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ORIGINAL ARTICLE

Predictors of slow responsiveness and partial mucosal recovery in adult patients with celiac disease

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ABSTRACT

Aim: The present study aims to determine the rate of mucosal recovery and predictors of persistent mucosal damage after gluten free diet (GFD).

Background: Celiac disease (CD) is a complex multi-systemic autoimmune disease triggered by exposure to dietary gluten in genetically predisposed individuals. There is still little evidence on the best method for assessing GFD adherence and mucosal recovery during treatment.

Methods: The retrospective study included only adult patients (age≥18 years old), with biopsy-proven CD evaluated at a tertiary referral centre between 2016 and 2021. We performed a logistic regression analysis to identify factors associated with partial mucosal recovery (MR) after GFD. We included in the multivariate analysis parameters available at the time of CD diagnosis.

Results: A total of 102 patients were enrolled, two thirds were females, median age of 39 years (yrs). The initial biopsy analysis showed different stages of villous atrophy (VA) in 79 (77.4%) cases, while in 23(22.5%) cases showed mild enteropathy (Marsh 1, 2). After at least 12 months of GFD, 26 (25.5%) patients had persistent VA despite good or excellent adherence to GFD. Younger patients (< 35yrs), who showed severe mucosal damage (Marsh 3c lesions) and who had increased anti-gliadin antibody (AGA) levels were at risk for failure to obtain mucosal recovery (MR). Logistic regression analysis demonstrated that complete mucosal atrophy (P=0.007) and high AGA antibody levels (cutoff 129 U/ml, P=0.001) were independent risk factors for lack of mucosal improvement after at least 12 months of GFD. Interestingly, genotype, tTG-IgA antibody levels, or duration of GFD levels did not influence the occurrence of MR.

Conclusion: Although AGA seropositivity has lost much of their diagnostic significance in recent years due to the introduction of the more sensitive and specific antibody tests, our study reported that patients aged < 35 yrs, who showed severe mucosal damage (Marsh 3c lesions) and who had increased AGA antibody levels at diagnosis were at risk for failure to obtain MR. The elevated AGA levels at diagnosis could be used as a prognostic tool for assessing MR.

Keywords: Celiac disease, Gluten free diet, Tissue transglutaminase, Mucosal recovery, Mucosal healing.

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Introduction

Celiac disease (CD) is a complex multi-systemic autoimmune disease triggered by exposure to dietary gluten in genetically predisposed individuals (1). CD is defined by the presence of small-intestinal mucosal injury of different extents and severity in the presence of specific auto-antibodies (2). The treatment for CD is primarily a gluten-free diet (GFD), which requires significant patient awareness, encouragement, and optimal follow-up (3). Slow responsiveness is rare among children but is frequently discovered among patients diagnosed in adulthood (3, 4). Hypothetically, this can be explained by a decreased regenerative capacity of the mature intestine, resulting in a slow and

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incomplete mucosal restoration (4, 5). Clinical response is typically observed in most adults with CD after treatment with a GFD, yet some patients remain symptomatic despite having documented mucosal recovery (MR) (5). However, physicians should pay attention and be more aware in case of persistence of symptoms despite a GFD to revise and rule out alternative diagnoses (3).

Because CD is an incurable disease, a GFD is a life-long commitment. The therapeutic goal is to achieve a normal mucosa (Marsh 0) or, at least, a partial resolution of mucosal injury. The rate of MRis, however, less certain. There is no obvious relationship between the extent of enteropathy in untreated patients, baseline symptom severity, clinical response to GFD, and rate of MR (5). Asymptomatic patients may not attain MR, and MR cannot be detected except for standard endoscopy with biopsy sampling as no surrogate markers are currently available (6). One plausible explanation as to why patients show incomplete MR despite a strict GFD is persistent but minimal inadvertent gluten consumption. The quantity ingested is not significant enough to induce symptoms or determine an increase in antibody levels but sufficient to induce some degree of inflammation and even villous atrophy (VA) (7, 8). A residual long-lasting immune response may play a role in the failure to heal the mucosa (7). Realistically, total avoidance of gluten is simply not possible. Therefore, we can safely assert that complete avoidance of gluten is currently an unachievable goal even for the more determined patients.

There is general agreement concerning regular follow-up of CD patients, however, the follow-up modalities are not currently standardized. A regular dietary assessment of GFD compliance by a trained dietitian is advised. Using the Marsh-Oberhuber classification, complete mucosal healing (MH) is the equivalent of the histological Marsh 0 grade (normal mucosa), while MR can be attributed to the histological improvement of villous architecture, with downgrading from total villous atrophy (VA) to partial atrophy or even Marsh 1-2. A second biopsy should be provided to confirm recovery, however, its invasiveness limits its use in regular follow-ups (7). Therefore, reliable non-invasive surrogate markers of MH are required to reduce the need for endoscopic procedures.

Identification of tissue transglutaminase (tTG) immunoglobulin A (IgA) as the autoantigen led to the development of highly sensitive tTG-IgA antibody screening tests which increased awareness and facilitated the diagnosis of active CD (8,9). A no-biopsy approach was suggested and it quickly became a valid option to diagnose CD among children by using tTG IgA > 10x as a new cut-off to reduce the burden of endoscopic procedures. However, this does not apply to adult CD patients. CD autoimmunity is highly efficient at diagnosis but these serological markers are less dependable and accurate during monitoring. Studies have shown that although constant positive tTG-IgA values among treated patients could suggest persistent mucosal damage probably due to dietary contamination, other reports have failed to provide similar results. Moreover, a negative tTG-IgA test fails to detect intestinal healing (reflecting only sufficient dietary compliance) and in some studies, they have proven to be poor markers in detecting persistent VA in treated CD cases (10, 11).

Documentation of MR after treatment with a GFD is important because patients with ongoing VA share a higher risk for developing malignant and non-malignant extra-intestinal complications (7). However, normalization of architectural mucosal changes does not occur in all patients with CD who have already achieved a complete clinical response. The clinical response occurs shortly after the implementation of GFD, but recovery may appear in months or years or remains incomplete in adults for longer periods of time (3). Because CD progresses and evolves with a variable combination of gluten-dependent clinical manifestations irrespective of the degree of VA and antibody levels, they are regarded as unspecific and unreliable markers for detecting VA.

The present study focuses on the assessment of clinical, serological, and histological responses for a cohort of patients diagnosed with CD following a GFD. In addition, we aimed to identify predictors of incomplete MR after GFD.

Methods

The study included only adult patients (age ≥ 18 years old), with biopsy-proven CD evaluated at a tertiary referral centre between 2016 and 2021, retrospectively identified through computerized biopsy

reports from the Department of Pathology. Data regarding symptomatology, serology, laboratory parameters, and histological assessment of biopsy samples were analysed at the time of diagnosis (baseline) and follow-up.

Upper endoscopy with biopsy was performed at diagnosis and during follow-up (12 months after GFD). For patients with more than one follow-up biopsy, the earliest follow-up biopsy within the period of 12 months to five years was included. A minimum of one biopsy from the bulb and four biopsy samples from the distal duodenum were required for morphological analysis.

Using the Marsh-Oberhuber classification in accordance with more recent studies, we defined complete mucosal healing (MH) as the equivalent of the histological Marsh 0 grade (no visible signs of VA, crypt hyperplasia, and an intraepithelial lymphocytes count less than 25 per 100 enterocytes), while MR was defined as the absence of VA, i.e., Marsh 0-2 compared to baseline (12,13). The biopsy specimens were reviewed by a single experienced pathologist. The final assessment was performed on the most severely damaged biopsy specimen.

Clinical response was defined as complete when no residual symptoms were declared by patients or partial when some clinical improvement was obtained after gluten withdrawal but without a return to normality. A dietitian with expertise assessed adherence to GFD and scored the adherence using criteria modified from Leffler et al as excellent (rare or non-existent exposure), good (once a month contamination), poor (ingestion of gluten once or two times/week), noncompliant (normal diet) (14). Patients with CD were assessed after a standardized protocol used in our department which implies clinical evaluation and questionnaire every 3 months, complete blood work every 6 months and upper endoscopy every 12 months during follow-up.

Serological markers, tTG2-IgA, anti-gliadin IgA (AGA-IgA), and total serum IgA levels respectively were assessed at baseline and after implementation of GFD. Quantitative analysis was performed using a commercial enzyme-linked immunosorbent assay, and ELISA kit. Serum levels of IgA and IgG-tTG2 were reported according to the manufacturer's cut-off as UI/ml and classified as negative < 15 IU/ml and positive ≥ 15 IU/ml. AGA-IgA levels were also assessed and classified as negative < 15 IU/ml and positive ≥ 15 IU/ml. In the case of selective IgA deficiency, the corresponding IgG-class antibodies were measured. A positive serological response was defined as a negative serological test at follow-up.

Complete HLA-DQ typing alleles were isolated using genomic DNA extracted from EDTA-anticoagulant peripheral blood employing QIA amp blood mini according to the manufacturer's instructions. Polymerase chain reaction (PCR) with sequence-specific primers (PCR-Olerup-SSP) using a commercial low-resolution kit (BAG, Germany) was performed. We identified and compared 3 study groups based on the CD-associated HLA types: high risk: DQ2.5/DQ2.5, DQ2.5/DQ2.2, DQ2.5/X, DQ2.5/DQ8, DQ8/DQ8, moderate risk: DQ2.2/X, DQ8/X, DQ2.2/DQ2.2, and low risk: DQ7/X, DQ7/DQ7, DQX/DQX, where DQX≠ DQB1*02, DQA1*05, DQB1*03:02, and DQ7 (DQA1*05: DQB1*03:01). CD is considered to have a high heritability involving HLA and non-HLA genes, which jointly provide the genetic risk to develop the disease and we aimed to see whether the genetic inheritance may correlate with a more severe CD phenotype, greater VA and suboptimal response to treatment.

Statistical and power analysis

Statistical analysis was performed using SPSS 18 software (SPSS Chicago Inc., IL, USA) and MedCalc software (version 11.4, Ostend, Belgium). Data were summarized by descriptive statistics, including percentages and counts for categorical data. Continuous variables were expressed as mean plus/minus standard variation for normally distributed continuous data, and as the median and interquartile range (IQR) to describe non-normally distributed continuous data. Groups were compared using $\chi 2$ test for categorical variables and using the independent t-test or Mann-Whitney U test for continuous variables (depending on data distribution). Univariate analysis was performed for each recorded data. The factors associated with MR in patients with CD were identified using univariate and multivariate logistic regression. A P-value<0.05 was considered statistically significant.

Ethics

The study was approved by the ethical committee and all participants were informed about the study

according to the study protocol and gave their written informed consent.

Results

A total of 102 patients were enrolled, two thirds were females, median age of 39 years, a range of 20-73 years. Overall, the majority of subjects presented with gastrointestinal complaints such as diarrhea (69 patients, 67.6%), abdominal pain (77 patients, 75.5 %), and anemia (63 patients, 61.8%). A total of 16 (15.6%) subjects were diagnosed via routine screening of family members diagnosed with CD. Autoimmune diseases such as type 1 diabetes or thyroiditis were diagnosed in 7 (6.9%) patients. No patient was IgA deficient. Supplementary data of demographics, and clinical and laboratory characteristics of patients with CD are shown in Table 1.

The initial biopsy analysis showed different stages of VA in 79 (77.4%) cases, while 23 (22.5%) cases showed mild enteropathy (Marsh 1, 2). Patients included in the study group underwent at least one follow-up appointment after the initiation of GFD. The median follow-up period was 22.6 months. At follow-up, complete VA (Marsh 3c) was confirmed in 2 (2%) cases, Marsh 3b in 4 (3.9%) cases, and Marsh 3a in 20 (19.6%) cases. More than two-thirds of patients 76 (74.4%) had Marsh 1 and 2 lesions, corresponding to mild enteropathy. No patient had Marsh 0- normal mucosa during follow-up. Therefore, after at least 12 months of GFD, 26 (25.5%) patients had persistent VA (Marsh3a-c lesions) despite good or excellent adherence to GFD.

TTG- IgA antibodies results were available for all 102 CD patients at diagnosis, with a median tTG-IgA value of 97.7 U/ml. AGA-IgA antibody levels reported similar patterns in detecting VA (P=0.004). Among

Table 1. Baseline characteristics of the study groups.

Parameter	Recovery group (n=73)	Incomplete recovery group (n=29)	P value
Age, mean +SD, yrs	39.54±12.70	42.79±12.48	0.245
Female (%)	58 (79.4%)	21(72.4%)	0.443
Residency, urban (%)	58 (79.4%)	20 (68.9%)	0.260
Reason for referral (%)			
Diarrhea (%)	48(65.7%)	21(72.4%)	0.517
Weight loss (%)	61(83.5%)	24(82.7%)	0.922
Abdominal pain (%)	56(72.4%)	21(72.4%)	0.649
Dermatitis herpetiformis (%)	8(10.9%)	2(2.7%)	0.534
Iron deficiency anemia (%)	46(63%)	17(58.6%)	0.680
Family history of CD (%)	14(19.1%)	2(2.7%)	0.124
Autoimmune disease (%)	3(4.1%)	4(5.4%)	0.081
TTG -IgA titer (U/ml), median (IQR)	97.7 (197.95)	67.0 (116.9)	0.183
AGA-IgA titer mean+SD (U/ml)	59.26±67.26	70.32±68.42	0.004
Biochemical parameters			
Hemoglobin, mean+SD g/dL	10.67±7.89	12.89±5.23	0.001
AST, mean+SD U/dL	39.31±26.50	42.58±26.53	0.647
Albumin, mean+SD g/dl	3.86±0.59	3.75±0.75	0.148
Iron, mean+SD µg/dl	47.26±40.85	57.35±42.71	0.490
Response to GFD			
Excellent	21 (28.7%)	7(24.1%)	
Good	38(52%)	22(75.8%)	0.022
Poor	9 (12.3%)	0	
Noncompliant	4(5.4%)	0	
Mild enteropathy (%)	14(19.1%)	9(31%)	0.196
Marsh I-II			
Villous atrophy (%)			
Marsh 3a	16(21.9%)	11(37.9%)	0.098
Marsh3b	13(17.8%)	5(17.2%)	0.946
Marsh3c	30(41%)	4(5.4%)	0.008
High-risk genotype (%)	49(67.1%)	14(48.2%)	0.077
Moderate risk genotype (%)	9(12.3%)	8(27.5%)	0.691
Low-risk genotype (%)	15(20.5%)	7(24.1%)	0.062

Abbreviations: AGA-IgA: anti-gliadin immunoglobulin A; AST: aspartate aminotransferase; CD: celiac disease; GFD: gluten free diet; IQR: interquartile range; SD: standard deviation; TTG –IgA- tissue transglutaminase immunoglobulin A.

patients who showed persistent VA while on GFD, tTG-IgA levels did not reflect the severity of intestinal damage (P=0.316). The serological response was documented in 86(84.3%) cases, whilst 16 (15.7%) still had a positive serology at follow-up. The majority of patients, both with persistent VA and with MR reported good or excellent adherence to the GFD, and one-third of patients were asymptomatic at the time of the follow-up endoscopy.

Both at diagnosis and at follow-up, patients who showed more severe mucosal damage (Marsh 3a-c) inherited the predisposing genotypes which conferred the highest genetic risk but showed no statistically significant difference when comparing the study groups (Table 1).

Younger patients (<35 yrs), who showed severe mucosal damage (Marsh 3c lesions) and who had increased AGA antibody levels were at risk for incomplete recovery. The logistic regression analysis demonstrated that complete mucosal atrophy (OR 8.503, 95% CI 1.590-45.478, P=0.007) and high baseline AGA antibody levels (OR 0.12, 95% CI 0.032-0.508, P=0.001) were independent risk factors for lack of mucosal improvement after at least 12 months of GFD. Interestingly, genotype, tTG-IgA antibody levels, or duration of GFD levels did not influence the occurrence of MR. The results of the univariate and multivariate logistic regression analyses are shown in Table 2.

Discussion

The results published to date across studies concerning complete MR ratios achieved by CD patients on a GFD are contradictory. It is currently unknown whether MR or complete MH is linked to survival among patients with CD. Nevertheless, a normal mucosa (Marsh0) is the expected goal of the therapy (15).

Although recent guidelines recommend regular monitoring of CD patients by either the general practitioner, a specialist or a trained dietician, there is still no standardized approach for assessing GFD adherence and MH (3). Monitoring of gastrointestinal and extra-intestinal signs and symptoms, together with CD autoimmunity, screening for comorbidities, biochemical, hormonal and bone abnormalities should be included in the follow-up appointments (16). Nevertheless, symptoms and serology correlate poorly with the follow-up histology, and patients with ongoing mucosal damage could be exposed to long-term complications (17). The need for re-biopsy is still a matter of debate but should be performed in symptomatic patients on long-term GFD. Although some studies argue that patients who do not obtain MR or MH are at higher risk of adverse outcomes in the long run, more recent evidence suggests that lack of MR is not associated with higher mortality compared to patients who progressed toward MR or the general population (14). These findings are supported by Lebowl et al who showed that persistent VA is not associated with increased mortality in CD in the population followed by a median of 11.5 years (18). Rubio-Tapia et al reported that the majority of adult patients diagnosed with CD while on GFD failed to

Table 2. Risk factors for incomplete mucosal recovery- univariate and multivariate analysis.

Parameter	Univariate analysis			Multivariate analysis		
	OR	CI 95%	P- value	OR	CI 95%	P- value
Female	1.09	0.852-1.413	0.614	0.92	0.080-1.195	0.089
Urban residency	1.15	0.879-1.510	0.386	2.32	0.654-8.227	0.120
Autoimmune disease	0.29	0.071-1.250	0.099	0.23	0.031-1.774	0.150
Age <35 years	2.05	1.059-4.393	0.034	3.01	0.932-9.676	0.066
Age ≥35 years	0.79	0.615-1.026	0.103	0.44	0.162-1.242	0.123
Family history	2.78	0.674-11.479	0.100	5.71	0.920-35.528	0.061
Marsh 3c	2.97	1.152-7.707	0.005	8.503	1.590-45.478	0.007
Diagnosis <3.5 years of GFD	0.89	0.649-1.246	0.537	0.64	0.197-2.123	0.294
Diagnosis >3.5 years of GFD	1.19	0.673-2.111	0.535	1.29	0.521-3.201	0.581
GI symptoms	1.32	0.392-4.469	0.647	0.24	0.036-1.618	0.114
High-risk genotype	1.39	0.923-2.094	0.080	1.69	0.554-5.173	0.402
TTG-IgA, *cutoff* 177 U/ml	1.87	0.937-3.745	0.082	0.91	0.229-3.655	0.958
AGA -IgA, *cutoff* 129 U/ml	0.69	0.524-0.926	0.025	0.12	0.032-0.508	0.001

OR: Odds ratio; CI: Confidence interval

achieve MR. Interestingly, serological response and a decreased rate of all-cause mortality were associated with confirmed MR, regardless of age and gender (7).

Szakács et al concluded in a recent meta-analysis that several celiac patients fail to achieve complete MR even if a strict GFD is maintained. The authors state that diagnosing CD in male patients, at a younger age, and showing less severe initial histologic damage are predisposing risk factors for achieving MR (19). Our results do not reflect the findings by Szakács et al, and, age, gender, or duration of GFD do not impact the rate of MR in our cohort of CD patients. Nevertheless, our study showed that the most important predictor of incomplete MR was the presence of severe mucosal damage, complete Mash 3c VA. The majority of patients at diagnosis showed different degrees of VA, but even after at least one year of GFD, the most prominent factor in predicting incomplete was the presence of severe enteropathy and higher antibody levels. As reported by our study, tTG-IgA levels correlated well with VA at baseline. Altogether, 74.5 % showed morphological improvement after at least one year of GFD, which is satisfactory compared to results reported by other authors.

An interesting aspect of our study results was the high proportion of patients having mild enteropathy (Marsh 1-2) at diagnosis compared to other clinical trials (13). Subjects were identified based on clinical presentation, positive celiac serologies while on a full-gluten diet, and they underwent a rigorous screening process to detect alternative diagnosis, as these lesions may be found in other illnesses. The patchy nature of mucosal involvement with different degrees of severity encourages the need for multiple biopsy samples, as indicated by guidelines. However, the natural history of Marsh 1-2 histology is still poorly understood, and that the need for GFD in these subjects is therefore an important area of uncertainty. Some studies report that patients with mild enteropathy may evolve into active CD, and therefore they should benefit from early implementation of the GFD (20).

Using antibody levels to assess restoration of the duodenal mucosa is not advised. EMA and tTG antibodies have satisfactory sensitivities and specificities for diagnosis, but a persistently positive or negative value during a 18-24 months follow-up can suggest either suboptimal or adequate reduction of gluten consumption. There are a number of variables to take into consideration from the type of assay used, timeline of testing, the type of antibodies used and dietary compliance when assessing tTG-IgA dynamics (21).

Interestingly, our results showed a lack of serological response in patients with VA, but this relationship failed to translate to follow-up when high antibody levels were unable to detect persistent VA. However, we found that elevated AGA IgA levels at baseline predicted a lack of MR. We are aware that AGA has lost much of its diagnostic sensitivity and specificity and in time allowed room for more accurate tests, but the positivity of AGA antibodies and tTG-IgA in patients with symptoms indicative of CD has a significant diagnostic value (17, 22). The AGA test can be used in the follow-up of CD patients following a GFD because normally IgA and IgG AGA disappear after 3–9 months of a GFD (23). In this case, inadvertent gluten contamination of the diet can be suspected due to high AGA antibody levels at follow-up. The additional roles of AGA serology as a prognostic factor for lack of mucosal restoration however should be further studied in prospective studies.

Husby et al highlighted in a recent paper that celiac serology has a restricted role in the detection of continued intestinal injury. Also, the authors encourage physicians to properly recognize when persistently positive serology is detected, usually, it is an indicator of ongoing intestinal damage and gluten exposure (17). However, when assessing patients with recurrent symptoms, upper endoscopy and biopsies should be performed even in the presence of negative tTG-IgA (24). Tomer Ziv-Baran et al reported that tTG but not EMA levels correlated with macroscopic (scalloping of duodenal folds) and microscopic mucosal damage (according to Marsh classification), but not with symptoms. Therefore, a single marker (either symptoms, serology, histology, or endoscopic appearance) is unreliable for disease diagnosis, management, and follow up (25). However, one type of antibody has shown more potential in non-invasive surveillance of CD patients under a GFD (25-28). In a recent paper by Spatola et al, the authors reported that increased levels of anti-deaminated gliadin peptide IgG antibodies in CD patients on strict GFD effectively identify patients with non-responsive CD. This assay may aid in detecting ongoing mucosal damage in CD patients on a strict GFD (28).

Interestingly, children diagnosed with CD and who are treated with GFD experienced 96% MR after 2 years, and 100% fully recovered in the long-term follow-up. Early data, although scarce, suggest a pattern of quick and complete MR among children which is significantly lost as they enter adulthood. Therefore, recent guidelines have proposed a no-biopsy diagnosis and follow-up in young CD patients because of 2 main reasons: there is a correlation between specific antibody levels and severity of mucosal damage, and are used to monitor MH and secondly the swift recovery of mucosa compared to the adult population. Some contributing factors could explain the excellent response rate: the younger intestine with adequate healing capacity, a high-nutrient, high-vitamin selective controlled diet provided by attentive parents, and a healthy functioning microbiota, which are deficient in the adult population. However, systematic follow-up with intestinal biopsies is recommended in adult patients with CD. A no-biopsy surveillance approach should be cautiously applied (28).

In agreement with recent guidelines, follow-up serology should be performed at least at 12 months after diagnosis, and every year afterward (29, 31), and we can state that our policy follows guideline recommendations for annual check-up of CD patients. Adherence to GFD should be addressed by an experienced and dedicated nutritionist. Between the use of upper endoscopy, which is invasive and difficult to implement for long-term monitoring, and dietary questionnaire which may be subjective this grey zone can be managed using easy, non-invasive tools to determine inadvertent gluten exposure (32). The detection of gluten immunogenic peptides (GIP) in urine and feces have been suggested as means to detect gluten consumption and verify GFD adherence in CD patients (33). These simple tests could overcome some of the troublesome clinical aspects of CD management, and give patients some control over their disease while awaiting promising new drugs (34).

Conclusion

In conclusion, a diagnosis of CD implies great responsibility given that it entails strict lifelong commitment to the burdensome GFD. Although the ultimate goal is to reach a new normality or at least come as close to it as possible, there are still some obstacles to surmount. Although our study has some limitations (small number of patients, the retrospective observational nature) this study confirms that MR is more likely in adult patients who have less significant mucosal lesions upon diagnosis and are compliant with the GFD. Nevertheless, tTG-IgA while dependable at diagnosis is a poor predictor of ongoing VA in CD patients on a GFD independently correlated with symptomatology. However, the role of AGA antibodies as a prognostic tool for assessing MR requires additional studies, as the information on the topic is scarce. There is an unmet need for non-invasive tools to address MR among CD patients and GFD.

Conflict of interests

The authors declare no conflict of interests.

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