower intakes of saturated fat, MUFAs and PUFAs for both sexes, no significant difference was found between the patients and controls regarding the percentage of total energy intake from saturated fatty acids, MUFAs and PUFAs for both sexes. The control group had higher saturated fat intake and the amount of saturated fat intakes were above the recommended level both for patients and controls (21). This finding may reflect the imbalance in the intake of fat subtypes in the general population rather than being related to a GFD (30). MUFAs and PUFAs can reduce total cholesterol and LDL cholesterol more than saturated fat (29). In this study, the cholesterol intake of patients with CD was significantly lower than that of the controls for both sexes. While cholesterol intake was below the recommended level in patients with CD, it was above the recommended level for healthy control males. Unlike our findings, a previous study reported that cholesterol intake was above the recommended level for both patients with CD and healthy controls (31).

The daily amount of protein intake, the amount of protein per body weight, and the percentage of energy from protein were lower in the patients than in the controls in this study. It was observed that protein intake of patients with CD was below the DRI levels and protein intake of controls was at the recommended levels. Similar to our study, a number of previous studies have also reported that patients with CD consume less protein as compared with their healthy peers (1, 26, 31, 32). However, there are also other studies reporting no difference in protein intake between patients with CD and healthy controls (24, 25, 33, 34). Varying outcomes obtained from these studies may be due to the differences in the dietary habits of control groups and variability in GFPs in different countries.

In the present study, fiber content of cereals is higher than that of other foods. Several studies have reported fiber intake level of children who are on diets with or without gluten to be below the recommended level (1, 26). Similarly, daily fiber intakes of patients and controls were also found to be below the recommended daily level (25 g/day) in the current study (21). Moreover, the mean daily fiber intake of patients with CD was significantly lower than that of the controls. The reasons underlying this finding may be due to reduced nutritional value of GFPs due to the refining process of flours making up the GFPs, imbalanced dietary habits and low vegetable and fruit consumption in patients with CD.

Grains are among the richest sources of B vitamins; thus, their elimination from a GFD may result in an insufficient intake of B vitamins (35). Our findings demonstrated that thiamine and riboflavin intakes of patients with CD were lower than those of controls for both sexes and that vitamin A, niacin, vitamin B6, folate and vitamin C intakes of females with CD were significantly lower than those of healthy control females. Similarly, another study reported that thiamine, riboflavin, vitamin B6, and niacin intakes were lower in children with CD than in their peers without CD (31). A previous study investigating GFPs by particularly focusing on their thiamine, riboflavin, and niacin contents reported that the GFPs were insufficient in their thiamine, riboflavin, and niacin contents (35). In this study, folate and vitamin C intakes of females with CD were significantly lower than that of healthy control females. While some studies have reported folate intake of patients with CD to be lower than that of the children on a normal diet as was in our study, some other studies have reported folate intake of patients with CD to be at the recommended levels (16, 24, 25, 33).

It has been suggested that patients with CD may experience mineral deficiencies such as iron, calcium, and zinc deficiencies at the time of diagnosis and such as iron, calcium, selenium, zinc, and magnesium deficiencies while on a GFD (36). GFPs tend to contain less calcium, iron, zinc, magnesium, and potassium (37). Some studies have reported that children and adolescents with CD have lower micronutrient intakes (iron, calcium, phosphorus, magnesium, zinc, and selenium) as compared with their healthy peers and with the recommended daily intake levels (1, 27).Within the scope of this study, calcium, magnesium, phosphorus, and selenium intakes of patients with CD were lower for both sexes as compared with their healthy peers and potassium, iron and zinc intakes of females with CD were significantly lower than healthy control females. The reason

for the insufficient calcium intake of patients with CD may be due to their consumption of fewer calcium sources than recommended. Additionally, lower protein intake of patients with CD may be the reason for lower intakes of phosphorus in patients with CD.

The current analysis evaluated dietary adequacy of the patients and controls using the NAR (%) and MAR (%) values (22). The MAR value was found significantly lower in patients with CD than in the controls for both sexes. Moreover, the MAR values of both patients and controls were below the optimal dietary adequacy (a MAR value of 100%), indicating that the diets of both patients with CD and healthy controls should be improved. Similarly, a previous study also reported that children and adolescents on a GFD had poor dietary quality (24).

The GFPs in the markets are commonly processed foods. Elimination of storage proteins from foods alters the macro- and micronutrient contents and nutritional values (7). GFPs have generally higher carbohydrate and fat content but lower vitamin B, folate, magnesium, and iron content (31, 37). In our study, evaluation of daily total energy and macronutrient intakes from the GFPs using the information on their labels revealed that GFPs fulfilled an average of 21.5% of the daily total energy intake of males with CD and an average of 19.5% daily total energy intake of females with CD. The mean percentage of energy derived from the carbohydrate content of gluten-free products (GFPs) was found to be relatively high among both male and female children with CD. The GFPs contributed only modestly to the overall dietary fiber intake in children with CD, regardless of sex. This finding is consistent with previous research indicating that many commercially available GFPs are low in fiber due to the refinement of gluten-free flours, the absence of whole grains in their formulation, and their reliance on high-carbohydrate ingredients with low protein and fiber content (36, 38).

To the best of our knowledge, the current study is the first to evaluate detailed nutritional assessment and dietary adequacy among children diagnosed with CD in Turkey. The strengths of this study were the comparison of nutritional status and growth between children with CD and their healthy peers, evaluation of dietary adequacy of both patients and controls by recording their three-day nutrition intake, and evaluation of the contribution of commercial GFPs on the daily energy and macronutrient intakes in patients with CD. On the other hand, one of the limitations of this research is that it was carried out at a single center, which limits the generalizability of the results to the broader population, including children with CD. Another limitation was that we were unable to access the complete vitamin and mineral compositions of certain GFPs in the national nutrient composition database, which resulted in an incomplete evaluation of vitamin and mineral intake in patients with CD. In addition, the necessity of conducting further studies with larger number of patients should be considered.

This study revealed that, despite good adherence to a GFD, children with CD experienced both nutritional inadequacies and excessive intakes. Nutritional assessment of the control group also revealed similar findings. Furthermore, the study demonstrated that the macronutrient composition of GFPs was imbalanced for patients with CD. To address these deficiencies, commercial GFPs should be fortified with fiber, iron, folate, calcium, zinc, B vitamins, and vitamin D. Additionally, the GFD, which is often high in fat and low in fiber, should be modified to ensure that children receive a balanced and adequate diet that supports their normal growth and development.

In conclusion, these results underscore the importance of not only ensuring proper adherence to a lifelong GFD but also addressing potential nutritional imbalances. Therefore, it is crucial to provide comprehensive dietary education and support to children diagnosed with CD and healthy children, with a focus on optimizing their nutrient intake. Furthermore, the study highlights the need for improved formulation of GFPs, particularly by increasing their fiber content, as many current products lack sufficient fiber. In addition, dietary counseling should emphasize the consumption of naturally gluten-free, fiber-rich foods such as fruits, vegetables, legumes, and pseudocereals like quinoa and buckwheat, to help ensure adequate fiber intake and promote better long-term health outcomes for children with CD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by The study was approved by the Clinical Research Ethics Committee of Gazi University, Ankara, Turkey. Informed consent was obtained from legal guardians of all children participated and also from each individual subject. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/ next of kin.

Author contributions

NE: Data curation, Writing – original draft, Writing – review & editing, Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization. RB: Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Methodology, Project administration, Supervision. EK: Data curation, Formal analysis, Investigation, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. BD: Data curation, Formal analysis, Investigation,

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Features of Celiac Disease in children and adolescents with Down syndrome: a single-center experience of annual screening

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Introduction: Coeliac disease (CD) manifests more frequently in individuals with Down syndrome (DS) and its prevalence varies across different studies. This study aims to assess the prevalence of CD in children with DS and to describe their clinical, serological, and histological features. A secondary aim was to analyze the time needed for the normalization of anti-transglutaminase IgA (TGA-IgA) and anti-endomysium IgA (EMA-IgA) levels in DS compared to non-syndromic (NS) children.

Materials and methods: This retrospective monocentric cohort study included patients with DS under 18 years of age, diagnosed with CD between 2005 and 2022. Each DS patient was matched for year of birth and sex with two NS celiac children. Follow-up was 6-, 12- and 24-months post-diagnosis.

Results: The prevalence of CD in 770 children with DS was 7.5% (95% CI: 5.8%–9.6%). 57 children with CD and DS were compared with 114 CD NS matched controls (total sample size = 171). DS demonstrated less symptoms than 114 NS CD children (26% vs. 79%, $P < 0.001$). In the CD DS group 81% had anti-TGA levels 10 times higher the upper limit of normal, compared to 72% in the control group. Among patients with CD and DS, 93% had histological damage equal to 3rd grade of Marsh-Oberhuber classification at diagnosis. The velocity of normalization of anti-TGA was higher in patients without DS ($P = 0.005$).

Discussion: This study reinforces the higher prevalence of CD in DS, emphasizing the necessity for routine screening, even in asymptomatic individuals. Despite less symptomatic presentation, patients with DS exhibited elevated antibody levels and severe histological damage. Clinicians should expect a prolonged time for antibody normalization following gluten-free diet in DS, mirroring potential challenges in diet adherence and altered immune responses.

KEYWORDS

Down syndrome, Celiac Disease, children, screening, anti-transglutaminase antibodies, anti-endomysium antibodies

Introduction

Coeliac Disease (CD) is an autoimmune enteropathy triggered by gluten ingestion in genetically predisposed individuals (1). The association between CD and Down Syndrome (DS) has been already extensively assessed; however, prevalence of CD in patients with DS varies considerably across the studies (range 0%–19%) (2–5). In a recent meta-analysis (6) including 4,000 patients with DS the prevalence of biopsy-confirmed diagnosis of CD was assessed at 5.8%, a considerably higher percentage compared to the general population (1% in Western countries) (7, 8). The prevalence of CD achieved 4.6% in an Italian cohort of patients with DS assessed over 20 years ago by Bonamico (9). To the best of our knowledge, no additional data focused on national cohorts have been published subsequently. Moreover, only few studies have assessed the specificities of CD in children with DS compared to non-syndromic (NS) otherwise healthy coeliac children. Furthermore, the time of normalization of IgA antibodies to transglutaminase (TGA) following gluten-free diet (GFD) has been studied in children with CD (10, 11), but no published data are available for patients with DS.

The primary aim of this study was to assess the prevalence of CD in a pediatric cohort of patients with DS and to describe its clinical, serological, and histological features. In addition, we aimed at reporting the DS-specific trendlines of TGA- IgA and anti-endomysium IgA (EMA-IgA) decrease over time, compared to NS children following GFD.

Materials and methods

Design of the study

We conducted a retrospective, monocentric cohort study. Clinical records of children with DS under the age of 18 followed by the Pediatric Genetics Outpatient Clinic of Fondazione IRCCS San Gerardo dei Tintori Hospital (Monza, Italy) were retrieved and reviewed by medical staff. All children with DS diagnosed with CD between January 1st, 2005, and December 31st, 2022, were eligible. Coeliac NS age- and gender-matched controls were identified from the Pediatric Gastroenterology Outpatient Clinic of the same Institution. In detail, we selected two NS coeliac patients with superimposable age and gender for each children with DS enrolled. Scheduled follow-up evaluations were performed 6- and 12-months following CD diagnosis and annually thereafter, until the patients turned 18 years. Detailed medical history collection, complete physical examination and CD serology were assessed upon every follow-up visit. The 6–12- and 24-month timepoints were considered for the present study. Informed consent was obtained by parents or legal tutor for each patient. All clinical and laboratorial data were collected and stored in a single excel worksheet anonymously. The study was approved by the Ethic Committee (n° 3896). Results are reported according to the STROBE checklist (12).

Patients with Down syndrome

In our Institution, from 2005 onwards, all patients with DS underwent an annual work up comprehensive of a follow-up clinical evaluation and laboratory assessment of CD-specific serology. The following data were collected for all patients with DS diagnosed with CD: age, sex, family history consistent with CD, associated symptoms (e.g., variation in appetite, faltering growth, abdominal pain, anemia, constipation, diarrhea, fatigue, vomiting, recurrent infections), anthropometric data (weight, height and body mass index - BMI), concomitant autoimmune disease (hyper/hypothyroidism, diabetes mellitus, psoriasis, vitiligo) and specific serology for CD, ie total IgA, TGA IgA and EMA IgA. When complete IgA deficiency was detected (defined as a total serum IgA level < 5 mg/dl), anti-TG IgG antibodies were considered.

Patients without Down syndrome

The same clinical and serological data were collected for NScontrols. Specific growth charts for DS (13) and NS patients (14) were used from the CDC (Centers for Disease Control and Prevention).

Celiac Disease: diagnostic criteria

The diagnosis of CD was made according to the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines (15–17) (see Supplementary Table S1). Over the observation period, our laboratory employed different assays to detect TGA-IgA. In detail, the historical Enzyme-linked Immuno Assay (ELISA) method was more recently replaced by chemiluminescence immunoassay (CLIA). On the other hand, EMA IgA have been always detected via immunofluorescent test. Biopsy samples were taken during upper endoscopy from the bulb (at least 1 biopsy) and from either the second or third portion of duodenum (at least 4 biopsies). The procedure was performed under deep sedation. Histopathological findings were classified according to Marsh-Oberhuber classification (18). Endoscopy was performed for all patients with IgA deficiency.

Statistical analysis

Qualitative variables were represented as absolute number and percentage. Quantitative variables were reported as median and first-third quartiles (Q1, Q3). Mann–Whitney U nonparametric test was conducted to compare the quantitative variables among patients with and without DS and Fisher test for categorical variables. Follow-up time was computed as time between the CD diagnosis to time of last available visit. The time between the CD diagnosis and the time to the first normalization of anti-TGA and EMA was computed to estimate the percentage of normalization by the Kaplan–Meier estimator. Patients lost to

follow-up before normalization were censored at their last visit. A multivariable Cox model stratified for period of diagnosis (before/after 2012 to account for the change in the method of detection of TGA-IgA) was also used to evaluate the variables associated with the velocity of normalization of anti-TGA in patients with DS. The velocity of normalization in patients with and without DS was compared by the Wald test with robust Huber sandwich estimator from the Cox model accounting for matched set, with and without prespecified (by a clinical point of view) confounders. Proportionality of hazards was checked by the Schoenfeld residuals. Type I error was fixed at 0.05 and R-cran software (version 4.3.1) was used for the analyses.

Results

Study population and prevalence of Celiac Disease in Down syndrome

From January 1st, 2005, to December 31st, 2022, 770 patients with DS were admitted to the Pediatric Genetics' Clinic, among which 58 received a diagnosis of CD, with an overall prevalence of 7.5% (95% confidence interval, CI: 5.8%–9.6%). In the same period, 848 children were diagnosed with CD by the Pediatric Gastroenterology Clinic. Only one patient in the DS group could not be matched by date of birth and sex with any NS, leaving a final sample of 57 CD DS and 114 CD NS controls. Main clinical features of DS compared with NS children were reported in Table 1.

TABLE 1 Main clinical, serological and histology characteristics of celiac patients with and without Down syndrome at diagnosis.

	Patients with Down syndrome (n = 57)	Patients without Down syndrome (n = 114)	P-value
Sex (males), n (%)	27 (47)	54 (47)	1
Age at diagnosis (years), median [Q1–Q3]	6 [4.4, 8.7]	5 [3.1, 8.7]	0.05
Diagnosis after 2012 (from 2013 to 2022), n (%)	36 (63)	74 (65)	0.866
Family history of Celiac Disease, n (%)	5 (9)	42 (37)	<0.001
Symptoms, n (%)	15 (26)	90 (79)	<0.001
Diarrhea, n (%)	8 (14)	12 (11)	0.614
Growth impairment, n (%)	7 (12)	28 (25)	0.071
Abdominal pain, n (%)	4 (7)	26 (23)	0.01
Constipation, n (%)	3 (5)	9 (8)	0.753
Tiredness, n (%)	3 (5)	18 (16)	0.051
Concomitant autoimmune disease, n (%)	16 (28)	7 (6)	<0.001
BMI percentile (kg/m^2), median [Q1–Q3]	50 [(25, 75)]	25 [(11, 70)]	0.414
Serological and histology characteristics			
IgA deficiency, n (%)	1 (2)	2 (2)	1
Total IgA * (mg/dl), median [Q1–Q3]	139 [(94, 190)]	96 [(66, 133)]	<0.001
TGA positivity**, n (%)	53 (98)	110 (97)	1
EMA positivity ***, n (%)	52 (95)	112 (95)	0.331
TGA-IgA ** (ULN), n (%)			0.289
0–7	7 (13)	27 (24)	
7–10	3 (6)	5 (4)	
≥10	43 (81)	82 (72)	
Patients undergone EGDS, n (%)	42 (74)	105 (92)	0.002
Marsh****			0.558
1–2, n (%)	2 (5)	6 (6)	
3a, n (%)	8 (19)	12 (11)	
3b, n (%)	17 (41)	41 (39)	
3c, n (%)	14 (33)	45 (43)	
HLA typing *****, n (%)	24 (46)	53 (47)	1

BMI, body mass index; TGA, IgA antibodies to transglutaminase; EMA, IgA endomysial antibody; EGDS, esophagogastroduodenoscopy; HLA, human leukocyte antigen; ULN, upper limit of normal.
*5.8% missing values, **2% missing values, ***1% missing values, ****14% missing values, *****4% missing values.

Comparison of clinical, histological, and serological features of Celiac Disease in children with Down syndrome and non-syndromic children

In the DS group the frequency of CD in a first degree relative was 9% compared to 37% of NS. Symptoms at time of diagnosis were lower in the DS groups as compared with NS (26% vs. 79%, $P < 0.001$), whereas the incidence of autoimmune disease was higher (DS 28% vs. NS 6% $P < 0.001$). Thyroid disease was the most common autoimmune comorbidity among children with DS (Supplementary Table S2). In DS group, 81% of the anti-TGA levels were 10 times higher than the upper limit of normal (ULN), compared to 72% in NS. An intestinal biopsy sample was taken in 74% of all DS vs. 92% in the control group. Among patients with DS, 93% had histological damage equal to 3rd grade of Marsh-Oberhuber classification while 2 (5%) presented a 1st–2nd grade of Marsh-Oberhuber with anti-TGA levels below 10 times the ULN. In NS patients 6 (6%) presented a 1st–2nd grade of Marsh-Oberhuber (4 with anti-TGA levels below 10 times the ULN and 2 with anti-TGA levels over 10 times the ULN).

Considering the whole sample, the median follow-up was 747 days (first-third quartile 685–802), with a total of 32 patients lacking the 2 years follow-up visit. Supplementary Figure S1 reports the flow of patients among different BMI percentile classes over the 2 years follow-up, showing a reduction of patients in the class of BMI below the 5th percentile in the first year, with a subsequent small increase, without relevant differences among the two groups.

Figure 1 reports the percentage of children with positive (unnormal) anti-TGA (panel A) and EMA (panel B) by time since diagnosis. The median time to normalization of anti-TGA was significantly higher in DS (727 days, 95% CI 516–805) compared to NS patients (356 days, 95% CI: 263–403) (Figure 1, panel A, robust Wald test $P = 0.005$). The normalization of EMA was quicker, requiring a median time of 370 days (95% CI 308–516) for DS and 263 (95% CI: 239,311) for NS patients (Figure 1, panel B), without a significant difference between the two groups (robust Wald test $P = 0.09$). As children with DS perform

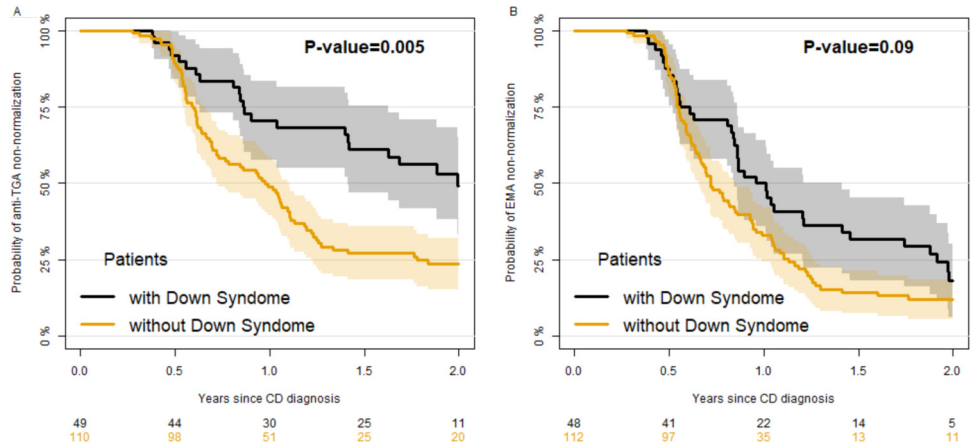

FIGURE 1
Kaplan–Meier estimate of the percentage of patients positive to anti-TGA (panel A) and anti-EMA (panel B) since Celiac Disease diagnosis in children with and without Down syndrome.

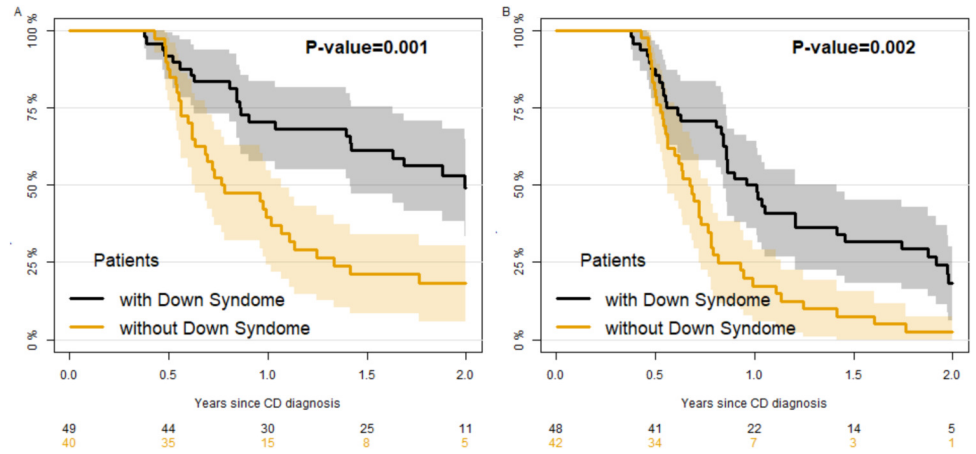

FIGURE 2
Sensitivity analysis: Kaplan–Meier estimate of the percentage of patients positive to anti-TGA (panel A) and anti-EMA (panel B) since Celiac Disease diagnosis in children with Down syndrome as compared with children without Down syndrome but with a familiarity for Celiac Disease.

yearly screening on CD, while others do not, we performed a secondary analysis selecting a more homogeneous group of controls including only children with a familial CD (and thus who probably had undergone antibody testing for screening). In those controls (Figure 2) the velocity of normalization of both anti-TGA and of EMA was higher, resulting in a significant difference between patients with and without DS ($P = 0.001$ and 0.002 respectively for anti-TGA and EMA). When we evaluated the factors associated with the velocity of anti-TGA normalization (Table 2, model A) in patients with DS, we found that the level of anti-TGA at diagnosis was associated with the velocity of normalization, in particular patients with anti-TGA values higher than 10 times the ULN showed a slower rate of normalization as compared with patients with values lower than 7 times the ULN (HR = 0.05, 95% CI 0.01–0.24). Over the total sample, (including patients with and without DS, Table 2 model B) level of anti-TGA at diagnosis and sex were both associated with velocity, with males being quicker in normalization of anti-TGA. As far as the comparison between patients with and without DS, the normalization of anti-TGA was slower in patients with DS as compared to patients without it (HR = 0.63, 95% CI: 0.40–1.001, $P = 0.051$).

Discussion

In the present analysis, the prevalence of CD in children and adolescents with DS was as high as 7.5%, remarkably greater than the occurrence reported in the historical Italian cohort assessed by Bonamico and colleagues (9). Several reasons may be

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TABLE 2 Results on the Cox regression model on TGA normalization since Celiac Disease diagnosis among children with Celiac Disease with positive TGA at diagnosis.

Variable	Model A on patients with Down syndrome*n* = 49, events = 29		Model B*n* = 159, events = 120	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Patients with Down syndrome vs. patients without it	–	–	0.63 (0.4–1.001)	0.051
Age at diagnosis (per year)	0.93 (0.8–1.09)	0.374	0.96 (0.91–1.01)	0.142
Sex (males vs. females)	1.52 (0.64–3.58)	0.339	1.53 (1.06–2.2)	0.006
Family history of Celiac Disease (yes vs. no)	1.76 (0.41–7.58)	0.448	1.35 (0.89–2.04)	0.192
TGA-IgA (ULN)				
7–10 vs. ≤7	0.6 (0.08–4.63)	0.626	1.19 (0.5–2.83)	0.641
≥10 vs. ≤7	0.05 (0.01–0.24)	<0.0001	0.39 (0.25–0.62)	<0.0001

CI, confidence interval; HR, hazard ratio; TGA, IgA antibodies to transglutaminase; ULN, upper limit of normal.
Model A includes only patients with Down syndrome ($n = 49$, normalized within the follow-up 29), while model B includes patients with and without Down syndrome ($n = 159$, normalized within the follow-up 120).

hypothesized to support this apparent discrepancy, such as a deeper awareness of the clinical spectrum CD, a different serologic approach employed to diagnose CD [antigliadin antibodies (AGA) and EMA by Bonamico vs. TGA and EMA in the present analysis] and the systematic screening strategy introduced in our Centre from 2005 onwards. In addition, despite a patchy geographical distribution worldwide, a growing body of epidemiological studies held in our Country have shed light on the progressive increase of the prevalence of CD in school age children over the last decades (from 0.88% in 1999–2000 to 1.65% in 2017–2020) (19). The data recorded in patients with DS may simply mirror the trendlines of the general pediatric population, though the underlying causes of this phenomenon still need to be clarified.

The question of whether screening for CD is beneficial in the light of a higher incidence among individuals with DS remains a subject of controversy. The ESPGHAN 2020 (17) and the National Institute for Health and Clinical Excellence (NICE) guidelines (20) promote lab screening in populations exposed to a higher risk of developing CD, including DS, but the best timing for scheduled screening remains unclear. Conversely, the American Academy of Pediatrics (AAP) guidelines about health monitoring strategies for children with DS do not recommend systematic screening for CD due to the lack of indisputable evidence about its potential benefits (21).

The prevalence of diarrhea (14%), weight loss (12%), and abdominal pain (7%) observed in this study is superimposable to the findings reported by published literature about patients with DS (9, 22, 23). In some analyses (9, 24), the occurrence of symptoms may be overestimated, as testing for TGA and EMA antibodies were performed exclusively on symptomatic patients. The lower occurrence of clinical findings among patients with DS may be regarded as an expected outcome in a population screened yearly for CD, with the serological diagnosis anticipating the onset of reported symptoms. In addition, gastrointestinal disorders are reported in 50% of children with DS (23), therefore gastrointestinal symptoms may not be reliable indicators for identifying potential cases of CD in this population. In our study, a clinically driven prescription of serological work-up only among symptomatic patients would have led to remarkable underestimation of the prevalence of CD among patients with DS, as only 26% of affected children would have been diagnosed. Accordingly, we find reasonable to suggest a yearly lab screening for CD in DS and to test individuals with new onset of suggestive signs and symptoms.

Even if the BMI percentile median values were unchanged among patients with DS, we witnessed a progressive decrease in the number of patients with low BMI following the prescription of GFD. This data agrees with those published by Nisihara and colleagues (25) on children with DS.

As already extensively reported (9, 22, 26), our study highlights a greater occurrence of autoimmune disorders among celiac patients with DS, compared to NS controls (DS 28% vs. NS 6%). In our study, the most frequently observed autoimmune pathologies were thyroid disorders with a reported prevalence of 19%. The immune dysregulation in DS seems to be correlated with the combination of an increase in the expression of proinflammatory cytokines, an aberrant expression of B lymphocytes and an increase in the production autoantibodies directed against the central nervous system, gastrointestinal tract, pancreas, and thyroid (27).

Regarding family history of CD, our study showed a significantly lower prevalence in the CD diagnosed DS population compared to the control group (9% vs. 37%). To the best of our knowledge, no published studies report the frequency of family history of CD in Down children.

From a diagnostic perspective, 81% of patients with DS showed an anti-TGA titer 10-fold or greater the ULN. Most patients with DS were asymptomatic upon diagnosis and 93% of those undergoing intestinal biopsy showed a severe histological damage. These data are in consistent with the published literature, that reports a poor association between clinically relevant complaints and antibody titers or the degree of histologic damage (28), but a reliable agreement between serological data and histologic damage (28, 29). To the best of our knowledge, our study is the first specifically focused on CD in children with DS.

An additional element of novelty is the longer-lasting time needed to achieve antibodies normalization in DS compared to otherwise healthy controls. Our explanation for this phenomenon

is the increased production of autoantibodies targeting the gastrointestinal tract, observed in individuals with DS (27), and the potential difficult adherence to GFD in this population. In a recent work published by Sbravati et al. (11), conducted on the general population, they found a time needed before the normalization of antibodies titer around 9 months from the beginning of the diet, irrespectively of the presence symptoms at diagnosis, with a longer time in those individuals with co-occurrent autoimmune diseases (e.g., diabetes or thyroiditis).

Given its retrospective nature, we are aware of some flaws affecting our analysis. Firstly, we did not have the chance to systematically collect data about the improvement gastrointestinal symptoms following GFD. Moreover, patients with DS were selected through the annual screening, so the probability to detect the antibody positivity before the surge of symptoms was higher than in NS. A multicentric prospective assessment is warranted in order to corroborate our outcomes achieved.

This study confirms a higher prevalence of CD in children and adolescents with DS and highlight the key diagnostic role of CD screening also among asymptomatic patients. Interestingly, even though the majority of DS are asymptomatic and detected through screening, they show higher serologic titers compared to NS controls. Moreover, the average degree of histopathological involvement was superimposable between Down patients and NS controls. This is one of a few works comparing clinical and serological characteristics between Down and non-Down patients. Moreover, it's the first analysis on the antibodies trend since diagnosis in patients with DS. Clinicians should expect a longer time of TGA IgA normalization after the start of a GFD. This should be anticipated to the families to avoid unuseful worries and blood samples to children with DS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethic Local Committee Board n° 3896. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

ML: Data curation, Writing – review & editing, Conceptualization, Supervision, Writing – original draft. PR: Writing – original draft, Methodology, Formal analysis, Writing – review & editing, Data curation. CF: Methodology, Writing – review & editing, Conceptualization. AL: Data curation, Conceptualization, Writing – review & editing. LP: Data curation, Writing – original draft, Formal analysis. AC: Writing – review & editing, Supervision, Conceptualization. RP: Supervision, Writing – review & editing, Conceptualization. MV: Data curation, Formal analysis, Methodology, Conceptualization, Writing – review & editing. AB: Writing – review & editing, Supervision. GZ: Supervision, Data curation, Methodology, Writing – review & editing, Writing – original draft, Conceptualization.

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Conflict of interest

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2025.1595256/full#supplementary-material

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Body image dissatisfaction, depression, and anxiety in adolescents with celiac disease

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Introduction: Celiac disease, also known as gluten-sensitive enteropathy, is an immune-mediated disorder with a broad clinical manifestations including psychiatric symptoms. The present study aims to evaluate body image dissatisfaction, depression, and anxiety among adolescents with celiac disease and to draw attention to the diagnosis and management of these comorbidities.
Methods: This study was performed in Pediatric Gastroenterology unit of Erciyes University between July 2022 and June 2023. Adolescents aged 12–18 years diagnosed with histopathologically confirmed celiac disease and their age- and sex-matched healthy peers, were recruited in the study.
Results: A significant difference was found between the patient and control groups in depression ($p < 0.001$), and body image dissatisfaction ($p < 0.001$). Adolescents who were non-compliant with the diet showed significantly elevated risk of body image dissatisfaction and depression compared with participants who adhered to the strict diet ($p = 0.001$, $p < 0.001$, respectively). A positive correlation was observed between tTGA-IgA antibody levels and depression ($r = 0.618$; $p < 0.01$), and a negative correlation was found between tTGA-IgA antibody levels and body image dissatisfaction scores ($r = -0.400$, $p = 0.014$).
Conclusion: The present results underscore adolescents with celiac disease are at an heightened risk for psychiatric burden. Therefore, periodic follow-up should be performed to determine body image satisfaction in adolescents with celiac disease and to recognize mood-related symptoms. Early identification of symptoms associated with mood disorders and body image dissatisfaction in adolescents is critical for efficient patient care within celiac disease and to enhance adolescents' holistic well-being.

KEYWORDS

celiac disease, body image, depression, anxiety, children

1 Introduction

Celiac disease (CD) is a prevalent autoimmune disorder of the small intestine precipitated by an immune response to gluten (wheat, rye, and barley) in genetically susceptible individuals (1). CD is typically manifests in the pediatric population with diarrhea, abdominal bloating, and failure to thrive, whereas in older children it more often presents with bloating, constipation, or weight loss (2). Extraintestinal symptoms are frequent in both children and adolescents. A wide range of neurological sequelae may

also occur in patients with CD, encompassing neuroinflammation, anxiety, recurrent headaches, and depressive features (3).

Depression and anxiety are among the most common emotional disorders in adolescents (4). Depression affects approximately 1.4% of adolescents aged 10–14, rising to over 3% by age 19 (5).

Anxiety disorders impact 4.4% of youths aged 10–14 and 5.5% of those aged 15–19 (5). Depressive disorders and anxiety can significantly disrupt school attendance and educational performance (6). Social withdrawal can deepen both disconnection and loneliness (7). Chronic illnesses, such as celiac disease, can precipitate the development and worsening of psychiatric conditions (8). Research on adult CD cohorts has documanted higher rates of depressive symptoms and anxiety, yet adolescentfocused data is limited (9). Pediatric patients with CD are more susceptible to depression and anxiety than their healthy peers, with observed rates of 3.5% and 3.7%, respectively (9). One investigation reported that nearly 40% of children with CD exhibited clinically significant levels of depressive and anxious symptomatology (8). Body image encompasses the thoughts, perceptions and feelings individuals hold about their physical form and the experiential aspects of embodiment (10). It has been estimated that body image disturbances affect 1.7%–37% of adolescents (10). In particular, these disturbances are often linked to mood disorders, pointing to a potantial overlap of psychological distress and body image dissatisfaction (BID) (10). Accordingly, it is reasonable to predict that body image issues will be a markedly prominent among adolescents with CD. Thus far, no study has specifically examined body image dissatisfaction in an adolescent cohort with CD, making this the first study the first of its kind.

Our clinical experience suggest a link between BID and depression in children with CD; nevertheless, data exploring the association between pediatric CD, body image concerns, and psychiatric symptoms remain sparse. These findings underscore the critical importance of early screening and management of these comorbid conditions. Given the complexity of CD and the distinct challenges posed by adolescence, integrated approach is vital to address the psychiatric comorbidities in this population.

2 Materials and methods

2.1 Study design

We performed a survey-based prospective cohort study on adolescents diagnosed with CD followed up at Erciyes University Department of Pediatric Gastroenterology, between July 1, 2022 and June 15, 2023. The informations of children were reviewed form the hospital clinical records, and children and/or their parents provided written informed consent to enroll in the study. Questionnaire responses were collected prospectively during follow-up visits. The study was ethically approved by the local committee (2022/459).

2.2 Participants, data collection and questionnaires

This study included adolescents who were diagnosed with CD based on positive serological markers (Anti-tissue Transglutaminase IgA antibody) and confirmation through duodenal biopsies, in accordance with the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines (11).

The control group consisted of healthy children with no chronic disease. Clinical and laboratory data were retrieved from hospital records. All participants filled out a series of standardized questionnaires, and the total scores were methodically recorded for analysis.

The Body Perception Scale consists of 40 items, each rated on a 5-point Likert scale, ranging from 1 'did not like at all' to 5 'liked very much'. The total score ranges from 40 to 200, with higher scores indicating a more positive perception of one's body image (12). The Kovacs Depression Inventory is a validated instrument used to assess cognitive, behavioral, and emotional symptoms of depression in adolescents (13). It consists of 27 items addressing aspects such as depressed mood, hopelessness, and impaired social functioning. The total score ranges from 0 to 54, with the following interpretation: 0–8: No indication of depression; 9–19: Subthreshold depressive symptoms; ≥20: Indicative of clinical depression. Elevated scores correspond to greater severity of depressive symptoms. The Childhood Anxiety Sensitivity Index includes 18 items evaluating children's emotional responses to anxietyinducing stimuli (14). Each item is scored as 1 'not at all', 2 'a little', or 3 'a lot', yielding a total score range of 18–54. Higher scores indicate increased sensitivity to anxiety-related sensations (15).

2.3 Statistical analysis

All data were analyzed using Statistical Package for the Social Sciences (SPSS), version 22.0 for Windows. Descriptive statistics [counts, percentages, means, standard deviations, medians and interquartile ranges (IQR)] were used. Chi-square test was used for categorical variables in comparisons between groups. For continuous variables that were not normally distributed, Mann–Whitney *U* test was applied to two-group comparisons and Kruskal–Wallis H test to three-group comparisons. When Kruskal–Wallis test showed a significant difference, pairwise group comparisons were used and the direction of the difference was indicated. Associations between continuous variables were evaluated using Spearman's rank correlation.

3 Results

3.1 Participant characteristics

A total of thirty-seven patients with CD were included, with a median age of 14.4 (IQR = 2.5) years; 64.9% were female. Eight

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TABLE 1 Descriptive profile of the CD and control groups.

Descriptives		CD		Control		p
		n	%	n	%	
Gender	M	13	35.1	14	37.8	$\chi^2 = 0.058$
	F	24	64.9	23	62.2	$p = 0.500$
Diet compliance	No	13	35.1			
	Yes	24	64.9			
Complaint	Abdominal pain	7	18.9			
	Inadequate weight gain	10	27.0			
	Short stature	10	27.0			
	Persistent diarrhea	2	5.4			
	Weakness	2	5.4			
	Family history of CD	6	16.2			
		Median	(IQR)	Median	(IQR)	MWU/p
Age		14.44	2.5	15.0	2.0	571.5/0.215
Weight SDS		−1.15	1.8	−0.29	1.6	402.0/0.002
Height SDS		−0.50	2.1	−0.20	1.58	546.5/0.136
Body Image score		131	36	154	48	354.5/0.000
Depression score		17	24	2	4	225.5/0.000
Anxiety score		31	9	31	7	630.0/0.555

Chi-Square Analysis; Mann–Whitney *U* Test.

patients (21.6%) had additional chronic diseases, including Type 1 Diabetes Mellitus ($n = 4$) (others: eosinophilic esophagitis, Hashimoto thyroiditis, vitiligo, and juvenile idiopathic arthritis). Of these patients, 64.9% reported adherence to the gluten-free diet (GFD), while 35.1% were non-adherent. The mean duration since diagnosis of CD was 3.92 ± 2.59 years, and the mean antibody level [tissue Transglutaminase IgA (tTG-IgA)] was 228.95 ± 55.64 U/ml.

According to the Mann–Whitney *U* test, significant differences were found between groups in weight SDS ($p = 0.002$), depression ($p < 0.001$), and body image ($p < 0.001$). Descriptive data for the groups are presented in Table 1.

3.2 Clinical outcomes

When body image, depression, and anxiety scores in CD group were examined by demographic characteristics, no significant differences found based on gender. Among patients who did not adhere to the GFD, the median depression score was 29.0 (IQR = 24), compared to 8.0 (IQR = 16) for those who followed it, indicating a significant difference ($p < 0.001$). Corresponding body image scores were 113.0 (IQR = 38) for those who did not follow the GFD and 140.5 (IQR = 31) for those who did, indicating a significant difference ($p = 0.001$). In contrast, no significant difference was observed in anxiety levels ($p = 0.089$) (Table 2). No significant difference was found between patients with and without additional chronic diseases in terms of depression, anxiety, and BID.

Table 3 presents group-based differences in body image, depression, and anxiety scores. A Kruskall–Wallis H test revealed significant differences in both depression and body image scores. The highest median depression score was observed in the GFD non-adherent group, followed by the adherent group and the control group, yielding a statistically significant difference (KWH = 32.941, $p < 0.001$). For body image scores, the control group recorded the highest score, followed by the adherent and the non-adherent group, again indicating a significant difference (KWH = 19.889, $p < 0.001$).

TABLE 2 Differences in body image, depression, and anxiety scores according to descriptive characteristics.

Descriptives	n	Body image	Depression	Anxiety
Gender		Median (IQR)	Median (IQR)	Median (IQR)
M	13	132.0 (23)	13.0 (19)	31.0 (9)
F	24	129.5 (55)	17.0 (26)	34.0 (9)
MWU=		154.0	154.0	144.0
p=		0.949	0.949	0.702
Diet compliance		Median (IQR)	Median (IQR)	Median (IQR)
No	13	113.0 (38)	29.0 (24)	35.0 (9)
Yes	24	140.5 (31)	8.0 (16)	29.0 (10)
MWU=		59.5	45.5	102.5
p=		0.001	0.000	0.089
		Body Image (r/p)	Depression (r/p)	Anxiety (r/p)
Age		0.115/0.499	0.194/0.250	0.2181/0.284
Weight SDS		0.294/0.078	0.134/0.431	0.187/0.269
Height SDS		0.215/0.201	0.010/0.952	0.232/0.168

Mann–Whitney *U* test; Spearman's rank correlation.

3.3 Correlation analyses

As shown in Table 4, there is a positive correlation between depression and anxiety ($r = 0.388$; $p = 0.018$). In contrast, a significant negative association was found between depression and body image scores ($r = -0.641$; $p < 0.01$), indicating that higher levels of depression correspond to more negative body image satisfaction. The positive correlation between depression

TABLE 3 Differentiation Status of scores according to groups.

Study measures	GFD non-adherent[1]		GFD Adherent[2]		Control[3]		KWH	*p* difference
	Median	IQR	Median	IQR	Median	IQR		
Depression	29.0	24	8.0	16	2.0	4	32.941	0.000 1 > 2,3; 2 > 3
Anxiety	35.0	9	29.0	10	31.0	7	3.278	0.194
Body Image	113.0	38	140.5	31	154.0	48	19.889	0.000 2.3 > 1; 3 > 2

Kruskall–Wallis H test.

TABLE 4 Correlation analysis.

Study measures	*r/p*	Depression	Anxiety	Body image	Disease duration	tTG-IgA
Depression	*r*	1.000				
	p	0.000				
Anxiety	*r*	0.388*	1.000			
	p	0.018	0.000			
Body Image	*r*	−0.641**	−0.357*	1.000		
	p	0.000	0.030	0.000		
Disease Duration	*r*	0.158	0.013	−0.084	1.000	
	p	0.350	0.939	0.620	0.000	
tTG-IgA	*r*	0.618**	0.122	−0.400*	0.066	1.000
	p	0.000	0.471	0.014	0.700	0.000

tTG-IgA, tissue transglutaminase IgA.
*<0.05; **<0.01; Spearman's rank correlation.

and disease duration ($r = 0.158$; $p = 0.350$) was not statistically significant. However, a strong, significant positive correlation detected between antibody levels and depression ($r = 0.618$; $p < 0.01$) and a negative correlation detected between antibody levels and body image scores ($r = -0.400$, $p = 0.014$), suggesting that higher antibody levels are linked to increased depression and decreased body image scores.

4 Discussion

This is the first study notably examining BID, depression and anxiety in adolescents with CD using a confirmed screening tool. Although CD was classically considered to be a gastrointestinal disorder mainly related to malabsorption, it is now more accurately classified as an autoimmune disease with systemic manifestations (16). The pathophysiological mechanisms behind neuropsychiatric aspects of CD remain controversial. Increased intestinal permeability allows the entry of molecules such as biomolecular aggregates, gliadin antigen, inflammatory mediators, and tissue transglutaminase (tTG)IgA antibodies into the circulation, contributing to the initiation or exacerbation of symptoms through production of the cross-reactive antibodies, direct toxicity and immune complex deposition in central nervous system (17). Additionally, molecular mimicry between gliadin and neural pathway proteins has been proposed to play a crucial role in the psychiatric manifestations of CD; however, the precise mechanism remains unclear (18). The most common psychiatric manifestations in CD are depression, anxiety, irritability, attention deficit hyperactivity disorder, and sleep complaints (19). Although studies have been conducted on depression and anxiety in CD (8, 20), its effects on adolescents are still worth investigating due to the limited available data and the significant impact of the negative consequences of the disease.

When individuals hold negative perceptions of their bodies or identify a difference between their ideal and actual physical characteristics, BID is present (21). Factors associated with BID include body mass index, social media exposure, peer pressure, sociocultural appearance norms, biological and psychological changes during adolescence, and chronic diseases that may influence physical appearance (22). The literature indicates that patients with chronic diseases have higher levels of BID compared to healthy controls (23). Although available data are limited, an association between BID and autoimmune diseases has been indicated in adults (24, 25). Studies investigating the relationship between GFD adherence and body image disturbances in adults with CD have reported conflicting results (26, 27). CD can lead to physical symptoms that adversely impact appearance, such as abdominal bloating/distension, underweight, and various skin problems such as dermatitis herpetiformis (16). In our study, BID was more prevalent in adolescents with CD compared to their healthy peers. In line with the literature, we suggest that the more unfavorable body perceptions seen in our patients may be associated with the negative physical consequences of CD.

Correlational studies have supported the link between food addiction, media exposure, and BID in adolescents. The most widely accepted theories that explain how media influences diet and body image are sociocultural and objectification theories. A key component of these theories is body surveillance, which may contribute to anxiety, eating disorders, and BID in adolescents (22). CD requires lifelong adherence to a strict GFD,

which may lead to feelings of social exclusion during meals, fear of making dietary mistakes, and perceptions of insecurity or inadequacy regarding one's body. This psychological burden may contribute to increased BID, particularly in adolescents. Additionally, constant reading of food labels, food refusal, and continuous monitoring of eating behaviors may lead to obsessive body awareness in this age group (28). Gluten exposure is known to trigger not only gastrointestinal symptoms but also psychiatric manifestations such as, fatigue, brain fog, and irritability (16). We propose that these symptoms may indirectly contribute to BID by affecting sensations of bloating, illness, and a lack of control over the body. Repeated gluten exposure may also disrupt eating behaviors and increase food-related anxiety.

In CD, increased intestinal permeability results from the impairment of the zonulin–tight junction relationship, epithelial damage, and villous atrophy (29). The ongoing inflammatory response due to barrier dysfunction is manifested by persistent serum CD antibody levels. In our study, we observed that both BID and depressive symptoms were more prominent in patients with elevated serum antitTG-IgA levels. It can be hypothesized that gluten, through its effect of both physical symptoms and gut barrier impairment, may also aggravate mental and psychological symptoms via the gut–brain axis. Therefore, we suggest that the elevated anti-tTG-IgA levels detected in our study may help explain the relationship with BID. Furthermore, we observed that dietary non-compliance was associated with more adverse body image perception. However, body image satisfaction was higher among patients who adhered to the GFD, similar to that observed in healthy adolescents. These findings suggest that eliminating gluten exposure may reduce both physical symptoms and mood disorders that negatively influence body image. Although previous studies have shown that BID is more prevalent in girls (10), we did not observe a gender difference. This divergence may be attributed to the limited sample size in our study.

The prolonged course of disease duration may adversely impact both psychological body image and well-being by leading to decreased quality of life, social isolation, and limitations in daily activities. These factors may facilitate the development of BID, particularly during adolescence. Moreover, many individuals with BID are sensitive to rejection and may hesitate to express their concerns for fear of being perceived as superficial. BID is a serious condition; affected adolescents often suffer significantly and may experience severe psychological distress, including suicidality (30, 31). In our study, however, we did not observe a significant association between extended disease duration and levels of depression, anxiety, or BID. Larger-scale research is needed to explore this relationship more comprehensively. The duration of untreated depression is the most important factor influencing both the severity of the disease and the likelihood of recovery. Active treatment reduces the duration of depressive episodes (32). The US Preventive Services Task Force recommends screening for a major depressive disorder in adolescents aged 12–18 years (33).

In our study, we found that non-compliant patients are more prone to depression and body image disturbances compared to GFD compliant patients with CD and healthy adolescents. At the same time, even in adolescents with CD who were compliant with GFD, this tendency was greater than in healthy ones. Gliadin increases zonulin-dependent intestinal paracellular permeability, irrespective of disease status (34). This mechanism may explain the higher prevalence of depression and body image disturbances even in patients adhering to a strict GFD. While many of the symptoms of CD improve with a strict GFD, fatigue and some neurological symptoms may persist for a prolonged period in certain patients (1).

There are limited studies investigating anxiety in adults with CD. Some reported greater anxiety in CD compared to controls (35), while others did not (36). In our study, we did not find any susceptibility to anxiety in adolescents with CD. The literature has shown a relationship between depression and BID in adolescents (37). The individual's negative perception of his/her own body, especially in adolescence and young adulthood, leads to psychological states such as decreased self-esteem, feelings of inadequacy, social withdrawal, and self-shame. This situation significantly increases the risk of depression over time. Although there was a strong correlation between BID and depression and anxiety in our study, a relationship was established between depression and anxiety. However, we did not apply a generic quality-of-life instruments, as the emotional subscale scores may offer only a relatively weak and indirect presentation of emotional functioning status and anxiety burden. Since data on the mental states of adolescents with CD are quite limited, more comprehensive studies are needed on this subject.

5 Limitations

This study has several limitations. The cross-sectional design prevented us from making causal inferences between variables. Although our study was conducted prospectively using a survey-based approach, the generalizability of the results is limited due to the small sample size. Additionally, the reliance on self-reported data may have introduced information bias. Furthermore, long-term effects could not be assessed due to the short follow-up period.

6 Conclusion

This study presents insights into the psychiatric manifestations of CD in adolescents. Body image dissatisfaction, depression, and anxiety are conditions that may occur in children with CD and can negatively affect quality of life. Dietary compliance was associated with reduced depressive symptoms and improved body image perception. Therefore, it is crucial to inform the families of adolescents with CD about potential psychiatric and body image vulnerabilities in order to facilitate adaptation to a GFD and improve overall well-being.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by the studies involving human/animal participants were reviewed and approved by Erciyes University local ethic committee with approval number 2022/459. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

BD: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. ED: Supervision, Writing – review & editing. DAl: Supervision, Writing – review & editing. DAr: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Vitamin D and calcium-phosphorus in serum of children with celiac disease in a zone of high sunlight exposure

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Actuality: The relationship between vitamin D levels and celiac disease (CeD) in children remains controversial. Uzbekistan is a country where the average number of sunny days is more than 300 days. There are few studies on the vitamin D status of children with celiac disease in an area of high insolation.
Aim of the study: To determine vitamin D status in children with CeD and to evaluate clinical and laboratory parameters in children depending on vitamin D levels.
Patients and methods: We examined 60 children with first diagnosed CeD aged from 1 to 16 years, the average age was 6 ± 2.3 years. The diagnosis was established on the basis of ESPGHAN 2012 criteria. In all children serum 25(OH)D, calcium, phosphorus, parathormone, alkaline phosphatase was determined. The control group consisted of 31 children of identical age.
Results: Children with CeD had significantly lower mean serum 25(OH)D levels (14.8 ± 1.04 ng/ml) compared to controls (45.1 ± 8.04 ng/ml; $p < 0.001$). Vitamin D deficiency (<20 ng/ml) was identified in 80% of patients with CeD, including 25% with levels <10 ng/ml. Vitamin D insufficiency was observed in 20%. Lower vitamin D levels were associated with more pronounced clinical features suggestive of metabolic imbalance, including stunting and growth retardation (observed in 41.7% and 43.8% of cases, respectively). Bone deformations were more frequent in vitamin children with D deficiency, with a significant inverse correlation between vitamin D levels and clinical bone manifestations. Serum alkaline phosphatase and parathormone levels were significantly higher in children with vitamin D deficiency and insufficiency ($p < 0.05$, $p < 0.001$), with inverse correlations between vitamin D and these markers.
Conclusion: Children with celiac disease living in a region with increased sun light exposure showed a high prevalence of vitamin D deficiency. In our study, vitamin D deficiency in patients with celiac disease was associated with more severe clinical manifestations.

KEYWORDS

celiac disease, children, vitamin d deficiency, parathormone, alkaline phosphatase, calcium, insolation

1 Introduction

Celiac disease (CeD) is a disorder caused by gluten intake in genetically predisposed individuals and characterized by atrophic enteropathy, which may present with a spectrum of both gastrointestinal and extraintestinal symptoms (1). It has been found to occur in approximately 1% of the population, and while it was previously identified more frequently in Europeans; studies in recent years have demonstrated a similar prevalence in Asians (2, 3). Our studies in 2021–2022 found that the incidence of CeD is 5.3% in at-risk groups (4).

Vitamin D is an essential micronutrient involved in the regulation of calcium homeostasis and bone metabolism. Deficiency of vitamin D during early childhood has been implicated in the development of various autoimmune disorders, including celiac disease. Vitamin D may also be a potential protective factor for CeD due to its role in the regulation of the immune system (5, 6). Vitamin D status plays an important role in the pathogenesis of intestinal diseases characterized by malabsorption and maldigestion syndromes, particularly because vitamin D is primarily absorbed in the duodenum and jejunum in the presence of bile acids (7–9).

There are conflicting data in the literature on the incidence of vitamin D deficiency in children with CeD. However, most studies have reported low vitamin D values in Turkey, the Russian Federation, and Iran (10, 11). Although vitamin D is often referred to as the "sunshine vitamin" a deficiency has been documented in many Asian countries, including China and India (12). As demonstrated in our previous studies, despite the fact that Uzbekistan has more than 300 sunny days per year, normal serum vitamin D levels were observed in only 18% of children even during the summer months (13, 14).

Taking into account that in Uzbekistan at the same time CeD is characterized by the predominance of severe forms with intestinal manifestations (4), the aim of the study was to determine the status of vitamin D in children with newly diagnosed celiac disease and to evaluate the impact of the degree of vitamin D deficiency on the clinical and laboratory manifestations of the disease.

2 Methods

2.1 Study design

This is cross-sectional study investigating status vimain D in children new diagnosed CeD, who were refered to the Gastroenterology department of the Republican Specialized Scientific and Practical Medical Center of Pediatrics of the Ministry of Health of the Republic of Uzbekistan during the period from Septeber 2016 till Desember 2017 year. None of the children had a history of vitamin D supplementation or any comorbid conditions that could have contributed to vitamin D deficiency or insufficiency (such as bone deformations or parathyroid gland diseases).

Children presenting with gastrointestinal symptoms indicative of celiac disease, who were referred to the Department of Pediatric Gastroenterology from community clinics or peripheral hospitals, were assessed based on the 2012 diagnostic guidelines of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (15). The study excluded participants who: (i) had a confirmed diagnosis of CeD prior to referral; (ii) were following a gluten-free diet at the time of enrollment; or (iii) did not provide informed consent to participate.

The study was carried out in accordance with international ethical standards and received approval from the Ethics Committee of the Republican Specialized Scientific-Practical Medical Center of Pediatrics (RSSPMCP) (approval number IP-2016, dated May 17, 2016). Written informed consent was obtained from the legal guardians of all participants, and the study complied with the principles of the Declaration of Helsinki. The physical development of children was assessed using reference tables of anthropometric indicators proposed by experts from the World Health Organization, using the WHO Anthro, WHO AnthroPlus programs (16).

2.3 Diagnostic work-up

For symptomatic children, the no-biopsy diagnostic pathway—applicable when anti-tissue transglutaminase IgA (anti-tTG IgA) levels exceeded 10 times the upper limit of normal and endomysial antibodies (EMA IgA) were positive in a second serum sample—was considered (11). However, due to the unavailability of EMA IgA testing in our country, all children with positive anti-tTG IgA results were advised to undergo esophagogastroduodenoscopy (EGDS) with histological examination of the duodenal mucosa.

Consequently, CD diagnosis was based on positive serologic findings (anti-tTG IgA) in combination with Marsh grade 2 or higher histopathological changes. In IgA-deficient individuals, anti-tTG IgG was measured, and a diagnosis was confirmed if histologic findings were consistent with CD. All patients diagnosed through this diagnostic process were also genotyped for HLA-DQ2 and DQ8.

Total serum IgA was quantified using a two-step sandwich ELISA with monoclonal anti-IgA antibodies (Cat. No. A-8666, Vector-BEST, Novosibirsk, Russia). In cases of reduced IgA levels, total IgG and anti-tTG IgG were also measured. Total IgG was assessed with a similar sandwich ELISA kit using monoclonal antibodies (Cat. No. A-8662, Vector-BEST, Novosibirsk, Russia). Quantitative determination of anti-tTG IgA (or anti-tTG IgG, when applicable) was performed using ELISA kits from Orgentec Diagnostika GmbH (Cat. No. 416-5400A, ORG 540G, Mainz, Germany).

HLA genotyping was conducted using sequence-specific primer polymerase chain reaction (SSP-PCR) with DQ kits targeting DQA1*05, DQB1*02, DQA1*0301, DQB1*0302, DQA1*0505, and DQB1*0202* alleles to detect DQ2.5, DQ2.2, and DQ8 haplotypes (Celiacstrip HLA DQ2DQ8, OPERON, Inmuno and Molecular Diagnostics, Caparoca, Spain).

25(OH)D and parathyroid hormone (PTH) in the serum were determined by the ELISA method on the Elecsys apparatus (Switzerland). Total and ionized calcium, inorganic phosphorus and alkaline phosphatase (ALP) were determined biochemically. The results were assessed in accordance with the recommendations of the International Society of Endocrinologists (2011): vitamin D deficiency—less than 20 ng/ml (less than 50 nmol/L); vitamin D insufficiency—21–29 ng/ml (51–75 nmol/L); normal vitamin D content—30–100 ng/ml (76–250 nmol/L).

A concentration below 10 ng/ml (less than 25 nmol/L) is interpreted as severe vitamin D deficiency. A level above 100 ng/ml (more than 250 nmol/L) is considered as excess vitamin D (17). The control group consisted of 31 children aged 3–15 years (mean age: 7 ± 2.1 years) who had not received vitamin D supplementation. The group included 14 boys and 17 girls.

Histological evaluation of duodenal mucosal changes was conducted by experienced histopathologists using the Marsh–Oberhuber classification system. According to this grading, Marsh–Oberhuber grade 2 is characterized by an increased number of intraepithelial lymphocytes along with crypt hyperplasia. Marsh–Oberhuber grade 3 (subtypes a, b, and c) indicates partial, subtotal, or total villous atrophy, respectively, in combination with intraepithelial lymphocyte infiltration and crypt hyperplasia.

2.4 Statistical analysis

Statistical analysis was carried out using Microsoft Excel with built-in statistical tools and STATISTICA 10.0 software [StatSoft, Inc. (2011)]. Methods of descriptive and inferential statistics were employed. This included calculation of relative frequencies (percentage, %), measures of central tendency and dispersion (arithmetic mean [M], standard deviation [σ], and standard error [m], and comparison of means using Student's t-test (t). A p-value of ≤ 0.05 was considered statistically significant. Correlations between variables were analyzed using Pearson's correlation coefficient. Descriptive statistics are presented as absolute numbers and percentages (%).

The sample size was not calculated preliminarily, a continuous study of children who came to our center with the first established CeD was carried out. Studies were carried out with the written consent of their parents.

Missing data were handled using the Complete Case Analysis method, in which rows/columns containing gaps were excluded from the data set. Statistical analysis was performed using GraphPad Prism (version 9.3.1, 2021). Descriptive statistics included the calculation of the mean (M), standard deviation (SD), median (Me), and interquartile range (Q1; Q3). The Kolmogorov–Smirnov test was used to evaluate the normality of data distribution. Group comparisons were conducted using either Student's t-test for normally distributed variables or the Mann–Whitney U-test for non-normally distributed data.

For measuring the strength and direction of the relationship between two variables Pearson's correlation coefficient was used. Categorical variables were expressed as absolute and relative values. 95% CI for the proportion was calculated using the Wald normal approximation method. The differences were considered statistically significant at $p < 0.05$, the calculation was made by the two-sided p-value.

3 Results

3.1 Study population: clinical features in children with celiac disease depending on vitamin D status

During the study period, celiac disease was diagnosed in 69 children who came to our centre, of whom 9 refused the study, therefore, the study population consisted of 60 children (age range: 1–16 years, 60 children with celiac disease aged from 1 year to 16 years were examined, the average age was 6 ± 2.3 y including 36 boys and 24 girls. According to the distribution of the decrease in vitamin D: deficiency was detected in 48 (80%) patients with CeD, and in every fourth patient (15/25%) extremely low levels were established (below 10 ng/ml). Insufficient vitamin D content was detected in 12 patients with CeD (20%) ($p < 0.05$) (Table 1).

Comparison of clinical manifestations in children with CeD depending on the deficiency and insufficiency of vitamin D demonstrated the severity of bone deformations and metabolic disorders in group with vitamin D deficiency compared to insufficiency: bone pain, dull hair, dry skin, hair loss (Table 2).

3.2 Nutritional status children with CeD depending vitaaamin D levels

When studying anthropometric data depending on vitamin D deficiency and insufficiency, we found that with its deficiency, every third patient with CeD suffered from severe weight deficiency, growth retardation of more than 3 SD was established in 41.7 ± 7.1% of cases. Whereas with insufficiency, these indicators were 8.3 ± 10.8% and 16.7 ± 10.8%, respectively (Table 3).

TABLE 1 Vitamin D levels in the examined children.

Groups	Vitamin D3, ng/ml
CeD ($n = 60$)	14.8 ± 1.04***
Control ($n = 31$)	45.1 ± 8.04

Reliability of data for the control group: *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

TABLE 2 Clinical features in children with celiac disease depending on vitamin D status ($n = 60$).

Symptoms	Vitamin D deficiency ($n = 48$)		Vitamin D insufficiency ($n = 12$)	
	Abs.	%	Abs.	%
PEI:				
Mild	6	12.5 ± 4.8	2	16.7 ± 2.3
Moderate	16	33.3 ± 6.8	1	8.3 ± 7.8*
Severe	5	10.4 ± 4.4	0	0.0 ± 0.0*
Bone pain	40	83.3 ± 5.4	4	33.3 ± 13.6*
Dental caries	30	62.5 ± 6.9	6	50.0 ± 14.4
Dental deformity	47	97.9 ± 2.1	5	41.7 ± 14.2*
Dull hair	46	95.8 ± 2.9	7	58.3 ± 14.2*
Hair loss	45	93.8 ± 3.5	5	41.7 ± 14.2*
Muscle hypotonia	46	95.8 ± 2.9	5	41,7 ± 14,2*
Dry skin	45	93.8 ± 3.9	5	41.7 ± 14.2*
Lethargy	44	91.7 ± 3.5	8	66.7 ± 13.6
Weakness	43	89.6 ± 4.4	9	75.0 ± 12.5
Adynamia	17	35.4 ± 6.9	3	25.0 ± 12.5
Sweating	48	100.0 ± 0.0	12	100.0 ± 0.0
Tachycardia	31	64.6 ± 6.9	5	41.7 ± 14.2

*Reliability of data between indicators for vitamin D deficiency and insufficiency ($P < 0.05$).

3.3 Results of studies of calcium, phosphorus, parathyroid hormone (PTH) and alkaline phosphatase (ALP) in the blood serum of children with celiac disease

The results of studies of calcium-phosphorus metabolism and its regulators demonstrated a relationship between the level of vitamin D deficiency and a deficiency of total and ionized calcium, phosphorus in patients with CeD, as well as an increase in alkaline phosphatase and parathyroid hormone in patients with CeD. An increased level of parathyroid hormone (PTH) was observed among patients with CeD, exceeding the values of the control group by 3.2 times ($p < 0.001$). Thus, the alkaline phosphatase (ALP) indicators were increased by 2.3 times with vitamin D deficiency and by 1.2 times with insufficiency; parathyroid hormone—by 3.2 times with vitamin D deficiency and by 2.6 times with vitamin D insufficiency ($p < 0.05$, $p < 0.001$) (Table 4).

A reliable significant difference in the levels of total, ionized calcium and phosphorus was also established in vitamin D deficiency compared to its insufficiency. Analysis of the correlation relationship between vitamin D concentration and biochemical parameters characterizing phosphorus-calcium metabolism and the level of parathyroid hormone showed that in CeD, an inverse correlation was found between vitamin D content and the level of alkaline phosphatase (respectively r = −0.710 and r = −0.623, r = −0.589) and parathyroid hormone (respectively r = −0.610 and r = −0.659, r = −0.623) (Table 5).

TABLE 5 Correlation indicators of the blood concentration of vitamin D3 with the concentration of parathyroid hormone, calcium, phosphorus and alkaline phosphatase.

Pathology	PTH	Calcium	Phosphorus	ALP
Celiac disease	−0.610	0.106	−0.365	−0.710

4 Discussion

Our studies have demonstrated a profound deficiency of vitamin D in children with CeD in the active phase of the disease (14.8 ± 1.04 ng/ml), in parallel with increased levels of parathyroid hormone and alkaline phosphatase, and reduced concentrations of calcium and phosphorus in the blood serum. The results of our studies were similar to those of Turkish researchers (10), who reported that the average serum 25(OH)D level in children and adolescents with CeD was 18.5 ng/ml, based on a large sample of patients ($n = 6,717$).

The results of a meta-analysis also confirmed that vitamin D levels in pediatric patients with CeD were lower than in healthy individuals (18). It was found that patients with CeD from South Asia had a significantly higher prevalence of vitamin D deficiency compared to Caucasian patients (70.8% vs. 32.8%, $p = 0.002$) (19).

According to van der Mei et al. (20), in the absence of vitamin D supplementation, vitamin D status is largely determined by endogenous synthesis, which is affected by skin pigmentation—a relevant factor for children in us.

As we have previously noted, the determination of vitamin D levels in healthy children in our Republic during the summer season demonstrated a high percentage of insufficiency and deficiency (82%) (13). Our data are close to the findings of Hataikarn Nimitphong and Michael F. Holick (21), who reported that vitamin D deficiency reached about 70% in South Asia and varied from 6% to 70% in Southeast Asia.

Most of Brazil's territory lies in the tropical zone, and only its southernmost part lies in the subtropical zone. This geographic location results in high solar radiation. A study of 599 children and adolescents aged 6–19 years found that 62 (10.4%) had vitamin D deficiency, 257 (42.9%) had insufficiency, and 280 (46.7%) had sufficient levels. Thus, suboptimal serum vitamin D levels (<30 ng/ml) were found in 53.3% ($n = 319$) of participants (22).

For many years, it was assumed that living in regions with abundant sunlight guaranteed sufficient vitamin D levels.

TABLE 3 Length/height and weight indicators in children with bowel diseases depending on vitamin D levels.

Vitamin D level	Short stature and growth retardation, SD				Underweight and low body weight, SD			
	−2SD-3SD		Lower −3SD		−2SD-−3SD		Lower −3SD	
	abs.	%	abs.	%	abs.	%	abs.	%
Deficiency								
CeD, $n = 48$	21	43.8 ± 7.2	20	41.7 ± 7.1	16	33.3 ± 6.8	14	29.2 ± 6.7
Insufficiency								
CeD, $n = 12$	3	25.0 ± 12.5	2	16.7 ± 10.8	2	16.7 ± 10.8	1	8.3 ± 7.9

TABLE 4 Biochemical parameters in children with celiac disease depending on vitamin D levels.

Vitamin D level	Ca	Ionized Ca	ALP	Phosphorus	PTH
Control group $n = 31$	2.35 ± 0.08	1.2 ± 0.04	95.5 ± 1.4	1.48 ± 0.05	9.1 ± 0.5
Deficiency, $n = 92$					
CeD, $n = 48$	2 ± 0.04**	0.96 ± 0.07**	219.5 ± 2.9***	0.98 ± 0.05***	29.3 ± 1.9***
Insufficiency, $n = 65$					
CeD, $n = 12$	2.2 ± 0.03^^	1.1 ± 0.02*^	179.1 ± 2.9**^^	1.13 ± 0.02***^	24.6 ± 3.2***^

Reliability of indicators to the norm (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$). Reliability of data between indicators for vitamin D deficiency and insufficiency (^$P < 0.05$; ^^$P < 0.01$).

However, accumulating evidence indicates that vitamin D insufficiency remains a commonly underestimated health concern, even in sunny countries.

Previous studies have shown that the level of vitamin D in the group of patients with CeD negatively correlates with the severity of symptoms, that is, the lower the level of vitamin D, the more severe the symptoms in patients with CeD (23). Our own findings align with this, demonstrating that children with vitamin D deficiency tend to have lower weight and height, along with more frequent metabolic and bone manifestations.

In previous retrospective studies conducted with a limited number of cases, the incidence of vitamin D deficiency in patients with CeD ranged from 27% to 70% (24, 25, 26). Several studies have reported conflicting results regarding the serum 25(OH)D levels at the time of CeD diagnosis (27, 28, 29). Ahlawat et al. (29) reported that there was no difference between 25(OH)D levels in patients newly diagnosed with CeD and controls. Similarly, Villanueva et al. (30) reported that vitamin D levels in patients with CeD were not different from controls. Lerner et al. (31) compared vitamin D levels in patients newly diagnosed with CeD and found no differences. In contrast, in the study by Lionetti et al. (32), vitamin D levels in children and adolescents with CeD were lower at the time of diagnosis compared to controls. Vitamin D deficiency is thought to be associated with decreased expression of the vitamin D receptor and epithelial barrier proteins E-cadherin and claudin-2, which play an important role in children with CeD in correlation with histological indicators of disease severity (33).

Malaguarnera's findings further supported the role of vitamin D in intestinal homeostasis, indicating that on the role of vitamin D in maintaining intestinal homeostasis through local synthesis of 1α,25(OH)2D3 and expression of Vitamin D Receptor, emphasizing the critical importance of optimal $1\alpha,25(OH)_2D_3$ levels, as this active form of vitamin D is involved in a range of regulatory processes, including not only calcium absorption, but also immune defense, preservation of epithelial barrier integrity, and modulation of the intestinal microbiota. This role is receiving increased attention, since an unbalanced microbiota may be associated with a number of negative health disorders, such as inflammation, allergic reactions, autoimmune diseases, heart disease, obesity and metabolic syndrome (34). The potential positive role of vitamin D on dendritic cells has been recently highlighted, demonstrating a close relationship between suboptimal vitamin D levels and the occurrence and progression of many autoimmune diseases (35).

As we mentioned, the time of year has a certain significance for vitamin D indicators, since when determining the values of vitamin D in the blood serum of conditionally healthy children, higher values were found in the summer (36). It is important to acknowledge the limitations of our study, particularly the relatively small sample size, which was primarily due to financial constraints. The study was conducted over the course of one year, and we did not analyze seasonal changes in serum vitamin D levels in children with CeD, due to the lack of statistically significant differences across seasons. Our previous studies showed that in summer, normal vitamin D levels were observed in only 18% of healthy children, while 17% had vitamin D deficiency and 65% had insufficiency (13). Also one limitation of our study is the use of data collected between 2016 and 2017. Although these data were obtained several years ago, they still provide relevant insights into the clinical and nutritional status of children with celiac disease prior to the implementation of updated diagnostic and therapeutic standards. The temporal gap is acknowledged and was considered in the interpretation of results.

5 Conclusions

A high proportion of children with celiac disease in a region with increased insolation were found to have vitamin D deficiency, along with altered biochemical parameters, including increased parathyroid hormone and alkaline phosphatase levels and decreased total and ionized calcium and phosphorus. In our study, vitamin D deficiency in children with celiac disease was associated with markers of increased disease severity, including metabolic bone abnormalities and lower physical development scores.

Considering the association observed between lower vitamin D levels and the severity of clinical symptoms in children with celiac disease, it may be advisable to assess vitamin D status in children residing in regions with high sunlight exposure and to consider differentiated correction strategies based on individual needs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the ethical committee of the RSSPMCP (Republican Specialized Scientific-Practical Medical Center of Pediatrics, approval no. IP-2016, 17 May 2016). Informed written consent was obtained from children's guardians. The research was conducted in compliance with the Declaration of Helsinki. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AK: Writing – original draft, Resources, Conceptualization, Supervision, Writing – review & editing. NA: Conceptualization, Software, Resources, Funding acquisition, Investigation, Visualization, Methodology, Project administration, Validation, Formal analysis, Writing – original draft, Supervision, Data curation. DA: Supervision,

Conceptualization, Writing – review & editing. BA: Investigation, Writing – review & editing, Data curation, Formal analysis.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Investigation of the frequency of molar incisor hypomineralisation in childhood celiac disease and evaluation with nutritional factors and calcium metabolism

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Background: The relationship between celiac disease and developmental enamel defects is complex and multifaceted. Although the presence of enamel changes in individuals with celiac disease is well documented, the exact etiology of these changes remains unclear. This study aims to investigate whether the enamel defects observed in children with celiac disease are due to malabsorption-related deficiencies or are a direct consequence of the autoimmune nature of celiac disease, thus informing the development of effective preventive strategies.

Materials and methods: This case-control clinical study included 150 children aged 3–18 years who were followed with a diagnosis of celiac disease, and 151 healthy controls with negative celiac serology, all evaluated at the Pediatric Gastroenterology Clinic between September 2023 and January 2025. The diagnosis of molar-incisor hypomineralization (MIH) was made based on the clinical criteria established by the European Academy of Paediatric Dentistry.

Results: Celiac disease diagnosis was confirmed through positive tissue transglutaminase IgA and anti-endomysial IgA antibodies, along with histopathological findings from upper gastrointestinal endoscopy. Among the celiac patients, 36.6% were newly diagnosed, 37.3% were compliant with a gluten-free diet, and 27% were non-compliant. Molar-incisor hypomineralization (MIH) was observed in 20.7% of the children with celiac disease, compared to 6% in the healthy control group. The likelihood of MIH occurrence in children with celiac disease was found to be 8.97 times greater than in healthy controls. MIH was most prevalent among newly diagnosed and non-compliant children with celiac disease, who also exhibited significantly lower vitamin D levels and elevated tissue transglutaminase values. However, there was no significant correlation between MIH prevalence and Marsh classification of intestinal damage.

Conclusion: MIH serves as a critical indicator of celiac disease, emphasizing the need for vigilant monitoring of vitamin D levels and dietary adherence to mitigate the development of MIH in affected individuals.

KEYWORDS

celiac disease, molar incisor hypomineralisation (MIH), vitamin D, calcium metabolism, children

Introduction

Celiac Disease (CD) is an autoimmune disease that occurs in genetically predisposed individuals after exposure to gluten for at least 6–8 months. As a result of this autoimmunity, the absorption of essential nutrients is impaired by causing histopathological damage to the small intestinal mucosa, leading to malabsorption with crypt hyperplasia, villous atrophy and inflammatory infiltration in the adjacent connective tissue, and this condition manifests clinically as diarrhoea, weight loss, fatigue, anaemia and growth retardation in children. Celiac disease is a multisystem disease. In addition to the intestines, it also affects other systems such as the heart, brain, skeleton, reproductive system, hormonal system, oral mucosa, skin and tooth enamel. Diagnosis is usually made by serological testing for specific antibodies such as anti-tissue transglutaminase and anti-endomysial antibodies, followed by a confirmatory intestinal biopsy. The basis of management is a strict lifelong gluten-free diet, which can lead to improvement of symptoms, normalisation of antibody levels and healing of the intestinal mucosa (1).

The effects of celiac disease on dental health were first observed systematically in the 1970s. Studies have gradually increased after the 2000s and Developmental Enamel Defects (DDE)s have started to be defined. Enamel defects such as pitting, grooving and discolouration have been reported in individuals with CD and have been identified as potential oral markers for this condition (2–4). Factors contributing to DDE's include immune dysregulation, nutritional disorders and genetic factors (5).

Developmental defects of enamel (DDEs) are encountered daily in clinical practice. Epidemiological data reflecting an increasing trend of this condition, with DDE prevalence in permanent dentition ranging from 10% to 49%, should be considered a public health problem and a challenge for dental practitioners (6).DDE can have a significant impact on oral health and aesthetics, tooth sensitivity and altered occlusal function (7, 8). Enamel defects are also risk conditions for dental caries and erosion in children (9, 10).

A 2015 study analysed 39 teeth from 30 children aged 13–19 using a calibrated reflectance spectrophotometer. The clinical visibility of enamel developmental defects (DDEs) is closely related to their location and optical integration with the surrounding enamel. Defects in the incisal area are more noticeable due to greater contrast in optical properties, while those in the cervical region are less perceptible. Loss of surface gloss and the presence of demarcated opacities can obscure tertiary anatomical features. Spectrophotometric analysis objectively quantifies these differences using CIE L*, a*, and b* values. Greater divergence from the optical properties of healthy enamel increases defect visibility, highlighting the importance of both localization and color contrast in clinical assessment (11).

The most commonly affected teeth are considered to be incisors and molars (5). In a meta-analysis published in 2018, a high prevalence of developmental enamel defects (DDE) was reported among individuals with celiac disease. Notably, a significant correlation was found specifically in patients undergoing primary dentition (12). Other differential diagnoses of DDE include enamel hypoplasia, fluorosis, amelogenesis imperfecta and localised trauma/infection (13, 14). Several studies have shown a high incidence of DDE in children with celiac disease, suggesting a correlation with the extent of intestinal lesions (13).

Molar incisor hypomineralization (MIH) is classified within the broader category of Developmental Defects of Enamel (DDE) and is recognized as a distinct dental phenotype with a potential association to systemic disorders such as celiac disease.

Mazur et al. reviewed the relationship between early life nutrition and the development of molar incisor hypomineralization (MIH), emphasizing that nutritional factors during pregnancy and early childhood may affect the risk of MIH, and drawing attention to appropriate maternal and infant nutrition. In addition, the study emphasizes that systemic diseases such as celiac disease may be involved in the etiology of MIH by causing nutritional deficiencies (such as calcium, vitamin D, and other minerals) that impair enamel mineralization and potentially contribute to the formation of MIH, and emphasizes the need for awareness and further research (15).

Recent systematic reviews and meta-analyses have demonstrated that children with Molar-Incisor Hypomineralization (MIH) are at a higher risk of developing dental caries compared to unaffected peers. The compromised enamel in MIH-affected teeth facilitates bacterial invasion and acid demineralization, leading to increased caries prevalence. This underscores the importance of early detection and targeted preventive interventions for children with MIH to mitigate their elevated caries risk (16).

The mechanisms underlying the formation of developmental enamel defects are hypothesized to involve hypocalcemia consequent to celiac disease, genetic predispositions such as specific HLA alleles, or autoimmune reactions (e.g., anti-amelogenin antibodies or IFN-γ/Stat-1 mediated effects) occurring during odontogenesis; however, the relationship remains debated and the precise triggers are not yet fully understood (17–20).

Studies suggested that gluten had a direct effect on enamel development and implied consequences for the mineralization process (21). The relationship between celiac disease and developmental enamel defects was complex and multifaceted. While the presence of enamel alterations in individuals with celiac disease was a well-documented fact, the exact etiology of these changes remained unclear (5, 12, 20, 21). This study aims to investigate whether the enamel defects observed in children with celiac disease result from malabsorption-related deficiencies of calcium, phosphorus, and vitamin D, or if they arise due to the autoimmune nature of celiac disease itself. Such investigations could enhance our understanding of the detrimental effects of celiac disease on dental health and contribute to the development of effective preventative strategies.

Materials and methods

Study design

This single-center, non-blinded, prospective case-control study was conducted at the Pediatric Gastroenterology Clinic of Ankara

Etlik City Hospital, University of Health Sciences, between September 2023 and January 2025.

Participants

A total of 150 children aged 3–18 years with celiac disease (CD) were included. Participants were either newly diagnosed or previously diagnosed based on positive tissue transglutaminase IgA and anti-endomysial IgA antibody tests, confirmed by small intestinal biopsy findings in accordance with the Marsh-Oberhuber classification:Marsh 1: Normal mucosa (low probability of CD), Marsh 2: Hyperplastic lesions (possible CD), Marsh 3: Destructive lesions (indicative of active, untreated CD).

CD patients were categorized into three subgroups:

- Newly diagnosed
- Diet-compliant (adhering to a gluten-free diet)
- Diet-noncompliant (not adhering to a gluten-free diet)

The control group comprised 151 healthy children matched for age and sex, who presented to the general pediatric outpatient clinic for routine well-child checkups or non-inflammatory conditions such as constipation, irritable bowel syndrome, or functional abdominal pain. All control subjects had negative celiac serology.

Sample size and power analysis

Sample size determination was conducted using G*Power version 3.1.9.7. For comparisons between the CD group ($n = 150$) and the control group ($n = 151$), a two-tailed independent samples *t*-test was assumed. With an expected medium effect size (Cohen's d = 0.5), $\alpha = 0.05$, the *post hoc* power analysis showed a statistical power of 98.9%, indicating adequate power to detect medium differences.

A second *post hoc* analysis was performed for comparisons among the three CD subgroups using one-way ANOVA. Assuming a medium effect size (Cohen's f = 0.25), $\alpha = 0.05$, and a total of 150 participants, the achieved power was 86.2%, indicating sufficient sensitivity to detect moderate subgroup differences.

Exclusion criteria

The following exclusion criteria were applied:

Presence of dental fluorosis
Undergoing fixed orthodontic treatment

Developmental Enamel Defects (DDEs) attributed to systemic conditions other than CD, including:

Respiratory disorders
Early childhood infectious diseases
Type 1 Diabetes
Genetic syndromes (e.g., Down syndrome, Turner syndrome)
History of premature birth
Use of any medications at the time of clinical assessment

Oral and laboratory examinations

All participants underwent an oral examination by a single calibrated pediatric dentist. Examinations were conducted with a mouth mirror and blunt dental probe under artificial lighting in the Pedodontics Clinic, with the patient seated in a dental chair.

The diagnosis of Molar Incisor Hypomineralization (MIH) followed the European Academy of Paediatric Dentistry (EAPD) criteria (6). MIH was recorded when at least one first permanent molar displayed one or more of the following:

Demarcated opacities
Atypical restorations
Post-eruptive enamel breakdown (PEB)
Extraction due to MIH-related complications

Laboratory data including serum calcium, phosphorus, magnesium, vitamin D, and parathyroid hormone (PTH) levels were obtained from routine follow-up records.

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 23.0.Descriptive data were presented as mean ± standard deviation, median (interquartile range), or frequency (percentage) as appropriate.Comparisons were made using:Chi-square test or Fisher's exact test for categorical variables, Student's t-test or Mann–Whitney *U* test for continuous variables,For comparisons across Marsh types, the Kruskal–Wallis test was applied. A *P*-value < 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Ethics Committee of Etlik City Hospital, Ankara (Approval No: AESH-EK1-2023-363, Date: 09/06/2023). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and its amendments. Informed written consent was obtained from all participants and/or their legal guardians prior to inclusion in the study.

Results

Demographic data

The mean age of 150 (102 girls/48 boys) patients in the celiac patient group was 9.76 ± 4.03 years (range 3–18 years); the mean age of 151 (78 girls/73 boys) patients in the control group was 11.59 ± 3.93 years. There was a significant difference between the two groups in terms of gender. ($p < 0.05$).

The rate of MIH in children with celiac disease was 20.7%, while this rate was 6% in the healthy control group (<0.001) (Table 1). In addition, our study found that celiac disease increased the probability of MIH by 8.9 times (95% Confidence Interval 8.976 ± 1.882). The location of enamel defects in permanent and primary teeth was more pronounced in the

TABLE 1 MIH positivity rates in children with celiac disease group and control group.

	Children with celiac disease group (n = 150) n (%)	Control group (n = 151) n (%)	p
MIH (+)	31 (20.7%)	9 (6.0%)	<0.001
MIH(−)	119 (79.3%)	142 (94.0%)	

TABLE 2 Laboratory findings in children with celiac disease group and control group.

	Children with celiac disease group (n = 150) n (%)	Control group (n = 151) n (%)	p
Vitamin D (20–40 ng/ml)	17.82 ± 7.72	19.23 ± 6.60	**0.024****
Calcium (8.8–10.8 mg/dl)	9.47 ± 1.02	10.41 ± 7.69	0.217
Phosphorus (4.5–5.5 mg/dl)	4.68 ± 0.83	4.56 ± 80.75	0.804
Magnesium (1.6–2.6 mg/dl)	2.52 ± 3.32	2.51 ± **0.31**	0.529
Parathyroid hormone (11.3–60 pg/ml)	45.56 ± 67.31	34.99 ± 12.8	**0.035****

Data are presented as mean ± standard deviation (SD). Comparisons between groups were performed using the independent samples t-test. A p-value of <0.05 was considered statistically significant. Statistically significant values are indicated in bold (**).

anterior teeth, and the coronal distribution included the incisors and the central parts of the teeth.

There was a significant difference between the children with celiac disease group and the control group in terms of the mean magnesium, parathyroid hormone and vitamin D levels measured in routine controls of all these patients (Table 2).

In the celiac patient group, there were 55 patients diagnosed for the first time (36.7%), 56 patients compliant with the diet for the last year (37.3%) and 39 patients not compliant with the diet for the last year (26%). The MIH incidence rates of these patients, the mean tissue TGA levels, calcium, phosphorus, magnesium, parathyroid hormone and vitamin D levels measured in routine controls are given in Table 3.

Vitamin D levels were significantly lower in the diet-adherent cases than in the other two groups. Vitamin D levels were significantly lower in patients with MIH than in those without. At the same time, tissue transglutaminase (tTG IgA) levels were significantly higher in patients with MIH than in those without (Table 4).

According to the Marsh Classification, which is the Pathological Classification of Children with celiac disease, no statistical difference was found between the rates of MIH (Table 5).

Table 5 shows that while the MIH rate was higher in type 3c (Marsh classification), the difference was not statistically significant ($p > 0.05$).

Discussion

Molar incisor hypomineralization (MIH) is a significant health problem that can affect the child's quality of life by negatively affecting their esthetics and function.

Regarding aetiology, perinatal hypoxia, prematurity and other hypoxia related perinatal problems, including caesarean section, appear to increase the risk of having MIH, while certain infant and childhood illnesses are also linked with MIH (22). In addition, genetic predisposition and the role of epigenetic influences are becoming clearer following twin studies and genome and single-nucleotide polymorphisms analyses in patients and families. Missing genetic information might be the final key to truly understand MIH aetiology (22).

In recent years, the worldwide prevalence of MIH has been reported to be between 2.9% and 44% (23, 24). In our study, the prevalence of MIH in the healthy control group was 6%.

The prevalence of celiac disease has been increasing in recent years (25). Therefore, many clinical manifestations of celiac disease are becoming more prominent. The prevalence of MIH was 61% in Çiğdem Elbek-Çubukçu's study (26), 66.9% in Ahmed A's study (14), 42.2% in Avşar and Kalaycı's (27), 40% in Acar et al. (28), reported a higher prevalence of enamel defects in children with CD than in controls; and respectively. Kuklik's study (29) also aimed to analyse the incidence of MIH in

TABLE 3 Comparison of diet compliance with laboratory parameters and tissue TGA and MIH presence in children with celiac disease group.

Children with celiac disease group (n = 150)	New diagnosis (n = 55)	Diet compliant (n = 56)	Diet noncompliant (n = 39)	p
Vitamin D (20–40 ng/ml)	18.76 ± 8.47	18.72 ± 6.78	**15.20 ± 7.47**	**0.046****
Calcium (8.8–10.8 mg/dl)	9.64 ± 0.46	9.37 ± 1.46	9.37 ± 0.78	0.070
Phosphorus (4.5–5.5 mg/dl)	4.90 ± 0.67	4.06 ± 0.82	4.48 ± 0.99	0.151
Magnesium (1.6–2.6 mg/dl)	2.29 ± 1.16	3.17 ± 5.41	1.99 ± 0.37	0.052
Parathyroid hormone (11.3–60 pg/ml)	40.48 ± 20.74	47.94 ± 101.28	49.29 ± 51.34	0.240
tTG IgA (IU/ml)[a]	135.41 ± 75.99	13.64 ± 40.06	81.17 ± 74.87	<0.001**
MIH(n = 31)	17	6	8	0.029**

Data are presented as mean ± standard deviation (SD). Group comparisons were performed using one-way ANOVA for continuous variables and chi-square test for categorical variables (e.g., MIH prevalence). A p-value <0.05 was considered statistically significant. Statistically significant values are indicated in bold (**).
Vitamin D and tissue transglutaminase levels were significantly different in patients with MIH (+).
[a]Tissue transglutaminase(tTG IgA) (IU/ml): negative <12, border = 12–18, positve >18.

TABLE 4 Comparison of calcium metabolism parameters between celiac children with and without MIH.

	CD with MIH	CD without MIH	*p*
Vitamin D (20–40 ng/ml)	13.75 ± 6.97	17.84 ± 7.66	**0.008****
Calcium (8.8–10.8 mg/dl)	9.57 ± 0.55	9.44 ± 1.11	0.070
Phosphorus (4.5–5.5 mg/dl)	4.79 ± 0.58	4.66 ± 0.88	0.541
Magnesium (1.6–2.6 mg/dl)	2.32 ± 1.56	2.58 ± 3.67	0.978
Parathyroid hormone (11.3–60 pg/ml)	42.91 ± 32.59	46.29 ± 74.15	0.905
tTG IgA (IU/ml)[a]	114.80 ± 85.77	65.70 ± 79.51	**0.006****

CD, celiac disease; MIH, molar incisor hypomineralization; tTG IgA, tissue transglutaminase IgA. Data are presented as mean ± standard deviation (SD). Comparisons were made using the independent samples *t*-test. A *p*-value <0.05 was considered statistically significant. Statistically significant values are shown in bold (**).

[a]Tissue transglutaminase(tTG IgA) (IU/ml): negative <12, border = 12–18, positve >18.

patients with CD compared with the CG. Among participants with CD, 20 percent had MIH, while among those without the disease, only 5 percent showed the condition. This difference was statistically significant ($p = 0.044$), indicating an association between CD and the occurrence of MIH. Most of the defects in patients with CD consisted of demarcated opacities. In our study, similar to this study, 20% of the participants with CD had MIH, whereas only 6% of those without CD had MIH. Kuklik et al. reported that the probability of MIH in children with CD is 4.75 times Ahmed A. et al. 8.1 times; higher than in controls (14, 29). In our study, we found that the probability of MIH in children with celiac disease is 8.97 times higher than in healthy controls. According to our findings, the rate of MIH was found to be 20.7% in the celiac patient group.

A predominance of female participants in children with celiac disease group resulted in a significant sex distribution difference between the patient and control groups. This observation aligns with the findings of a comprehensive systematic review and meta-analysis by Jansson-Knodell et al., which demonstrated a 42% increased risk of undiagnosed celiac disease in females compared to males, potentially reflecting underlying immunological and hormonal factors as well as differences in healthcare utilization (30).

When the nutritional values of the celiac and control groups were compared, statistically significant lower values were observed in vitamin D and parathormone levels in the celiac group (Table 2). This was expected in our patient group which is a mixed group in terms of dietary compliance (31). Vitamin D levels were lower in paediatric patients with CD compared with healthy controls (32).

When we compared the nutritional values within the celiac group to better evaluate the low nutritional values in children with celiac disease, we observed that vitamin D was statistically significantly lower especially in diet-incompliant patients. In addition, the rate of MIH was higher in diet-incompliant patients 8/39 (20%) and in newly diagnosed patients 17/55 (30.9%) compared to diet-compliant patients 8/56 (14.2%). Poor intestinal absorption of some nutrients due to celiac disease is thought to cause enamel defects (32). In a 2017 study, it was observed that there was a significant relationship between the age of starting gluten-free diet and Molar Incisor Hypommineralisation (MIH) in children with celiac disease (5). With respect to MIH, results are conflicting (5). In a German study, a positive relationship between lower vitamin D (25(OH)D) levels and increased prevalence of MIH was determined (33); however, van der Tas and colleagues reported no link between vitamin D levels at 6 years of age with MIH or hypomineralized second primary molars(HSPM) in Dutch children (34). In a recent study, a link with higher levels of vitamin D and HSPM was reported; however, the authors stated that caution should be taken when interpreting the results as they could be influenced by unknown confounding factors (29). Furthermore, a 10 nmol/L increase in serum 25(OH)D concentrations was significantly associated with a lower likelihood of having MIH (OR = 0.89; $P = 0.006$). Moreover, higher 25(OH)D values were associated with fewer caries-affected permanent teeth (29).

The findings of Nørrisgaard et al.'s randomized clinical trial provide compelling evidence for the modulatory role of prenatal high-dose vitamin D supplementation in reducing the incidence of enamel defects, including Molar Incisor Hypomineralization (MIH), in offspring (35). Given the pivotal function of vitamin D in calcium homeostasis and amelogenesis, their results suggest that adequate maternal vitamin D status during critical periods of tooth development may mitigate hypomineralization processes (35). This aligns with the hypothesis that nutritional and metabolic factors during gestation exert a significant influence on enamel quality, potentially modulating susceptibility to MIH (35). Consequently, these findings underscore the importance of optimizing prenatal vitamin D levels as a preventive strategy against developmental enamel defects, warranting further investigation into the mechanistic pathways linking vitamin D metabolism and enamel biomineralization (35).

In our study, when the nutritional parameters of children with celiac disease with MIH were compared with those without MIH, low vitamin D levels as well as high tissue transglutaminase A levels were statistically significant. There was no study in the literature on this subject with a sufficient number of patients. In our study, the significant elevation of Tissue Transglutaminase A in MIH positive patients and the fact that the majority of MIH positive patients were newly diagnosed patients and non-compliant to diet indicate an increase in autoinflammation.

TABLE 5 Comparison of MIH patients with the Marsh classification for Celiac Disease.

	Marsh 2 (*n* = 51)	Marsh 3a (*n* = 35)	Marsh 3b (*n* = 38)	Marsh 3c (*n* = 26)	Total (*n* = 150)	*p*
Patients of MIH n (%)	9(%21.4)	5(%16.6)	8(%26.6)	9(%52.9)	31(%20.6)	0.240
Patients without MIH(−) n (%)	42(%78.6)	30(%83.4)	30(%73.4)	17(%47.1)	119(%79.4)	

MIH, molar incisor Hypomineralization.
Data are presented as number of patients and column percentage (%).
Statistical analysis was performed using the chi-square test.

Especially proinflammatory cytokines, parathyroid function abnormalities and mostly nuclear factor B receptor activator/nuclear factor B receptor activator-ligand/osteoprotegerin system disorders are thought to cause bone damage (36, 37).

Our results showed that there was no significant correlation between the MIH variable and Marsh types in children with celiac disease. Although the incidence of MIH is high in Marsh type 3c, no statistically significant difference was observed (Table 5). In another study conducted in our country including 62 children with celiac disease, there was also no significant correlation between MIH and Marsh classification. Only in children with Marsh 2 scores, a higher number of dental careers in permanent teeth was reported (26).

Conclusion

Our study is one of the studies with the highest number of cases in the literature. Celiac disease increases the incidence of MIH 8.9 times. In our study, the incidence of MIH was 6% in healthy children and 20.7% in children diagnosed with celiac disease. Vitamin D deficiency was low in all children with celiac disease, especially in diet non-compliant patients, but it was significantly low in children with celiac disease with MIH. These findings suggest that vitamin D deficiency due to malabsorption and unstoppable inflammation are important in the pathogenesis of MIH in celiac disease. MIH is an important indicator of celiac disease and attention should be paid to vitamin D levels and dietary compliance to prevent the development of MIH in patients with celiac disease.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by Ankara Etlik City Hospital AESH-EK1- 2023-363// 09/06/2023. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

AT: Conceptualization, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. NA: Data curation, Writing – original draft. FH: Conceptualization, Writing – original draft.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prevalence of acute reactions to gluten contamination of the diet in children with celiac disease

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Background and aim: The prevalence and clinical spectrum of symptoms due to inadvertent gluten exposure in children with celiac disease (CeD) on a gluten-free diet (GFD) are not well defined. This study aimed to assess these acute reactions through an online survey.
Methods: Parents of children with CeD treated with a GFD for at least 12 months completed an online questionnaire. The survey focused on symptoms occurring within 24 h of gluten-contaminated food ingestion.
Results: Data were collected for 296 children. Acute reactions after unintentional gluten ingestion were reported in 98 cases (33.1%). The most common symptoms were abdominal pain (57.1%), diarrhea (42.9%), vomiting (31.6%), headache (12.2%), and fatigue (14.3%). Less frequent symptoms included nausea, constipation, urticaria, aphthous stomatitis, and arthropathy (each ~5%–7%). In 86% of cases, symptoms appeared within 2–3 h. Gluten exposure most often occurred while dining out, especially in restaurants and school cafeterias.
Conclusions: One-third of children with CeD on a GFD experience acute reactions to accidental gluten ingestion. These reactions typically arise rapidly and are dominated by gastrointestinal symptoms, aligning with reports from existing literature, where vomiting and nausea have been observed in 3%–46% of patients at the time of CeD diagnosis and in 13%–61% during gluten challenge.

KEYWORDS

celiac disease, gluten-free diet, gluten exposure, gastrointestinal symptoms, gluten contamination

1 Introduction

Celiac disease (CeD) is an autoimmune enteropathy characterized by a chronic inflammatory response to the ingestion of gluten, a protein found in wheat, rye, and barley (1, 2). The disease can cause a wide variety of symptoms, both gastrointestinal and extraintestinal, and is estimated to affect approximately 1%–2% of the global population (3–5).

The treatment of CeD is a strict, lifelong gluten-free diet (GFD) which allows the intestinal mucosa to heal and prevents long-term complications of the disease (6, 7). However, some patients continue to report persistent symptoms despite following a GFD, often caused by gluten contamination into the diet (8).

Adhering to a GFD, which eliminates a common dietary staple across many countries, poses significant challenges and can negatively impact patients' psychosocial

well-being and quality of life, particularly during vulnerable periods like adolescence. The complete avoidance of gluten is difficult to achieve, as naturally gluten-free items like oats and lentils can be cross-contaminated during processing. Furthermore, gluten is a widely used ingredient added for its functional properties and can be found in unsuspected food products (9). Cross-sectional studies have found that up to 50% of individuals with CeD who follow a GFD report consuming gluten, either intentionally or unintentionally (10, 11). Incomplete adherence to a GFD is more prevalent among males, adolescents, and individuals with clinically silent CeD (12). This unintended gluten intake can trigger an immune response and the reappearance of gastrointestinal and other symptoms (13, 14). Symptoms of active CeD usually manifest gradually over weeks or months. However, after starting treatment with the GFD, acute reactions to gluten ingestion are frequently reported by patients. To date, the prevalence of symptomatic acute reactions following unintentional gluten ingestion while on a GFD has not been fully investigated, particularly in children.

The aim of this study was to assess the occurrence and characteristics of such symptoms through an online survey of a large cohort of patients with CeD.

2 Materials and methods

2.1 Study design

This is a cross-sectional study, with data collected through an online survey performed from March to July 2024 at a regional referral center for pediatric CeD (Ancona, Italy). Prior to participating in the survey, parents of children with CeD who had been followed for at least 1 year were provided comprehensive details about the study and required to give written informed consent. All respondents were informed about the study's objectives, data usage, privacy, anonymity, confidentiality, and the voluntary nature of their participation, including the right to withdraw. The survey took approximately 15 min to complete. Participants who reported experiencing symptoms were followed up by a trained dietitian to verify the accuracy of their responses. Individuals were classified as having a positive reaction if they met the following criteria: (a) consistent symptom patterns following gluten exposure on at least two separate occasions, (b) symptom onset within 24 h of consuming a gluten-containing meal, (c) complete resolution of symptoms within 72 h. The research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Marche, section AOU delle Marche (Ancona, Italy, ID 220059, approved 8th August 2023).

2.2 Survey participants

This online survey involved children/adolescents (age <18 years old) with a confirmed CeD diagnosis according to the ESPGHAN guidelines (15). Participants were asked about the occurrence of symptoms that manifested within 24 h following a documented incident of unintentional gluten consumption. The list of symptoms included abdominal pain, diarrhea, vomiting, headache, fatigue, nausea, constipation, urticaria, aphthous stomatitis and arthropathy. In symptomatic patients the timing, duration and severity of symptoms, as well as the setting in which the contamination occurred, were asked.

2.3 Statistical analysis

Descriptive statistics were used to summarize the data. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were reported as median and interquartile range (IQR) and compared using the Mann–Whitney *U* test. Statistical significance was defined as a p-value < 0.05. All analyses were performed using the R software (version 4.3.3).

3 Results

3.1 Study population

A total of 422 eligible patients were invited to participate in the study, and 296 of them completed the online survey (70%). Of these, 113 participants reported experiencing symptoms after gluten ingestion. However, following a structured follow-up with a trained dietitian to verify the timing, pattern, and resolution of symptoms, 15 participants did not fulfill the predefined criteria for a clear positive reaction to inadvertent gluten exposure. Ultimately, 98 participants (33.1%) (herein defined as "symptomatic") reported experiencing symptoms after consuming gluten-contaminated meals. Demographic and clinical characteristics of the study population are reported in Table 1.

Female participants were more likely to report experiencing symptoms (66%) after the ingestion of contaminating gluten. The group of patients who reported symptoms differed from the asymptomatic group in the timing of their CeD diagnosis and symptoms at diagnosis. No significant differences were found among different age groups.

3.2 Symptom profile

The most prevalent symptoms were abdominal pain (56/98, 57.1%), followed by diarrhea (42/98, 42.9%), vomiting (31/98, 31.6%), headache (12/98, 12.2%), fatigue (14/98, 14.2%), nausea (7/98, 7.1%), constipation (7/98, 7.1%), urticaria (7/98, 7.1%), aphthous stomatitis (5/98, 5.1%) and arthropathy (5/98, 5.1%). The majority (>90%) of patients who experienced adverse effects reported that the symptoms emerged within a brief timeframe of less than 3 h (Figure 1).

Among the symptomatic participants, 63% (95% CI: 47.55–76.79) reported experiencing the same symptoms they had prior

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TABLE 1 Comparative analysis of clinical and demographic features of symptomatic and asymptomatic celiac disease patients.

	Symptomatic (n = 98)	Symptomless (n = 198)	p value
Female, n (%)	65 (66%)	107 (54%)	**0.043**
Age, median (IQR), years	10 (7–12)	10 (7–13)	0.287
Age at diagnosis, median (IQR), years	5 (3–8)	7 (5–10)	**0.001**
Symptomatic at diagnosis, %	91%	74%	**0.026**
Diagnosis confirmation:			
Serology-based diagnosis (ESPGHAN guidelines) %	74%	68%	0.256
Biopsy-based %	26%	32%	
Age			
≤6 years (%)	25.5%	30.8%	0.327
7–12 (%)	52%	51.5%	0.930
13–18 (%)	22.5%	17.7%	0.344
Gluten ingestion to appearance of symptoms median lag time (IQR), minutes	60 (30–120)		

Bolded values indicate a statistically significant result (p-values <0.05).

to CeD diagnosis and the initiation of the GFD. The most frequently reported new symptoms were gastrointestinal, such as diarrhea (58.8%), abdominal pain (47.0%), and vomiting (35.3%). Notably, 13 of the 98 symptomatic patients (13.3%) had been completely asymptomatic before diagnosis, indicating that acute reactions may occur even in children without previous clinical manifestations of CeD.

3.3 Context of gluten exposure

The reported contamination incidents most frequently occurred in external dining settings, such as restaurants (46.2%), school cafeterias (26.9%), and during international travels (7.7%). Nonetheless, contamination events were not limited to external environments, as 19.2% of the cases occurred in the home setting. Further analysis of the types of foods implicated in these episodes revealed that contamination most often involved commonly consumed, high-risk items. In the majority of these episodes, the foods were believed by caregivers to be gluten-free at the time of consumption. Often, they were either purchased as labeled gluten-free products (e.g., certified gluten-free ice cream) or prepared in settings where caregivers had received assurances about gluten-free preparation, such as restaurants or social events. All of these food types were reported at similar frequencies (25%).

4 Discussion

This study highlights the high frequency of symptoms experienced by children with CeD on treatment with the GFD following unintentional gluten exposure, predominantly manifesting as gastrointestinal disturbances such as abdominal pain, diarrhea, and vomiting. These symptoms usually manifest abruptly, may be severe but tend to disappear spontaneously within hours or a few days. Interestingly they can present also in children who have been symptomless before starting treatment with the GFD. This finding suggests that acute reactions can occur regardless of pre-diagnosis symptom profile.

Our findings are consistent with other studies evaluating symptoms after gluten challenge reporting vomiting in 8%–44% and nausea in 13%–61% of the patients (15). A survey conducted by Silvester et al. (16) found a higher prevalence of symptomatic patients after suspected gluten exposure compared to the findings in the current study. This discrepancy may be attributed to population differences. Specifically, the adult population in Silvester's study may have experienced higher exposure rates due to less stringent supervision compared to the

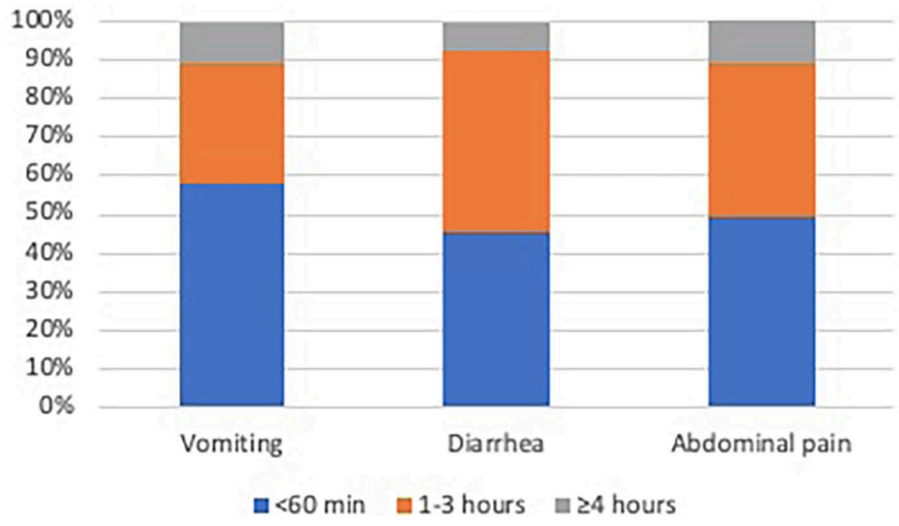

FIGURE 1
Cumulative frequency of the onset timing of the three most commonly reported symptoms (vomiting, diarrhea, abdominal pain).

pediatric population in the current study, where parents or caregivers likely ensure greater dietary vigilance and reduce the likelihood of gluten contamination.

As expected, patients who were symptomatic at diagnosis and those diagnosed at an earlier age appeared more likely to experience symptoms following inadvertent gluten exposure. This may be due to the heightened mucosal sensitivity and immunological responses in those with more severe or long-standing disease.

The context of symptom onset is also of considerable importance. The high proportion of patients reporting symptoms when dining outside the home underscores the challenges faced by individuals with CeD in strictly adhering to a GFD (13, 14). This is particularly problematic in settings where they lack direct control over food preparation and ingredients. Interestingly, a study by Monzani et al. (17) found that one-third of survey respondents experienced improved adherence to the GFD during COVID lockdown measures, especially among those with previously poorer disease control. This suggests that the opportunity to avoid potential sources of gluten contamination and increased use of naturally gluten-free products contribute to better dietary adherence and symptom management in this patient population. Current methods for monitoring GFD adherence, such as dietary questionnaires, celiac serology, or clinical symptoms, are not sensitive enough to detect occasional dietary transgression (18). Novel non-invasive biomarkers such as gluten immunogenic peptides (GIP), while looking promising for assessing gluten ingestion, fall short of reliably capturing all meaningful exposures and comprehensively monitor adherence to a GFD (19).

While the reported symptoms may be attributable to factors other than gluten, such as FODMAPs, fructose or lactose intolerance, or the "nocebo" effect, a recent double-blind study found that patients with challenged with vital wheat gluten exhibited an elevated interleukin-2 response in 97% of participants, which correlated with the severity of nausea and vomiting, in contrast to a sham low-FODMAP challenge (20). This suggests that inadvertent gluten consumption is a key driver of the elevated immune response and associated symptoms in these individuals. Additionally, the rapid onset of symptoms within 2–3 h of gluten ingestion indicates that unintentional gluten exposure is the primary trigger for an heightened non-IgE immune response, not only in the chronic exposure scenario typical of the T cell-mediated condition, but also following an acute gluten challenge. A study by Tye-Din et al. (21) demonstrated that serum interleukin-2 levels, which were undetectable at baseline, became elevated within 4 h in 92% of patients with CeD following an acute gluten challenge. Additionally, the peak interleukin-2 concentration was correlated with the severity of symptoms, particularly nausea and vomiting. Other research has corroborated these findings, with most reactions occurring within 1 h of suspected gluten ingestion and resolving within 48 h (22). These findings are of major significance for understanding the pathophysiology of CeD, as they highlight the previously unappreciated importance of interleukin-2 together with interleukin-8 and interleukin-10 in driving the gluten-specific CD4+ T cell response responsible for the early immune events and clinical symptoms observed after gluten exposure (23). These recent insights into the acute immune response to gluten exposure highlight an evolving trend in CeD research. Traditionally, CeD has been considered a condition primarily driven by chronic immune activation. However, increasing evidence points to the presence of immediate, measurable immune responses following even minor gluten exposure, fundamentally shifting our understanding of symptom manifestation in patients with CeD (23). Future research should aim to further elucidate the mechanisms underlying these reactions and develop strategies to mitigate inadvertent gluten exposure.

A particularly noteworthy observation from our study is that 63% of symptomatic participants reported experiencing symptoms similar to those they had at the time of CeD diagnosis, while a distinct subset reported new symptom patterns following gluten re-exposure. This variation suggests a complex and individualized clinical response to gluten that may change over time. The recurrence of similar symptoms in the majority of cases likely reflects the reactivation of immune pathways previously involved in the initial disease presentation (24). However, the emergence of new symptoms in others—most commonly gastrointestinal—points to a dynamic interplay between immunological memory, dietary factors, and mucosal adaptation. One potential explanation is that ongoing low-level immune sensitization, despite mucosal healing on a strict GFD, may prime the gut for exaggerated responses upon re-exposure (25). Alternatively, shifts in gut microbiota composition, evolving dietary patterns, or partial recovery of intestinal barrier function may alter the symptomatic profile over time (26, 27). These evolving insights into the acute phase of gluten-induced symptoms have practical consequences for clinical care and research. They reinforce the concept that acute responses to gluten are multifaceted and patient-specific, which has important implications for clinical follow-up. It also highlights the need for individualized dietary counseling and symptom tracking, particularly for patients who develop novel symptoms post-diagnosis.

The retrospective design and reliance on self-reported data in this study may have led to potential recall bias. Additionally, the researchers did not independently confirm the reported instances of gluten contamination. However, the responses were validated by a dietitian, and strict criteria were used to determine a positive reaction. Furthermore, the relatively large sample size and real-world referral context help to mitigate these limitations, as this type of information is commonly encountered by clinicians during their interactions with patients. Most previous studies exploring symptoms in response to gluten exposure have focused on controlled gluten challenges, but we know that the specific type of grain consumed, and the food processing methods can also influence the resulting symptom profiles. Therefore, the variable nature of the inadvertent gluten exposures encountered in real life may yield symptom patterns that differ from those observed in the controlled challenge settings.

5 Conclusion

This study offers valuable insights into the frequency and nature of symptomatic responses experienced by children and adolescents with CeD following an acute gluten exposure. The findings in symptomatic patients highlight the high prevalence of gastrointestinal symptoms, including abdominal pain, diarrhea, and vomiting, within this patient population. The reactions are acute, usually occurring within 1–3 h after ingestion, with the most suspected settings of contamination being school cafeterias and dining outside the home. These results emphasize the critical need for continued research and development of effective tools to monitor and manage inadvertent gluten intake, in order to improve the quality of life of individuals living with CeD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Marche, section AOU delle Marche. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

DP: Formal analysis, Writing – review & editing, Writing – original draft, Data curation, Investigation. DD: Data curation, Writing – review & editing, Investigation, Writing – original draft. CM: Data curation, Formal analysis, Writing – review & editing. SR: Writing – review & editing. MA: Writing – review & editing. SG: Writing – review & editing. CC: Validation, Supervision, Conceptualization, Writing – review & editing, Methodology. EL: Writing – review & editing, Validation, Methodology, Supervision, Conceptualization.

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Conflict of interest

CC reports personal fees for consultancy for Dr. Schar Food.

The remainingauthors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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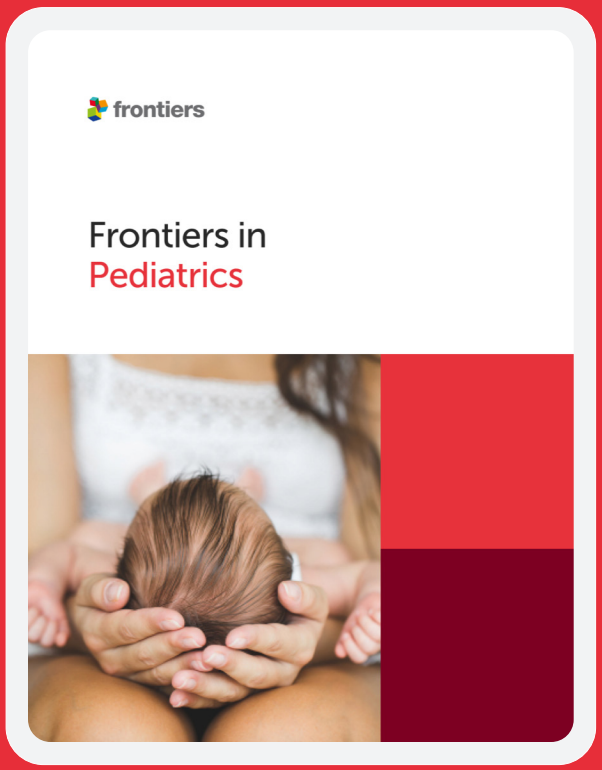

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