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Retrospective Study

Upper gastrointestinal endoscopic findings in celiac disease at diagnosis: A multicenter international retrospective study

Endoscopic findings in CeD

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Abstract

BACKGROUND

Background/Aim: Gastroduodenal endoscopy and biopsy following positive specific serology is considered the gold standard to diagnose celiac disease (CeD) in adults. Whether upper endoscopy also helps detect co-morbid conditions is unknown.

AIM

We investigated the prevalence of non-celiac endoscopic findings in patients in whom endoscopy was performed to confirm CeD diagnosis.

METHODS

This is an observational, descriptive, multicenter, retrospective study that reports endoscopic findings obtained in adult patients enrolled in local registries from four tertiary centers. We collected data related to findings from the first endoscopy performed for the diagnosis of CeD. The disease was diagnosed based on histology (≥Marsh 2 type mucosal damage) and serologic criteria. Two European and one North American center investigated new, biopsy-confirmed CeD following positive serology. A fourth center (South America) included symptomatic patients undergoing endoscopy, irrespectively of CeD serology, which included a non-CeD control group.

RESULTS

A total of 1328 patients (80% female; 35 yr median age) were enrolled, of whom the majority (95.6%) had positive specific serology. In 135 patients, endoscopy revealed 163 abnormalities unrelated to CeD (prevalence: 10.1%). Erosive reflux esophagitis (6.4%), gastric erosions (1.9%), and suspicion of esophageal metaplasia (1.1%) were the most common findings. Biopsy-confirmed Barrett's esophagus was infrequent (0.2%). No endoscopic evidence of cancer was detected. Older patients (≥51 years of age) had a higher prevalence of endoscopic findings than younger ones (≤50) (p<0.01). Within the South American cohort, CeD was associated with a lower rate (8.2%) of co-morbid

endoscopic findings compared with controls (29.1%; $p<0.001$). In the adjusted multivariate analysis of this cohort, having CeD was associated with a 72% reduction in the risk of any endoscopic abnormality ($p<0.0001$), and having alarm symptoms was associated with a 37% reduction in the risk of having at least one endoscopic lesion ($p<0.02$).

CONCLUSION

In this large multicenter study, young adults with positive CeD serology had few co-morbid endoscopic findings. Although patients over 51 yrs had a high prevalence of non-CeD gastroduodenal mucosal damage, no malignancy or premalignant lesions were found in these cohorts.

Key Words: Celiac disease; upper GI endoscopy; concomitant endoscopic lesions; malignancies.

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Core Tip: We offer novel data on the prevalence of non-celiac endoscopic findings at the time of endoscopy performed to confirm CeD diagnosis. Based on the very high performance of specific serology tests, the diagnosis of CeD without duodenal biopsy has been proposed in recent years. However, some guidelines do not recommend avoiding endoscopy, because relevant co-morbid diagnosis can be missed. Our results found that co-morbid upper GI endoscopic pathology is uncommon in patients with positive CeD serology at the time of diagnostic endoscopy suggesting that a non-biopsy strategy is unlikely to miss clinically significant concomitant endoscopic findings unrelated to CeD.

INTRODUCTION

Celiac disease (CeD) is one of the most common life-long chronic diseases affecting people with genetic predisposition conferred by HLA-DQ2 or DQ8 (*1*). Current recommendations for diagnosing CeD in adult patients involve a combination of specific serology tests and a duodenal biopsy demonstrating some degree of intestinal atrophy (*2,3*). When CeD is clinically suspected, upper gastroduodenal endoscopy with duodenal biopsy provides histological diagnosis (*4*). Based on the very high specificity and predictive values of specific serology tests (5), the diagnosis of CeD without duodenal biopsy has been proposed in recent years (*6-8*). Indeed, European pediatric societies recommend a non-biopsy diagnostic approach under specific and strict criteria (*9-10*). However, other pediatric societies (e.g. the North American Pediatric Gastroenterology Society) do not recommend avoiding endoscopy and biopsy confirmation, because relevant co-morbid diagnosis can be missed (*11*). Despite several studies have suggested that such a diagnostic strategy can be implemented in adults (*12*). The strategy is a concern for adults, particularly in those with alarm symptoms such as body weight loss, anemia, or abdominal pain (*2,12,13*). However, only relatively small studies have explored this in-depth, particularly in adult patients undergoing endoscopy to confirm CeD diagnosis (*14-16*).

Thus, we conducted a multicenter study involving four cohorts of patients diagnosed in three countries to investigate the prevalence of coincidental upper gastrointestinal (UGI) endoscopic findings in CeD patients at the time of diagnosis. We also compared UGI mucosal injury diagnoses across centers and age groups. Finally, we studied the pathological findings in patients with a confirmed diagnosis of CeD *vs* those in whom the disease was ruled out.

MATERIALS AND METHODS

We conducted a descriptive multicenter retrospective study that reports endoscopic findings from adult patients who met standard clinical, serologic, and histological

criteria for CeD. Patients from four different CeD-specialized centers were included. Two European cohorts (Universities of Naples/Salerno and Padua; Italy) and a North American cohort (McMaster University, Hamilton; Canada) recruited consecutive patients enrolled in local registers. CeD was diagnosed by positive serology and confirmed by biopsy. The Naples/Salerno cohort included consecutive patients seen between 1987 and 2021, the Padua cohort between 2017 and 2021, and the Hamilton cohort between 2018 and 2020. A fourth (Small Bowel Section, Dr. C. Bonorino Udaondo Gastroenterology Hospital, Buenos Aires; Argentina) included patients referred for endoscopy and duodenal biopsy due to the presence of symptoms and/or signs compatible with CeD but, irrespective of serology, all of them part of prior research and study (*7*,*15*). Thus, the fourth cohort included CeD and non-CeD participants (controls). Figure 1 and Table 1 summarize the demographic characteristics of the cohorts. The Ethics and Research Board of the Dr. C. Bonorino Udaondo Gastroenterology Hospital approved the study because of the prospective design and intervention in the Buenos Aires cohort. Ethics was obtained from Hamilton Integrated Research Ethics Board (HiREB# 14460/ 5415). In Italy, Ethical Committee review is not required for retrospective studies while patient data remained anonymously coded.

Endoscopic procedures

In all CeD centers, experienced gastroenterologists performed upper gastrointestinal endoscopies and obtained duodenal biopsies per shared standard of care protocols. Endoscopic reports were generated using a standard format, and the data were entered into a common database. Duodenal biopsies were sent to each institution's experienced pathologist. A standard number of biopsies were taken when any endoscopic abnormality was detected (e.g. endoscopic evidence of esophageal metaplasia). Endoscopic abnormalities have been defined as follows (*17*): 1- Erosive esophagitis: esophageal mucosal damage characterized by one or more mucosal breaks that do not extend across the tops of the mucosal folds and confluent lesions or ulcers of any size. 2- Suspected esophageal metaplasia: endoscopically suspected columnar mucosa without histological confirmation of specialized intestinal metaplasia. 3- Barrett's esophagus

confirmed by biopsy: when a metaplastic columnar epithelium replaces the stratified squamous epithelium in biopsies from suspected metaplasia or when intestinal metaplasia is present. 4- Gastric and duodenal erosions: erythematous and eroded stomach regions or duodenum. 5- Esophageal, gastric, or duodenal ulcers are distinguished by a break in the inner lining of the gastroduodenal that extends into the *muscularis propria* layer. 6- Esophageal, gastric, or duodenal cancer: the diagnosis was established after pathological confirmation.

Celiac disease diagnosis

CeD was diagnosed in each institution based on duodenal histology (Marsh's classification) (*1,18*). Inclusion criteria required a Marsh 2 enteropathy or more, a positive CeD-specific serology (presence of either anti-TTG IgA, Anti-EmA IgA, anti-DGP IgA/IgG). When serology was negative, CeD was diagnosed based on histology and clinical response to the GFD (*18*). If patients had been exposed to gluten sufficiently before having an endoscopy, intestinal biopsies were taken. As previously stated, the Buenos Aires cohort was part of a research study in which the diagnosis was made first on histological grounds and then confirmed by serology. The standard specific CeD test for all centers was IgA transglutaminase 2 (IgA tTG) (*5*). Patients with normal biopsy or minimal inflammation (Marsh 0 or 1) were excluded from the study, regardless of a positive serology or GFD response. In the Hamilton cohort, diagnosis of seronegative CeD patients was based on histology and clinical and histological response to the GFD.

Data analysis

Statistical analysis was carried out using STATA (Stata version 14.0 Corp, College Station, TX, US). Categorical variables are reported as frequencies and percentages, while continuous variables will be reported as mean (±SD) and/or median and 25%-75% interquartile ranges (25-75% IQR), according to distribution. Comparisons of categorical variables between groups were made using the $\chi 2$ test or Fisher's exact test. *P* values <0.05 were considered statistically significant. For comparisons of continuous variables the ANOVA test was used. Logistic regression was used to assess the risk of endoscopic lesions. The model includes the report of significant lesions in endoscopy

and/or histology reports as a dependent variable and factors such as age, sex, personal history, and signs/symptoms as independent variables.

Given the different recruitment times between centers, a subgroup analysis was performed to compare results in the Naples/Salerno cohort, focusing on cases diagnosed between 2018 and 2021 vs. previous endoscopies, estimating that such analysis can detect differences by using more actualized endoscopic protocols which were temporally concordant with those reported from patients collected in Padua and Ontario cohorts.

RESULTS

Overall, 1404 patients were diagnosed with CeD, and 1328 of them were included in the study (Figure 1). Excluded patients were those with positive serology but Marsh 0 or 1 (n = 76).

Demographic and clinical characteristics of patients

The number of participants recruited varied between centers (Tables 1 and 2). The Naples/Salerno cohort contained the majority of patients (70.0%), while the Buenos Aires cohort had the fewest (7.3%). The difference between the European and North American centers were due to the length of time the celiac centers had been established. In contrast, the South American center included patients and controls only over a specific time following an ongoing research protocol. There was a female predominance in all groups. There was no difference in the age at which diagnostic endoscopy was performed. There were no differences in baseline demographics across centers. The percentage of patients testing positive for celiac specific antibodies ranged from 88% (Hamilton) to 100% (Buenos Aires).

Endoscopic findings in celiac disease patients and age-related damage

Endoscopies revealed 163 distinct abnormalities in 135 patients with CeD (10.1%) (Table 1). The most common finding was erosive reflux esophagitis (6.4%), with the highest prevalence in Naples/Salerno (8.4%) and the lowest in Buenos Aires (1%) and Padua (0%). Peptic esophageal ulcers were found in only one patient within the total cohort.

Although Barrett's esophagus was suspected in 1.2% of the patients, it was only biopsy confirmed in 0.2% of cases (18.7% of those suspected and subsequently biopsied). The Hamilton cohort had a higher suspicion of metaplasia (n = 13), but Barret's was confirmed in one patient (Table 1). Gastric ulcers were found in one patient (0.1%) within the Naples/Salerno cohort while gastric erosions were found in 2.0% of the total population, with a higher prevalence in the Buenos Aires (7.2%) and the Hamilton (9.6%) cohorts. In the latter, 9.1% of patients with duodenal erosion were documented. Overall, 1.1% of duodenal ulcers were discovered, with higher frequency encountered in Hamilton cohort (3.6%). There was no reported cancer during diagnostic endoscopies at any level of the upper GI tract.

Patients under the age of 50 had less risk of presenting of at least one endoscopic abnormality compared with patients over the age of 51 (p<0.01). This indicates a 96.6% increase in lesions found in older patients (8.9% vs. 17.5%), which was primarily driven by erosive esophagitis and gastric erosions (Table 2). We performed a subgroup analysis of the Naples/Salerno cohort, including only patients diagnosed between 2018 and 2021. Compared with the overall Naples/Salerno cohort, patients diagnosed recently (n = 86) had a higher percentage of at least one significant endoscopic abnormality (29.2% vs. 9.6%, respectively), owing to a higher proportion of cases with reflux esophagitis with erosions (20% vs. 8.4%) and duodenal ulcers (8.2% vs. 0.9%, respectively). These endoscopic features were more common in the Naples/Salerno cohort (after 2018) than in the other cohorts reporting findings at the same time (Padua and Hamilton) (p<0.01). In comparison to the Padua cohort, the Salerno cohort had a higher proportion of patients with at least one endoscopic abnormality (29.1% *vs* 3.0%; p <0.01) (Supplemental Table).

Endoscopic findings in celiac patients and non-celiac controls from the Buenos Aires cohort.

We compared CeD patients (n = 97) *vs* non-CeD controls (n = 674) (Table 3) using the Buenos Aires cohort. The median age at endoscopy in non-CeD controls was 11 years more than in patients with CeD, and the percent of females was lower (p<0.01 for both).

Compared with patients with CeD, a higher proportion of controls were under the age of 50 in controls (p<0.001),(Table 3). CeD specific serology was positive in 1.3% of non-CeD controls. Controls' IgA tTG positive levels were less than three times the upper limit of normal. Endoscopic findings were discovered in a higher proportion of controls than in CeD patients (p<0.001). In all age groups of controls, gastric erosions were most common. Two control subjects, both older than 51, had a stomach adenocarcinoma, and another a duodenal cancer at diagnostic endoscopy. In contrast, no cancers were discovered during diagnostic endoscopy in CeD patients. While metaplasia was not suspected in CeD patients, it was found in 1% of controls, with Barrett's esophagus being confirmed after biopsy in two of these cases. Controls over the age of 51 had a 12.9% increase in mucosal damage compared with younger subjects (overall prevalence 31.4% vs. 27.8%, respectively).

The crude multivariate analysis based on CeD patients and non-CeD controls found that having CeD diagnosis and alarm symptom (for this cohort: weight loss, anemia, bleeding, dysphagia, epigastric pain or malignancy history) reduced the risk of having at least one lesion by 78% and 49% (p<0.0001 for both), respectively. According to the adjusted multivariate analysis, having CeD was associated with a 72% reduction in the risk of any endoscopic damage (p<0.0001), and having alarm symptoms was associated with a 37% reduction in the risk of having at least one endoscopic lesion (p<0.02; Table 4).

DISCUSSION

The study's main finding is that upper endoscopy performed concurrently with duodenal biopsies for CeD diagnosis discovered no concomitant damage in 92% of cases. Only 1.6% of CeD patients had relevant findings with the potential to progress to severe disease, comprised by esophageal and gastric ulcers, and Barrett's esophagus. While 8.9% of patients 50 years or younger demonstrated upper GI injury, only 1.3% had potentially dangerous lesions. The low yield of relevant concomitant findings

in this study does not support the usefulness of upper endoscopy beyond the need of obtaining biopsies for the diagnosis of CeD.

The possibility of detecting important or relevant esophageal, gastric, or duodenal pathology during diagnostic endoscopy has been put forward as an added benefit to confirmation of CeD diagnosis. Previously findings in CeD patients include reflux esophagitis, esophageal eosinophilia or eosinophilic esophagitis (mostly in children), Barrett's esophagus, *H. pylori* infection, autoimmune gastritis, among other conditions (*14-16*). These were however reported in small populations and single centers. Our study, which included cohorts from the EU, North America, and South America, gathered the largest sample of patients reported to date. The sample size obtained from the four separate specialized centers in three different countries allowed for subgroup and age category comparisons. The majority of CeD patients were young and female, as expected. The Buenos Aires cohort was prospectively designed to diagnosing patients attending a specialized clinic due to the presence of CeD symptoms and regardless of serology results, and therefore allowed for comparisons between CeD (12.6% of histologic CeD prevalence was later confirmed by serology) patients and those in whom CeD was ruled out by duodenal biopsy (Marsh's 0 or 1 histology categorization). In this cohort, we detected that non-CeD controls (98.7% of them with a negative CeD specific serology) had a higher proportion of concomitant upper GI findings compared with CeD patients at any age group (p<0.001).

Our findings confirm, in a larger multicenter population, recent reports indicating that adult patients with alarm symptoms have a very low prevalence of major endoscopic and histological findings in the upper GI tract other than CeD features at presentation, which was comparable to that of patients without alarm symptoms (*14,16*). The definition of what constitutes an alarming symptom for CeD at the time of diagnosis appears to be central to this analysis. Weight loss, iron deficiency anemia, pain, or malabsorption symptoms are prevalent among symptomatic patients, the vast majority of currently diagnosed patients since a case finding strategy is strongly recommended (*19*). However, our findings were limited to the upper GI tract and the lower GI tract

was not explored (interestingly, prevalence of colon malignancies is low in CeD patients).

Overall, erosive reflux esophagitis was the most common endoscopic finding at the time of diagnosis (6.9%). Notably, undiagnosed patients with classical or subclinical CeD frequently seek treatment for gastroesophageal reflux symptoms prior to diagnosis, which has been shown to be more common than in subjects who have CeD ruled out or in those treated with the GFD (*20*). We have previously reported that up to 30% of newly diagnosed CeD patients perceive moderate to severe reflux symptoms and that mostly did not respond to anti-reflux therapy prior to CeD diagnosis (21). Most of these symptomatically "non-responsive" patients to anti-reflux therapy, will rapidly improve after starting the GFD. However, a proportion of patients will remain symptomatic requiring specific therapy. Surprisingly, between 2018 and 2021, the Naples/Salerno cohort revealed higher prevalence of overall endoscopic lesions, and especially of erosive reflux esophagitis, compared with diagnoses made before that time period. This finding could be attributed to the characteristics of the CeD population over time (for example, the increased number of subclinical presentation or increased BMI of patients at diagnosis) or to differences in endoscopic and histology reports.

The possibility of missing severe lesions or potentially dangerous diseases in CeD patients if a diagnostic endoscopy is not performed, has been a source of concern in CeD guidelines (*2,4*). With respect to Barrett's esophagus or esophageal metaplasia, an Italian study published in 2005 discovered histological evidence of metaplasia in 26.6% of CeD patients compared with 10.9% of the control population (*23*). This link was not confirmed in studies from United States (*24*) and South America (*15,21*), nor by the present study. Reasons for this discrepancy could be related to differences population and in the definition of Barrett's esophagus, which required confirmation by biopsy in our study.

In the present study, we did not find mucosal eosinophilic infiltration. A pediatric prospective longitudinal study based on systematic esophageal biopsies found that diagnoses of eosinophilic esophagitis and/or eosinophilia were not clinically relevant,

suggesting esophageal biopsy is not necessary in the absence of clinical suspicion (*25*). A 2015 cross-sectional population study in the United States based on a national pathology database involving over 88,000 CeD patients with both esophageal and duodenal biopsies, discovered a slight increase in co-morbid eosinophilic esophagitis and CeD (*24*). However, no link between reflux esophagitis or Barrett's esophagus and CeD has been reported. Finally, autoimmune atrophic gastritis has been associated with a modest increased coexistence of CeD (*26*). However, no esophageal or gastric malignancies were discovered in CeD patients from our and other population-based studies or systematic reviews (*27,28*). Although the current study suggest that missing potentially serious events is unlikely, this should be confirmed in a larger population.

An earlier prospective study (*15*) collected consecutive patients and non-CeD controls in a high-risk population for having CeD, and gastric and duodenal biopsies were performed systematically at the time of the diagnostic endoscopy CeD and biopsy. Gastric biopsies from untreated CeD patients also revealed a significantly higher intraepithelial lymphocyte count in the antrum and corpus when compared with controls (*15, 29,30*). According to an Irish study, 10% of CeD patients have lymphocytic gastritis, which is twice the rate of non-CeD controls (*12,14*). These findings are attributed to both, *H. pylori* infection and autoimmune atrophic gastritis (*15,26*) or a pan-mucosal gluten-related inflammation (*14,15,29,30*).

Our study showed only one CeD patient had a gastric peptic ulcer. Previous studies found in 18.1% of CeD children with gastric ulcers, with a higher prevalence in *H. pylori* negative patients and those with no history of NSAID use (*31,32*). The rate of *H. pylori* infection across centers was not consistently reported here, and this could explain the difference in results. Previous research, however, has shown that high rates of biopsy-confirmed *H. pylori* infection are not associated with an increased risk of malignancy in the long term (*27,33*). However, several studies have also shown that when endoscopic appearance is normal, histological evaluation (both in the stomach and the esophagus) is not cost-effective, especially when performed in experienced academic centers. (*34-36*)

There were no CeD cases with gastric adenocarcinoma. Despite the small number of cases studied, this is consistent with previous findings that the prevalence of other cancers (breast, colon, pulmonary, and gynecological cancers) in CeD appears to be lower than in the general population (*27,28*). Small bowel carcinoma is extremely rare in the general population, and it is known that CeD patients are three times more likely to develop it (*1,28*). However, malignancies in the duodenum are still uncommon at the time of diagnosis, implying that diagnostic endoscopy should not be considered a surveillance endoscopy because a program has not been implemented in CeD patients and is unlikely to be implemented in the future (*28*). Overall, the current findings, as well as those from previous studies, contribute to possibility of a biopsy-avoiding approach for the diagnosis of patients who meet recommended and strict serological criteria (*12,37-40*).

The strengths of our study include its multicenter design, the large number of patients diagnosed at specialized centers for CeD in whom confirmatory biopsy diagnosis was obtained, as well as the use of standard endoscopic protocols. Despite the small numbers in sub-analyses, the study also provides novel data related on the association of endoscopic findings according to age, and time. We acknowledge study limitations related to its observational design, the retrospective collection of endoscopic reports (with potential missing data), the differences in time of enrollment across the four centers, the lack of systematic collection of biopsies from the esophagus and stomach, and the limited number of- non-CeD controls.

CONCLUSION

In conclusion, this multicenter, retrospective study found that co-morbid upper GI endoscopic pathology is uncommon in patients with positive CeD serology at the time of diagnostic endoscopy. The risk of severe or premalignant lesions is extremely low, as no malignancies were found in patients who displayed potential warning signs. Our findings suggest that a non-biopsy strategy for diagnosing CeD in adults is unlikely to miss clinically significant concomitant endoscopic findings unrelated to CeD. The

results of this study should encourage future population-based or prospective studies in this area.

ARTICLE HIGHLIGHTS

Research background

Celiac disease is currently diagnosed in adult patients using a combination of specific serology tests and a duodenal biopsy obtained though an upper endoscopy. Upper endoscopy is also considered necessary for celiac disease diagnosis because non-celiac disease co-morbidities can be missed.

Research motivation

The prevalence of upper GI co-morbidities at the time of celiac disease diagnosis has received little attention.

Research objectives

To investigate the prevalence of coincidental upper GI endoscopic findings at the time of diagnostic endoscopy in four cohorts of patients diagnosed in three different countries.

Research methods

We conducted a descriptive multicenter retrospective study reporting endoscopic findings from adult patients who met standard criteria for diagnosing celiac disease.

Research results

Results:1328 adult patients were enrolled, of whom 95.6% had positive specific serology. In 135 patients, endoscopy revealed 163 abnormalities unrelated to CeD (10.1%). Erosive reflux esophagitis (6.4%), gastric erosions (1.9%), and suspicion of esophageal metaplasia (1.1%) were the most common findings. Biopsy-confirmed

Barrett's esophagus was infrequent (0.2%). No other neoplastic or malignancies lesions were detected. Patients with alarm symptoms or signs had a lower rate of concommitant findings.

Research conclusions

Adults with positive CeD serology had few co-morbid endoscopic findings when celiac disease was diagnosed.

Research perspectives

These findings raise the possibility that adult patients who meet recommended and strict serological criteria for celiac disease could be diagnosed without undergoing endoscopy and biopsy.

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ORIGINALITY REPORT

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SIMILARITY INDEX

PRIMARY SOURCES

1	Juan P. Stefanolo, Carolina Gizzi, Fabiana Zingone, Ilaria Marsilio et al. "1088: UPPER GI ENDOSCOPIC FINDINGS IN CELIAC DISEASE PATIENTS AT THE DIAGNOSTIC BIOPSY. A MULTICENTER INTERNATIONAL RETROSPECTIVE STUDY.", Gastroenterology, 2022 Crossref	20 words — < 1%
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