Clinicopathological, endoscopic and serological patterns of Celiac disease in children: A retrospective study from a Tertiary Center in Upper Egypt

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Abstract

Background: Celiac disease (CD) is a common enteropathy due to loss of dietary gluten tolerance. The resultant immune interaction leads to intestinal damage, malabsorption, and intestinal and extraintestinal manifestations.

Objectives: This retrospective study tried to illustrate the clinical, serological, endoscopic, and histopathological characteristics and treatment outcomes of pediatric CD patients attending Sohag University Hospital.

Patients and methods: The clinical, endoscopic, pathological and serological data of CD patients who were previously admitted over the previous three years(2022 to 2024) were obtained from the patients' hospital files. Also, the outcomes of maintenance on gluten-free diet (GFD) were also defined.

Results: Sixty-six patients were included with abdominal distension & pain, diarrhea, and anemia were the most common manifestations. Seven patients (10.6%) had type-1 diabetes mellitus (T1DM). Endoscopy detected atrophy of duodenal mucosa and scalloping of its folds in 92.4% and 83.3% of patients ,respectively. Serologically, 95.5% of samples were positive for IgA tissue transglutaminase antibodies. Pathologically, Marsh type 3b, 3c, and 3a were the diagnoses of 60.6%, 21.2%, and 18.2% of duodenal biopsies, respectively. Most of intestinal and extraintestinal manifestations significantly (P=0.0002 and P=0.0001, respectively)decreased while body weight, and abdominal distension were insignificantly(P=0.321) improved after GFD.

Conclusion: Children in this study had variable intestinal & extra-intestinal manifestations, typical endoscopic features of CD and majority of them had Marsh 3 b classification. Maintenance on GFD resulted in significant improvement of most of manifestations.

Keywords: Celiac disease; Clinical manifestations; Endoscopy; Gluten-free diet; Outcomes Pathology; Serology.

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Introduction

Malabsorption is a complex condition that is characterized by the defective passage of nutrients into the blood and lymphatic streams secondary to several congenital or acquired disorders, which may cause selective or global malabsorption in children and adults, such as celiac disease (CD) **(Lenti et al., 2025)**.

CD is a common autoimmune-mediated enteropathy caused by a loss of gluten tolerance secondary to the interaction between the immune system and the dietary gluten in genetically predisposed individuals **(Kelley et al., 2025)**. Mechanistically, the immune response leads to intestinal damage and malabsorption with subsequent intestinal and extra-intestinal manifestations **(Di Tola et al., 2025)**.

The diagnosis of CD and its timing is still a dilemma (**De Luca et al., 2025),** where genetic and epigenetic markers for B and T cells at birth did not impact susceptibility to childhood-onset CD **(Ulnes et al., 2025)**. Also, a case-control study of intraepithelial lymphocyte counts in biopsies of potential CD patients detected low concordance between histological and immunohistochemistry with anti-CD3 evaluation and recommended caution on patients' classification as Marsh-0 or Marsh-1 **(Mandile et al., 2025)**.

Thus, diagnosis of CD is still dependent on defining the intestinal damage histologically and was confirmed by the abolishment of these changes after maintenance on a gluten-free diet (GFD) for a suitable period with subsequent monitoring of CD patients who were maintained on GFD **(Di Tola et al., 2025)**.The well-established association between CD and type 1 diabetes mellitus (T1DM) indicated the necessity for early screening of T1DM patients for CD to promote timely CD diagnosis and treatment **(Ramharack et al., 2025)**.

The current study aimed to explore and present the clinical, serological, endoscopic, and histopathological characteristics and treatment outcomes of pediatric CD patients admitted to Sohag University Hospital

Patients and methods

This retrospective hospital- based study included data of children, who were previously diagnosed with CD, was collected between January 2022 and December 2024 from Gastroenterology and Hepatology Unit at the Department of Pediatrics, Sohag University Hospital, Sohag University.

The study protocol was approved by the Medical Research Ethics Committee- Faculty of Medicine- Sohag University, by approval number: Soh-Med-24-11-10MS.

Inclusion criteria: All children diagnosed with CD and were admitted to the Pediatric wards at Sohag University Hospital and their files contained the full patients' data, including follow-up data, were included in the study.

Exclusion criteria: Patients who were admitted for differential diagnosis with CD, especially those of patients with clinical findings including inflammatory or irritable bowel diseases, functional chronic constipation, chronic diarrhea secondary to metabolic disorders, anemia secondary to hematological diseases, bone marrow disorders, or hemoglobinopathy, were excluded from the study. Also, patients with files that missed any of the required data were excluded.

Clinical assessment data

The clinical assessment data included demographic data that included age and gender. Historical data including birth weight, neonatal feeding as breast or formula feeding, the presence of intestinal symptoms, including diarrhea, distension, constipation, anorexia, nausea, vomiting, and extra-intestinal manifestations, the date of the pathological diagnosis as CD, the

presence of comorbidities, especially type 1 diabetes mellitus (T1DM), family history of CD, and Clinical examination data with special regard to weight and abdominal circumference before and after inclusion of gluten-free diet (GFD) and the extent of change after maintenance on GFD as the percentage of difference in weight and abdominal circumference relative to data obtained before the start of the GFD. The frequency of the intestinal and extraintestinal manifestations at the last follow-up visit after including the GFD, and its change relative to that obtained before the start of the GFD.

Serological data

The results of the serological tests specific for celiac disease, including the frequency of detecting the total IgA, and IgA tissue transglutaminase antibodies (tTG-IgA) and their levels. Also, the data concerning the detection of endomysial (EMA) antibodies (IgA & IgG), if available, were extracted from the files .

Serological tests specific for celiac disease were performed by the following methods

1. Total IgA was estimated using an Abcam quantitative (Cat. No. 137980; Abcam Inc., San Francisco, USA) ELISA kit for the measurement of Human IgA. The measuring unit was mg/dl
2. IgA tissue transglutaminase antibodies (tTG-IgA) were ELISA-detected using Abcam ELISA kits for human tTg-IgA (Cat. No. ab277414).The measuring unit was IU/mL
3. In case of samples quantified as negative, deficient, or not detection for IgA, human tTG-IgG antibodies were ELISA-detected using Abcam ELISA kits for human tTG-IgG (Cat No. 195215).The measuring unit was IU/mL. All ELISA tests were performed according to the manufacturer's instructions, and results were read using a 96-well microplate ELISA reader (Dynatech, MR 7000).
4. If indicated endomesial (EMA) antibodies (IgA & IgG) by HELIOS Automated immunofluorescence assay (IFA) System (Wendelsheim, Germany / Oakland, California).

Endoscopic data

The findings of esophagastroduodenoscopy (EGD) on visualization of the esophagus, stomach, and duodenum, especially mucosal atrophy and scalloping of duodenal folds were obtained.

EGD was performed under general anesthesia provided by an anesthesiologist according to the patient's age, weight, and coexisting medical conditions. EGD was performed by expert pediatric endoscopists using pediatric-size flexible gastro-duodenoscopes model EG-2790K, developed by Pentax (Tokyo, Japan)with compatible biopsy forceps. Four biopsies were obtained from the second and third part of the duodenum and one from the duodenal bulb.

Pathological examination findings and scoring:

Obtaining the data concerning the microscopic examination of the Hematoxylin and Eosin(H&E)-stained sections of duodenal biopsies particularly the detection of increased intraepithelial lymphocytes(IEL), crypt gland hyperplasia, and villous atrophy, which were documented by **Pai (2014),** as the microscopic diagnostic criteria for CD. The disease was graded according to the Modified March grading classification **(Oberhuber et al., 1999),** depending on the detected CD disease severity and the degree of villous atrophy.According to this classification;March type 0=IEL<40/100 enterocytes , March type 1=IEL>40/100 enterocytes),March type 2(Crypt hyperplasia+IEL>40/100 enterocytes),March type 3a(Crypt

hyperplasia+mild villous atrophy+IEL>40/100 enterocytes), ,March type 3b(Crypt hyperplasia+moderate villous atrophy+IEL>40/100 enterocytes) and March type 3c(Crypt hyperplasia+total villous atrophy+IEL>40/100 enterocytes)

Statistical analysis

The data are presented as mean, standard deviation, numbers, and percentages. Statistical analyses were performed by the unpaired t-test and Chi-square test using the IBM® SPSS® Statistics software (Ver. 27, 2020; IBM Corporation; Armonk, USA). The significance of the analysis was evaluated at the cutoff point of P less than 0.05.

Results

There were 80 patients who were previously diagnosed with CD during the last three years. However, 14 patients' files missed some data, especially the histopathology report or duration of inclusion of gluten in the diet, and were excluded from the study. The data of the remaining 66 patients were obtained and analyzed. The data concerning age, gender, history, and body mass index before the start of the GFD are shown in (**Table.1**).

Table 1. Patients' enrolment data

Data			**Findings (n=66)**
Demographic data	**Age (Years) (at diagnosis)**		8.25±4.1
	Gender	**Males**	27 (40.9%)
		Females	39 (59.1%)
History data	**Birth weight (kg)**		2.93±0.53
	Feeding history	**Breast**	55 (83.3%)
		Formula	11 (16.7%)
	Age at inclusion of gluten in diet (months)		6.4±1.9
	Presence of comorbidities	**Type-1 diabetes mellitus**	7 (10.6%)
	Positive parental consanguinity		40(60.6%)
	Weight (kg)		18.7±8
	Height (cm)		112.63±19
	Body mass index (kg/m^2)		14.88±3.24
Duration of GFD years(mean+ std)			1.5 ±1

GFD= gluten free diet

Serologically, total IgA level was normal in 63/66(95.4%) patients with a mean value of 235.3 (±175.6) and was deficient in 3 children (4.6%) .Sixty three samples were positive for the tTG-IgA antibodies for a positivity rate of 95.5% and a mean level of 162.6 (±78.5). Two of the three samples that were considered negative for tTG-IgA were positive for EMA-IgA at dilutions of 1:10 and 1:40, and the third sample was positive for tTG-IgG at a dilution of 1:5 (**Table.2**).

Table 2. Serological data of the studied patients

Marker			**Findings(n=66)**
Total IgA (mg/dL)	**Frequency**	**Normal level**	63 (95.4%)
		Deficient	3 (4.6%)
	Mean (±SD) level		235.3±175.6
tTG IgA(IU/mL)	**Frequency**	**Positive**	63 (95.5%)
		Negative	3 (4.5%)

	Mean (±SD) level	162.6±78.5

IgA=immunoglobulin A, tTG IgA=Tissue trabsglutaimanse IgA

All patients showed abnormalities of the duodenal mucosa on endoscopic examination; 61 patients (92.4%) showed atrophy of duodenal mucosa on endoscopic examination, and 55 patients (83.3%) had scalloping of duodenal mucosal folds. Pathological examination of the obtained biopsies detected 40 biopsies (60.6%) of Marsh type 3b, biopsies of 14 children (21.2%) were classified as Marsh type 3c, and 12 children (18.2%) had Marsh type 3a (**Table.3, Fig.1**).

Table 3. Patients' distribution according to the endoscopic and pathological findings

Data			**Findings(n=66)**
Endoscopic findings	**Atrophy of duodenal mucosa**	**Present**	61 (92.4%)
		Absent	5 (7.6%)
	Scalloping of duodenal mucosal folds	**Present**	55 (83.3%)
		Absent	11 (16.7%)
Pathological findings	**Marsh type**	**3a**	12 (18.2%)
		3b	40 (60.6%)
		3c	14 (21.2%)

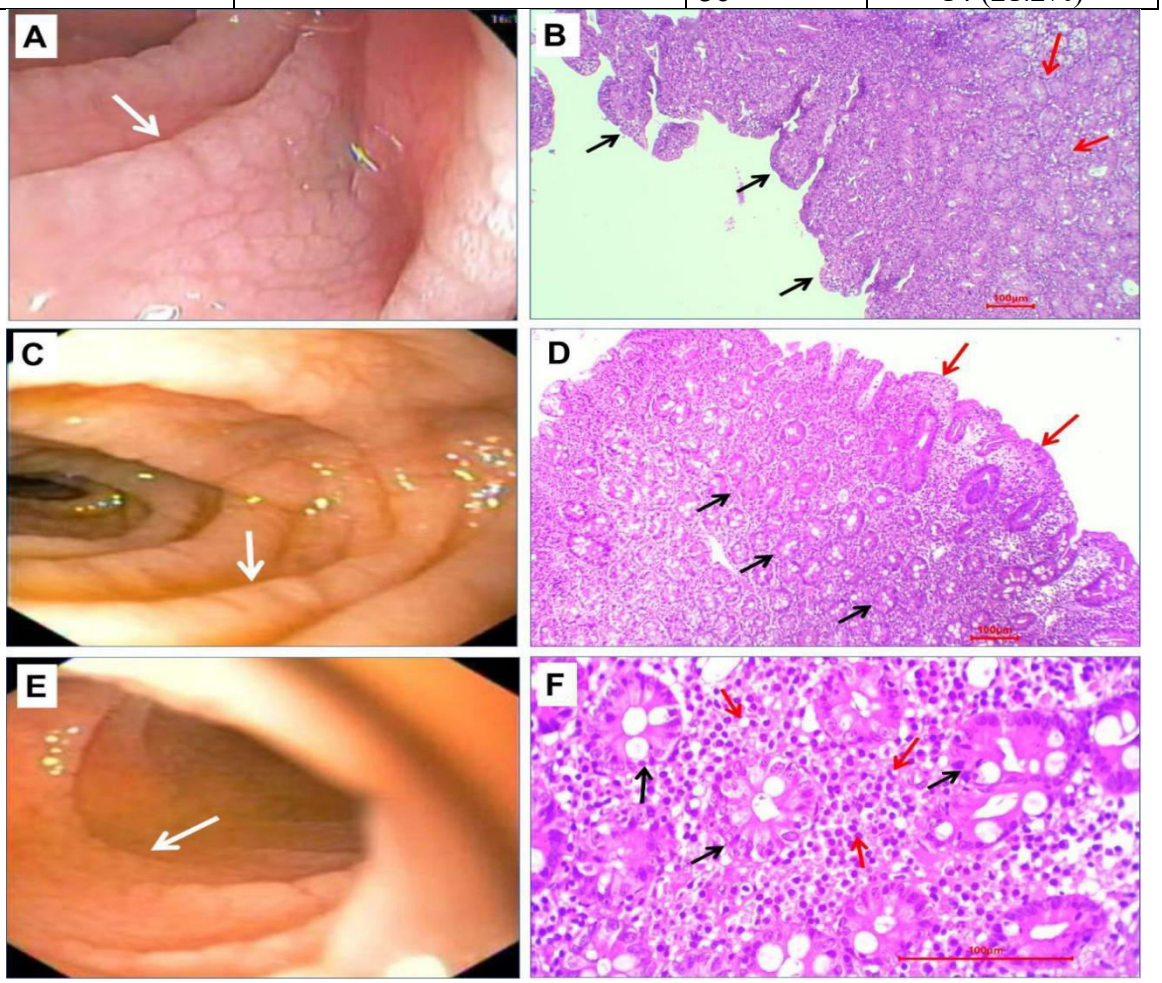

Fig.1. Endoscopic and corresponding histopathology findings of the same patients

A=scalloping of duodenal folds (arrow) B=March 3b, C=Atrophy & scalloping of duodenal folds (arrow), D=March 3c, E=scalloping of duodenal folds (arrow), F= March 3a

The mean duration of gluten free diet in the studied cases was 1.5 ±1 year. Before the start of GFD, abdominal distension and pain, diarrhea, and vomiting were the highly frequent intestinal manifestations with frequencies of 84.8%, 74.2%, 71.2%, and 47%, respectively. Nausea and anorexia, and constipation were encountered in 16.7% and 13.6% of patients, respectively. These metrics for the intestinal manifestations were dramatically changed after maintenance on GFD. The frequency of abdominal distention and pain, diarrhea and vomiting were decreased to 15.2%, 10.6%, 15.3%, and 12.1%, respectively, with significant (P<0.001) differences in the frequency between before and after GFD, while nausea and constipation were still present in 6.1% and 7.6%, respectively, of patients, with insignificant differences between before and after GFD.

Anemia was the most commonly encountered extraintestinal manifestation with a frequency of 60.3% and 27.6% before and after GFD, respectively, with significantly (P=0.0007) lower frequency after GFD. The frequencies of other extraintestinal manifestations either changed insignificantly or did not change. The frequency of complaining of recurrent aphthous stomatitis and dermatitis herpetiformis was decreased from 8.6% and 6.9% to 3.4% and 1.7%, respectively. However, the frequency of complaining of arthritis, and arthralgia was minimally decreased from 8.6% to 6.9%, while the frequencies of other extraintestinal manifestations did not change. Collectively, the mean values of the number of intestinal and extraintestinal manifestations were significantly (P=0.0002 and P=0.0001, respectively) decreased after GFD than before its inclusion (**Table.4, Fig. 2**).

Table 4.The frequency of intestinal and extra-intestinal manifestations of patients before and after the star of GFD

Manifestations		Findings(n=66)		P-value
		Before	After	
Intestinal	Diarrhea	47 (71.2%)	10 (15.2%)	<0.001*
	Abdominal pain	49 (74.2%)	7 (10.6%)	<0.001*
	Abdominal distention	56 (84.8%)	10 (15.2%)	<0.001*
	Vomiting	31 (47%)	8 (12.1%)	<0.001*
	Nausea & Anorexia	11 (16.7%)	4 (6.1%)	0.056
	Constipation	9 (13.6%)	5 (7.6%)	0.258
	Mean number	4.4±1.7	1.1±0.96	0.0002*
Extra-intestinal	Anemia	35 (60.3%)	16 (27.6%)	0.0007*
	Recurrent aphthous stomatitis	5 (8.6%)	2 (3.4%)	0.244
	Dermatitis Herpetiformis	4 (6.9%)	1 (1.7%)	0.171
	Arthritis & Arthralgia	5 (8.6%)	4 (6.9%)	0.730
	Dental enamel defects	2 (3.4%)	2 (3.4%)	1
	Neurological	2 (3.4%)	2 (3.4%)	1
	Osteopenia	1 (1.7%)	1 (1.7%)	1
	Delayed puberty	1 (1.7%)	1 (1.7%)	1
	Mean number	0.83±0.38	0.44±0.5	0.0001*

Statistical analysis was performed using Chi-square and paired t-test. *P value < 0.05= statistically significant

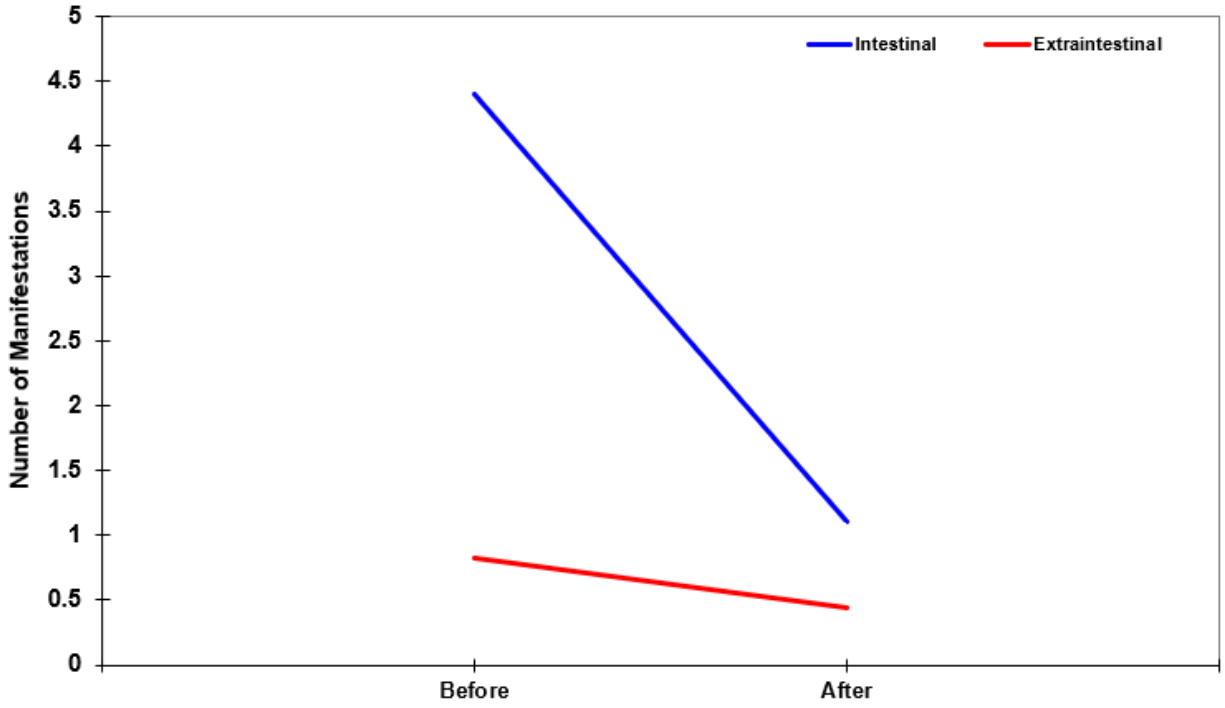

Fig. 2 . The change in the mean value of the number of clinical manifestations after GFD relative to that detected before GFD

The body weight was insignificantly (P=0.321) increased on the GFD, with a mean value for the change was 25.7 (±12.8%). In turn, the decreased abdominal distension resulted in a decrease of abdominal circumference, but the change was insignificant (P=0.731) and the extent of change was only by 7.5% (±3.3), as shown in (**Table.5 , Fig.3**).

Table 5. Body weight and abdominal circumference of patients estimated before and after the inclusion of gluten-free foods in their diets

Data		**Findings(n=66)**	
		Before	**After**
Body weight (kg)	**Mean (±SD)**	18.7±8	22.9±8.5
	P-value		0.321
	% of change	25.7±12.8	
Abdominal circumference (cm)	**Mean (±SD)**	68.4±11.3	63.4±11
	P-value		0.371
	% of change	7.5±3.3	

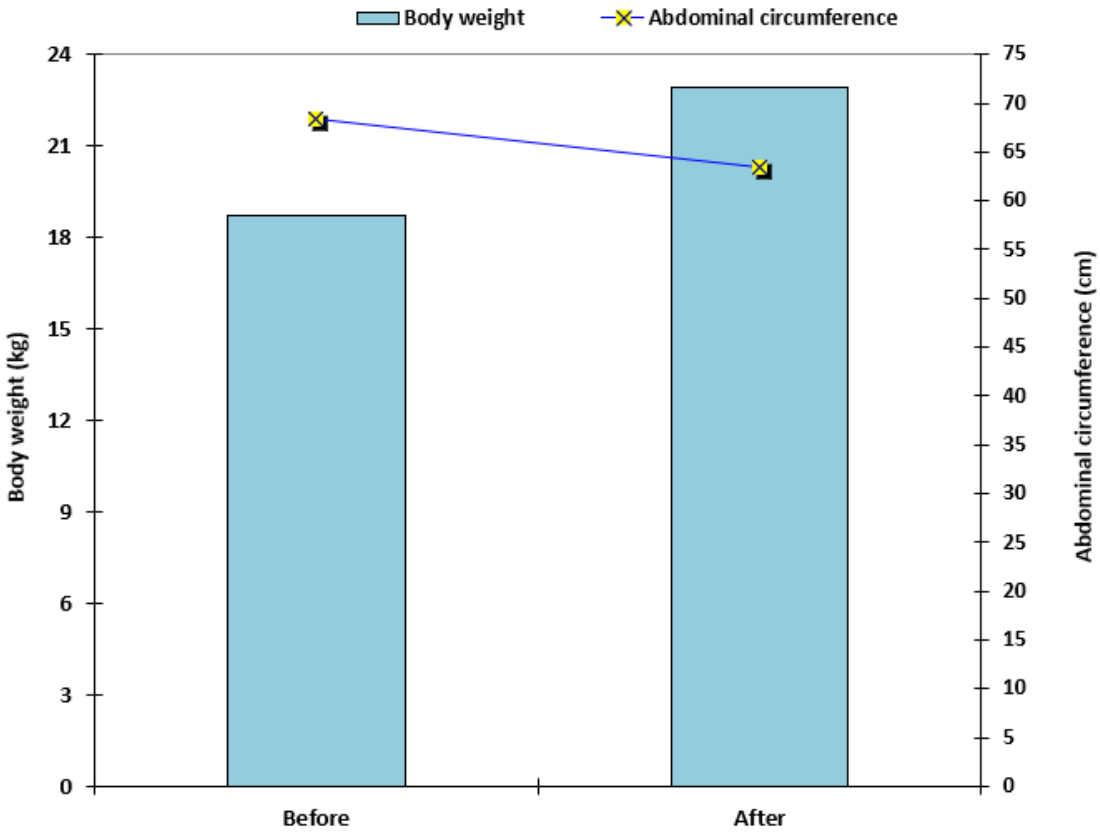

Fig. 3. The change in the body weight and abdominal circumference of patients after GFD relative to that detected before GFD

Discussion

The presenting clinical manifestations are a mosaic of characteristics between typical and atypical CD. The most common complaints were diarrhea, abdominal distension, pain, and anemia is the highly prevalent extraintestinal finding. These data align with those of **Mansour et al. (2022)**, who retrospectively identified high clinical variability among CD patients, with chronic diarrhea and anemia being the most common intestinal and extraintestinal symptoms. Also, **Wang et al. (2022**) reported that chronic diarrhea, and anorexia are the common intestinal, while anemia, fatigue, weight loss, sleep disorders, and osteopenia are the common extraintestinal symptoms. Further, **Bari et al. (2023)** found bloating, diarrhea, and abdominal pain are the most common gastrointestinal symptoms, and dermal manifestations are the commonest extraintestinal manifestations of CD patients. Thereafter, **Ahmed et al. (2024)** reported that weight loss, diarrhea, and abdominal pain are common symptoms of CD patients with stunted growth is a common extraintestinal symptom. The obtained and the aforementioned data emphasize the inclusion of CD in the differential diagnosis of chronic diarrhea for early diagnosis and management.

Regarding extraintestinal manifestations, recurrent aphthous stomatitis and dental enamel defects were reported in 12% of patients. This finding indicated the necessity of inclusion of CD among the differential diagnoses of children presenting with these oral signs. Similarly, **Cicekci et al. (2024)** reported that CD enhanced the likelihood of observing some oral manifestations, especially recurrent

aphthous stomatitis and developmental enamel defects. Also, dermatitis herpetiformis was detected in 6.9% of CD patients, and this aligns with **Iversen et al. (2025)**, who documented that dermatitis herpetiformis is an extraintestinal manifestation of CD and the link is through activation of the gluten-specific $CD4^+$ T cells through B-cell receptor-mediated internalization of transglutaminase 3-gluten enzyme-substrate complexes

Endoscopic examination detected duodenal mucosa atrophy and scalloping in 92.4% and 83.3%, respectively. In line with these findings **Wang et al. (2022)** endoscopically reported crypt hyperplasia and/or duodenal villous atrophy that was manifested as nodular mucosal atrophy, grooves, and fissures as the prevalent findings in CD patients. Additionally, **Bari et al. (2023)** documented that duodenal scalloping is the most common endoscopic finding in their series of CD patients, and **Ahmed et al. (2024)** found fissuring of the duodenal mucosa is the commonest endoscopic finding that was followed by decreased height of duodenal folds and nodularity.

Marsh 3b grading was the commonest among pathological grading of the obtained duodenal biopsies and was followed by Marsh 3c and Marsh 3a gradings (60.6%, 21.1%, and 18.2%, respectively). These figures are consistent with **Mansour et al. (2022)**, **Bari et al. (2023)**, and **Ahmed et al. (2024)**, who detected higher frequencies of pathological grading of Marsh III b, c, and a in their series of CD patients.

The reported 60.6% of positive parental consanguinity in this study along with stationary living circumstances and environmental exposures over the years may underlie the reported incidence of CD among the inhabitants of the referral area of Sohag. In line with the implications of consanguinity, previous studies reported consanguinity rates of 96.77% **(Waheed et al., 2016)** and 77.4% **(Hoşnut et al., 2022)** among the parents of patients who experienced celiac crisis and persistent diarrhea in newborns, respectively. Additionally, **Senapati et al. (2015)** found a higher degree of consanguinity among parents of celiac disease patients in the north Indian population compared to Europeans. Recently, **Eurén et al. (2024)** indicated a significant impact of the season of birth on the risk of celiac autoimmunity, with this effect being dependent on polymorphisms in CD247 gene encoding the CD3ζ chain of the T-cell co-cluster of differentiation 3 complex. Children with major alleles for the single nucleotide polymorphism rs864537A > G, in CD247 (AA genotype), faced a higher risk for both celiac autoimmunity and febrile infections **(Eurén et al. 2024)**.

As another support for the provided suggestions, the current study detected a frequency of T1DM of 10.6% of the studied patients. Further, the frequencies of detection of positive tTG-IgA antibodies in 95.5% of cases.These findings are in line with **Baseer at al.,(2024)** who reported that the overall prevalence of celiac disease in Egyptian children with T1DM was 4.5%.Also, **Hakami et al. (2024),** detected a high prevalence of CD among T1DM Saudi patients and found that CD has multiple impacts on glycemic control, growth, and puberty of these patients, and recommended early and periodic screening for CD on diagnosis of T1DM. In addition, **Ramharack et al. (2025)** detected that among T1DM patients, with positive EMA and TTG-IgA ≥8 times the upper limit of normal were diagnosed with CD.

GFD improved clinical manifestations, body weight, and abdominal circumference.The improvement in clinical symptoms was statistically significant,however the improvement in body weight and abdominal circumference

was statistically insignificant compared to the data obtained before the start of GFD. These findings align with those of **Villanueva et al. (2020)**, who reported that gastrointestinal symptoms in addition to failure to thrive were more prevalent in CD patients younger than 2 years, and despite improved nutritional status at diagnosis and during follow-up, undernutrition remains more frequent in children younger than five years. Thereafter, **Barone et al. (2023)** reported that only 9% of CD patients transitioned from the underweight/normal BMI category to the overweight/obese category during a GFD, while 20% moved into a lower BMI category.

The reported dis-coordinated improvement of body weight and abdominal circumference with that of symptoms, might be attributed to the non-strict adherence to the GFD due to the low economic status of parents to cope with the price of the GFD, the negligence of the mothers to follow-up their kids who may consume gluten containing food staffs, or the intentional refusal of kids to follow the dieting regimen. In support of these attributions, **Rodrigues et al. (2019)** reported non-adherence to the GFD by 20% of their series of CD patients and found this mostly occurred intentionally at home or parties. Also, **Jordá et al. (2020),** during the "CELIAC-SPAIN" project, reported that during the GFD, 90 % of patients reported good adherence to treatment, which resulted in improved symptoms and weight gain, but documented that GFDs are expensive and the price may limit their use. Also, **Bayrak et al. (2020)**, using Multivariate Regression analysis, documented that adequate weight gain, adherence to GFD, sufficient iron and vitamin D status are essential factors for salubrious puberty in CD patients. Recently, **Kowalski et al. (2024)** reported that CD patients who were maintained on GFD showed typical and atypical symptoms of the disease and attributed this to the finding that more than half of CD patients unconsciously or consciously make dietary mistakes, and recommended the need for plans to improve the general knowledge of CD, the appropriate diet and the importance of strict adherence to GFD.

Limitations: The present study is limited by being a retrospective study as data may be incomplete or inconsistently recorded .The absence of an age- and sex-matched control group was another limitation of this study .However, the strong point of our study is that it the first study to investigate the clinical, serological, endoscopic, and histopathological characteristics and treatment outcomes of pediatric CD patients in our locality.

Conclusion

Children in this study had variable typical and atypical manifestations and most of them had endoscopic findings suggestive of CD and advanced March classification.The implementation of GFD resulted in significant improvement of most of manifestations .The reported dis-coordinated improvement of body weight and abdominal distension with that of symptoms, might be attributed to the non-strict adherence to the GFD.This emphasis the necessity for early diagnosis of CD and strict adherence to GFD.

Recommendations: Larger-scale studies including CD patients residing in other governorates were required to determine the impact of the living circumstances on the prevalence of the disease and its related characteristics. Also, inquiry for CD manifestations among T1DM is important for early diagnosis and interventions. Lastly, the search for easier access to low-cost gluten-free foods is mandatory to obviate the non-adherence to GFD by parents.

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