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Predictive Factors and Clinical Impact of Deep Remission in Celiac Disease

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Keywords

Celiac disease · Deep remission · Endoscopic reassessment · Gluten-free diet

Abstract

Introduction: The ultimate indicator of adherence to a gluten-free diet is the demonstration of mucosal healing. However, the need for histological reassessment is subject to controversy among "experts". The aim of this study was to evaluate celiac patients who underwent histological reevaluation after starting a gluten-free diet in order to identify those with histological remission and associated factors. ***Methods:*** This retrospective study included patients who agreed to a histological reassessment after apparent clinical and serological remission and reported at least 12 months of diet adherence. In all cases, informed consent was signed for upper endoscopy. ***Results:*** A total of 69 patients were included. In 67.9% of cases, the diagnosis was made in the context of "classic" symptomatology, 17% had "nonclassical" presentation, and 15.1% were in latent phase. 69.2% of the diagnoses were initially suspected by serology. Endoscopically, 11.8% of the patients did not present suggestive features macroscopically, and a histological grade of Marsh IIIa–c was observed in 75.5% of all cases. The histological findings were normalized in 37.7%, which was associated with the presence of lower Marsh score values at diagnosis ($p = 0.014$) and lower DEXA T-score values ($p = 0.038$). A histological improvement was observed in 55 patients (≥2 grades in 37 cases), which was related to the initial transferrin saturation ($p = 0.027$) and with higher Marsh scores at diagnosis ($p = 0.007$). ***Conclusion:*** Even under a gluten-free diet, celiac histology normalization is difficult to obtain and appears to be independent of most clinical and serological findings at diagnosis. Patients with less severe histological levels at diagnosis reach remission more easily, but only represent the minority of the population.

Fatores preditivos e impacto clínico da remissão profunda na doença celíaca

Palavras Chave

Doença celíaca · Remissão profunda · Reavaliação endoscópica · Dieta isenta de glúten

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Resumo

Introdução: O indicador final da adesão a uma dieta isenta de glúten é a demonstração da cicatrização da mucosa. No entanto, a necessidade de reavaliação histológica é um assunto controverso entre "experts." O objetivo deste estudo foi avaliar doentes celíacos submetidos a reavaliação histológica após o início da dieta isenta de glúten, a fim de identificar aqueles com remissão histológica e fatores associados. ***Métodos:*** Estudo retrospectivo, incluindo doentes que concordaram com reavaliação histológica após aparente remissão clínica e serológica, com pelo menos doze meses de adesão relatada à dieta. Em todos os casos, o consentimento informado foi assinado para endoscopia digestiva alta. ***Resultados:*** Um total de 69 doentes foram incluídos. Em 67.9% dos casos, o diagnóstico foi feito no contexto de sintomatologia clássica, 17% de apresentações não clássicas e 15.1% em fase latente. A maioria (69.2%) dos diagnósticos foram inicialmente suspeitos com base na serologia. Na endoscopia, 11.8% dos pacientes não apresentavam características macroscópicas sugestivas de doença celíaca, observando-se um grau histológico de Marsh IIIa-c em 75.5% dos casos. Os achados histológicos normalizaram em 37.7% dos doentes, o que foi associado à presença de menores valores de Marsh no momento do diagnóstico ($p = 0.014$) e menores valores no T-score da densitometria óssea ($p = 0.038$). Melhoria histológica foi observada em 55 doentes, em dois ou mais graus em 37 casos, o que se relacionou com a saturação inicial da transferrina ($p = 0.027$), e com maiores scores de Marsh no momento do diagnóstico ($p = 0.007$). ***Conclusão:*** Mesmo sob uma dieta isenta de glúten, a normalização da histologia na doença celíaca é difícil de obter e parece ser independente da maioria dos achados clínicos e serológicos no momento do diagnóstico. Doentes com níveis histológicos menos graves ao diagnóstico alcançam a remissão mais facilmente, mas representam apenas a minoria da população.

Introduction

Celiac disease (CD) is a chronic autoimmune disease that is triggered by gluten intake in genetically predisposed individuals [1]. CD can affect all age groups [2], with an overall prevalence of 1% [3, 4]. As there is growing knowledge and awareness about CD and its manifestations, there has been an increase in its incidence, particularly in Western countries [5, 6]. Although it is a multisystemic disease, it mainly affects the small intestine [7], presenting a wide clinical spectrum, which may include typical/classic manifestations secondary to intestinal malabsorption and atypical/nonclassical manifestations, where the extraintestinal symptoms are included, as well as the absence of symptoms (subclinical disease) [8].

Currently, the only established treatment for these patients is to maintain a gluten-free diet (GFD) throughout their lives [9]. Indeed, when gluten is ingested, celiac patients suffer an increase in serum levels of certain antibodies, such as IgA antitransglutaminase, which is the most commonly used marker for diagnosis because it has a high sensitivity and specificity [10]. In addition, as these antibodies tend to normalize with strict GFD maintenance, they become useful in monitoring patients after the onset of the diet and over time. However, although decreasing concentrations of CD-specific antibodies indicate a reduction in gluten intake, they have a limited ability to define complete compliance, and there is evidence that small amounts of gluten exposure may not be detected in this way [11]. Once antibody titers have normalized, a subsequent increase in their levels is considered a good indicator of undue gluten intake, which is currently widespread [12].

Despite the usefulness of serology in the follow-up of CD patients, the ultimate indicator of adherence to the diet is the demonstration of mucosal healing, although this may not occur even in compliant patients. The need for duodenal biopsies to assess healing and GFD adherence is a subject of controversy among experts [13–16]. Although this approach is often used in clinical practice, it is not clear whether it is necessary in patients who are clinically responsive and who show decreasing or negative levels of autoantibodies [1, 6, 17]. Among those recommending repeated biopsy, the timing for when samples should be obtained is not well defined [18]. Complete healing of the intestinal mucosa is also often slow or incomplete, especially among adults [19]. The maintenance of villous atrophy can lead to persistent nutritional deficiencies or complications such as osteoporosis, or it can mimic the irritable bowel syndrome [11]. Recently, it has been shown that the majority of CD patients do not have a satisfactory histological response [19], and, therefore, duodenal biopsy may be the only tool capable of identifying these patients and consequently those with a potential risk of complications. Current evidence on this issue is scarce, and further studies are required to determine whether histological reassessment should be on a routine basis, and, in whom confirmation of mucosal healing may be important in clinical decision making.

This research project aimed to epidemiologically characterize the population of CD patients followed in a specialist consultation in the Department of Gastroenterology of the São João Hospital Center. In particular, it was intended to study the patients submitted to histological reevaluation after initiation of GFD in order to identify those that present histological improvement, including complete remission of the mucosa and demographic, clinical, and therapeutic factors associated with these outcomes.

Materials and Methods

Study Design

After ethics committee approval, a retrospective study was carried out without any intervention in the population. Indeed, in this investigation, endoscopic reassessment was proposed by the attending physician of the CD patients under study after explaining that their achievement is still controversial and as such optional.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. Written, informed consent was obtained from each patient included in the study.

Participants

Thus, the study sample included all patients diagnosed with CD (based on the criteria of the World Gastroenterology Organization Global Guidelines, 2016 [1]) followed by a specialized consultation in the Gastroenterology Department of the São João Hospital Center. In total, 161 patients with a confirmed diagnosis of CD were studied. In this study, we specifically assessed patients in apparent clinical remission (indicated by a normalization of the antibody titers after at least 12 months of reported GFD) who, at follow-up, agreed to undergo histological reassessment through endoscopy with duodenal biopsies. The study included female and male patients aged 18 years or older. The follow-up of celiac patients in the consultation follows the algorithm proposed by the American College of Gastroenterology and published in their guidelines in 2013 [20].

Data Extraction

The data needed to carry out this research were obtained from the electronic clinical records of the patients, including clinical diaries and laboratory and imaging examinations performed by patients.

Statistical Analysis

The clinical data obtained in this project were stored in a database using SPSS, which was later subjected to treatment and statistical analysis in order to evaluate the proposed objectives. Subsequently, a descriptive analysis of the same data was carried out in order to answer the research questions. Categorical variables were characterized by relative frequency and studied using the Pearson χ^2 test. Since there was no normal distribution between groups, continuous variables were studied using the Mann-Whitney U test. For groups of variables with a small number, Fisher's exact test was used. For all comparisons, a value of α of less than 0.05 was considered statistically significant.

Study Variables

Based on the July 2016 WGO guidelines [1], patients were classified as classical, nonclassical, and subclinical CD patients, depending on the symptoms they showed at the time of diagnosis. Symptoms of classical disease included chronic diarrhea, weight loss, iron deficiency anemia, abdominal distension, malaise, and fatigue, edema, osteoporosis, growth retardation, vomiting, sarcopenia, and irritability. The symptoms of nonclassical disease included abdominal pain, CD, chronic fatigue, constipation, chronic migraine, dermatological manifestations, peripheral neuropathy, hypertransaminasemia, folic acid deficiency, bone density reduction (by DEXA scan at diagnosis), infertility, pubertal delay, late menarche and early menopause, dental alterations, dyspepsia, and psychopathy.

Regarding the diagnosis, this depends on the combination of several factors, namely the clinical history, physical examination, presence of specific antibodies, and compatible intestinal biopsy. Thus, IgA antitissue transglutaminase antibody was used in serology, the value of which was considered negative when <7.0 U/mL. In IgA-deficient patients, an IgG assay was performed. Regarding the histological evaluation, the included endoscopic reassessment biopsies were performed 12–24 months after the initiation of GFD, and the Marsh classification was used to classify them. All patients with Marsh I and II had serology compatible with CD.

Deep remission was defined by the absence of histological findings suggestive of the disease, described as Marsh 0. Histological improvement was defined by reducing at least one value in the Marsh score, including those in histological remission.

Results

During the investigation, 69 patients met the inclusion criteria. Most of the CD patients were female (79.7%). The mean age at the time of diagnosis was 22.5 years. All patients were Caucasians. In terms of age distribution at diagnosis, 36.2% of the cases were diagnosed at pediatric age. The most frequent age group was between 18 and 39 years (42%), followed by those 40–65 years old (20.3%). A minority was diagnosed between 11 and 17 years (5.8%), and only 1 case (1.4%) was older than 65 years. For more detailed information regarding the age groups consult Table 1. Based on the July 2016 WGO guidelines [1], 36 (67.9%) were classified as classical, 9 (17.0%) nonclassical, and 8 (15.1%) in latent phase. Regarding family history, 15.9% of the patients had celiac relatives, 9 had first-degree relatives, and 1 had second-degree relatives. A minority of patients (7.2%) had concomitant diagnosis of other autoimmune diseases: 2 cases of diabetes mellitus and 3 cases of autoimmune thyroiditis. There were no autoimmune hepatitis or gastritis, Down, Turner, or Williams syndrome observed in the study population. In terms of complications, only 5.8% were affected, 1 of the patients had type II refractory CD, another had ulcerative jejunitis, and the other 2 osteoporosis. Most of the pa-

Table 1. Characteristics of the study population

Variables	*n* (%)
Gender	
Female	55 (79.7)
Male	14 (20.3)
Age at diagnosis	
<2 years	12 (17.4)
2–10 years	9 (13.0)
11–17 years	4 (5.8)
18–39 years	29 (42.0)
40–65 years	14 (20.3)
>65 years	1 (1.4)
Diagnosis at pediatric age	
Yes	25 (36.2)
No	44 (63.8)
Family history	
Yes	11 (15.9)
No	58 (84.1)
Type of presentation	
Classic	36 (67.9)
Atypical	9 (17.0)
Latent	8 (15.1)
Type of symptoms	
Classic	35 (67.3)
Atypical	18 (35.3)
Both[1]	9 (13.0)
Associated conditions	
Diabetes mellitus type I	2 (2.9)
Autoimmune thyroiditis	3 (4.3)
Complications	
Yes	4 (5.8)
No	65 (94.2)
Diet compliance	
Total	53 (76.8)
Partial	16 (23.2)
Nutrition consultation	
Yes	49 (71.0)
No	20 (29.0)
Nutritional deficiencies	
Yes	20 (29.9)
No	47 (70.1)

[1] This value includes patients from the classic and atypical groups.

tients (76.8%) had a total diet compliance. 29.9% had nutritional deficiencies at the time of diagnosis (Table 1).

The frequencies of the clinical presentations studied can be analyzed in Figure 1. It is important to highlight iron deficiency anemia (37.7%) and diarrhea (36.2%), which were the most commonly reported symptoms during the investigation (Fig. 1).

Only 30.8% of the population performed endoscopy before serology, and in most patients the diagnosis was initially suspected by serology. At endoscopy, 11.8% of the patients did not present macroscopic features suggestive of CD, and only 10.8% had *Helicobacter pylori* infection. A Marsh IIIa–c histological grade was observed in 75.5% of all cases (Table 2).

Eight patients (11.6%) underwent reassessment endoscopy within 24 months of starting the diet, and the remainder after 24 months. The average time between the start of GFD and reassessment endoscopy was 7.98 (±5.6) years. The histological findings were normalized in 37.7% ($n = 26$), which was associated with the presence of lower Marsh score values at diagnosis ($p = 0.014$) and a statistical trend for the presence of other autoimmune conditions ($p = 0.067$). Deep remission was also associated with lower DEXA T-score values ($p = 0.038$). A histological improvement over baseline was observed in 55 patients (79.6%), of 2 or more grades in 37 cases, which was related to a lower initial transferrin saturation ($p = 0.027$) and with higher values of the Marsh score at diagnosis ($p = 0.007$) (Tables 3–5).

Discussion

Duodenal histological revaluation after GFD adherence is still a controversial subject [13–16] but one with a major significance in the field of CD investigation. In fact, there are some experts who argue that profound remission can take a long time or even not happen [19]. In this investigation, we tried to determine the clinical factors related with histological improvement and deep remission. This investigation may indicate if histological reassessment should be routinely performed or not, and who could clinically benefit from this revaluation.

In this sense, during this study, we analyzed the correlations between multiple variables related to CD and histological improvement or deep remission. In fact, the study showed that there is a statistically significant relationship between histological improvement and lower transferrin saturation levels at the time of diagnosis (17.91 vs. 36.25%, $p = 0.027$). This may be explained by the fact that patients with lower levels of transferrin saturation may represent a more severe spectrum of the disease and therefore be more susceptible to improvement after starting the diet.

We also showed a statistically significant relationship between the histological grade at the reassessment endoscopy and the T score in bone densitometry ($p = 0.038$). In fact, patients with deep histological remission had a mean T score of –2.21 ± 0.865, and those who did not show deep remission had a mean T score of –0.40 ± 0.422. This is an

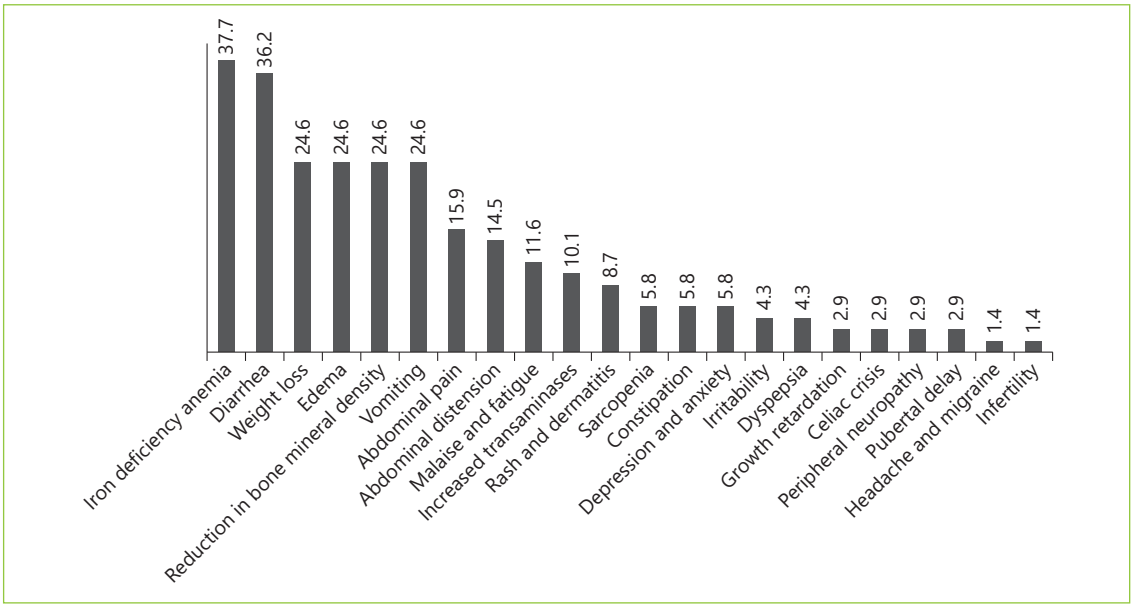

Fig. 1. Clinical presentation at diagnosis.

Table 2. Endoscopic features at diagnosis

Variables	*n* (%)
Histology before serology	
Yes	16 (30.8)
No	36 (69.2)
Endoscopy (when described)	
Suggestive findings	44 (88)
Without change	6 (12)
Macroscopic findings	
Waxing of villi	21 (47.7)
Scalloping folds	11 (25.0)
Waxing of folds	10 (22.7)
Nodular appearance of the bulb	2 (4.5)
Helicobater pylori infection	
Yes	4 (10.8)
No	33 (89.2)
Histological grade	
Marsh I	5 (10.2)
Marsh II	7 (14.3)
Marsh IIIa	8 (16.3)
Marsh IIIb	20 (40.8)
Marsh IIIc	9 (18.4)

Table 3. Endoscopic features: reevaluation

Variables	*n* (%)
Period of revaluation	
First 24 months	8 (11.6)
After 24 months	61 (88.4)
Histological grade	
Marsh 0	26 (37.7)
Marsh I	28 (40.6)
Marsh II	3 (4.3)
Marsh IIIa	8 (11.6)
Marsh IIIb	5 (7.2)
Marsh IIIc	1 (1.4)
Degrees of improvement	
0	14 (20.3)
1	18 (26.1)
2	19 (27.5)
3	11 (15.9)
4	7 (10.1)
Normalization of histology	
Yes	26 (37.7)
No	43 (62.3)
Normal endoscopy	
Yes	49 (74.2)
No	17 (25.8)

unexpected finding given that one of the frequent signs of CD is the premature reduction in bone density [21]. Such a result may be related to the fact that celiac patients without improvement have closer surveillance of their bone density and begin treatment earlier. In addition, bone density is dependent on several other factors, including sex, age, smoking, medication, and genetics, factors for which this association was not controlled.

Table 4. Continuous variables studied for improvement of histological grade and histological remission

	Improvement of histological grade			Histological remission		
	yes	no	*p* value	yes	no	*p* value
Initial hemoglobin	11.84±0.437	12.90±0.643	0.235	12.22±0.451	11.98±0.519	0.918
Initial ferritin	23.84±5.999	52.43±23.766	0.275	22.14±7.400	36.21±11.152	0.823
Initial transferrin saturation	**17.91±3.392**	**36.25±4.230**	**0.027**	16.85±4.296	24.04±4.333	0.282
Initial DEXA scan T score	–0.98±0.529	–1.10±0.502	0.574	**–2.21±0.865**	**–0.40±0.422**	**0.038**
Initial AST	29.03±2.475	27.40±3.833	0.828	27.71±4.012	29.09±2.491	0.658
Initial GGT	16.43±3.299	24.20±5.581	0.118	13.08±1.380	20.22±3.947	0.315
Initial FA	96.48±9.272	90.20±15.312	0.640	94.62±14.337	95.20±9.597	0.724
Initial total bilirubin	1.85±0.350	1.73±0.645	0.803	1.97±0.585	1.76±0.361	0.608
Initial folic acid	3.95±0.403	4.67±2.206	0.352	4.83±0.768	3.74±0.719	0.076
Initial vitamin B_{12}	506.31±62.510	607.00±158.889	0.599	606.92±133.357	490.24±60.448	0.267
Initial antitransglutaminase	1,150.15±749.148	71.08±25.657	0.135	2,429.61±2,237.480	409.04±147.023	0.543
Initial antigliadin	31.89±8.055	–	0.444	26.93±12.660	31.87±10.148	0.750
Ionized calcium	3.01±0.189	2.65±0.418	0.490	3.35±0.279	2.66±0.203	0.145
Magnesium	1.57±0.031	1.63±0.024	0.289	1.61±0.021	1.57±0.039	0.389
Phosphorus	3.53±0.094	3.52±0.189	0.916	3.65±0.121	3.45±0.112	0.258
Vitamin A	40.19±1.744	42.80±5.660	0.687	38.80±2.615	41.41±2.154	0.388
Vitamin D	25.05±1.533	20.12±3.011	0.193	27.20±3.166	22.66±1.354	0.163
Vitamin E	972.21±41.596	1,029.80±121.259	0.789	979.30±47.836	984.26±52.777	0.603
Zinc	72.11±3.372	–	0.200	70.33±8.876	71.14±3.370	0.833
Age	20.98±2.284	30.14±5.685	0.096	19.12±3.075	25.05±2.932	0.314

For continuous variables, the entries are means ± SD. The Mann-Whitney U test was used for statistical analysis.

Evidence also indicated that there was a trend towards a relationship between histological normalization and CD-associated autoimmune conditions ($p = 0.067$). In this case, there may have been a significant loss of statistical power because of the limited number of patients in the study.

On the other hand, it was found that the presence of lower Marsh score values at diagnosis was significantly associated with histological normalization ($p = 0.014$). Probably, this may be due to the fact that the higher the histological grade, the more difficult it is to obtain a complete recovery of the duodenal mucosa. This is in accordance with what is now known, which makes it difficult to find a justification for the need to prove deep remission in all patients within a certain time period. In fact, it is not known how much time each patient needs for histological remission [18, 22].

Finally, it was found that only a third of the patients reached deep histological remission, regardless of clinical and serologic response, which indicates that, as Wahab et al. [19] argues, deep remission may take a long time, especially in adulthood, or it may not even be reached by some patients, without relevant clinical impact. In addition to the absence of histological remission in most patients, no clinical factors were found to be related to the absence of this remission. In fact, during this investigation, none of the clinical variables, including complications, were related to outcome. This further complicates the identification of the patients who benefit from the histological reevaluation, stressing the controversy of this issue. As such, the challenge will be to select the patients for whom that evidence may be beneficial for follow-up. Given that, this may lead us to rethink a more appropriate follow-up for CD patients.

During the conduct of this investigation, we faced some limitations. In fact, since this is a retrospective study, there was lack of information in some variables, something inherent to this type of investigation. Likewise, we had a limited number of patients with histological reassessment, and although patients needed to have started the diet for at least 12 months to be included in this study, the time interval during which they underwent endoscopic reassessment was found to be quite disparate among participants. Moreover, a selection bias may have occurred because histological reassessment is not mandatory, and possibly less compliant patients may have refused to perform this more sensitive examination for fear of the result. Additionally, the population that adhered to the revaluation endoscopy had a low complication rate, which made the prognostic assessment not feasible.

Table 5. Categorical variables studied for improvement of histological grade and histological remission

	Deep remission			Improvement of histological grade		
	yes	no	*p* value	yes	no	*p* value
Gender						
Female	76.9%	81.4%	0.654	80.0%	78.6%	0.582*
Male	23.1%	18.6%		20.0%	21.4%	
Age group						
<2 years	15.4%	18.6%	0.103*	16.4%	21.4%	0.140*
2–10 years	26.9%	4.7%		14.5%	7.1%	
11–17 years	7.7%	4.7%		7.3%	0.0%	
18–39 years	38.5%	44.2%		45.5%	28.6%	
40–65 years	11.5%	25.6%		16.4%	35.7%	
>65 years	0.0%	2.3%		0.0%	7.1%	
Smoking						
Yes	11.5%	4.8%	0.281*	7.4%	7.1%	0.728*
No	88.5%	95.2%		92.6%	92.9%	
Family history						
Yes	23.1%	11.6%	0.208	81.8%	92.9%	0.290*
No	76.9%	88.4%		18.2%	7.1%	
Presentation type						
Potential	0.0%	0.0%	0.197*	0.0%	0.0%	0.235*
Latent	11.8%	16.7%		14.6%	16.7%	
Classic	82.4%	61.1%		73.2%	50.0%	
Atypical	5.9%	22.2%		12.2%	33.3%	
Iron deficiency anemia						
Yes	52.6%	47.1%	0.697	54.8%	27.3%	0.104
No	47.4%	52.9%		45.2%	72.7%	
IgA deficiency						
Yes	8.7%	2.7%	0.325*	6.1%	0.0%	0.538*
No	91.3%	97.3%		93.9%	100.0%	
Histological grade						
Marsh I	5.6%	12.9%	**0.014***	2.6%	40.0%	**0.007***
Marsh II	27.8%	6.5%		12.8%	20.0%	
Marsh IIIa	33.3%	6.5%		15.4%	20.0%	
Marsh IIIb	22.2%	51.6%		46.2%	20.0%	
Marsh IIIc	11.1%	22.6%		23.1%	0.0%	
Associated conditions						
Yes	15.4%	2.4%	0.067*	7.4%	7.1%	0.728*
No	84.6%	97.6%		92.6%	92.9%	
Refractory disease						
Yes	0.0%	2.3%	0.623*	1.8%	0.0%	0.797*
No	100.0%	97.7%		98.2%	100.0%	
Diet compliance						
Total	80.8%	69.8%	0.700*	78.2%	57.1%	0.280*
Partial	19.2%	30.2%		21.8%	42.8%	
Nutrition consultation						
Yes	61.5%	76.7%	0.117	69.1%	78.6%	0.367*
No	38.5%	23.3%		30.9%	21.4%	

For categorical variables, the entries are percent patients with the characteristic. For statistical analysis, Pearson's x^2 test was used, but for variables with small groups Fisher's exact test* was used instead.

This study has several strengths, such as studying the follow-up of CD in adulthood, because the majority of the studies are still performed at pediatric age, and the fact of addressing a topic that is still very scarcely mentioned in the current literature, such as the relevance of deep remission and its clinical impact.

Surprisingly, this type of studies on CD deep remission and its possible long-term impact in adult patients are still scarce. For this reason, this study may serve as an impetus to further study this relevant subject in future investigations.

Concluding, even under GFD, normalization of the histological findings of CD is difficult to obtain and appears to be independent of most clinical and serological findings at diagnosis. Patients with less severe histological levels at diagnosis reach remission more easily, but only represent the minority of the population. This work may add value to the importance of follow-up of these patients, since a more in-depth evaluation has not yet demonstrated clinical value, as suggested by our work.

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Statement of Ethics

The study protocol, which received ethics committee approval, conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee. Written, informed consent was obtained from each patient included in the study.

Disclosure Statement

The authors declare no conflicts of interest.

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