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Increased risk of esophageal eosinophilia and eosinophilic esophagitis in patients with active celiac disease on biopsy

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Abstract

Background and Aims—The possible association between eosinophilic esophagitis (EoE) and celiac disease (CD) is controversial as prior results have been contradictory. We aimed to determine the relationship between EoE and CD among patients with concomitant esophageal and duodenal biopsies.

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Methods—We conducted a cross-sectional study in a U.S. national pathology database, using data from January 2009 and June 2012. Our primary case definition was defined by the presence of esophageal eosinophilia with ≥ 15 eosinophils per high-power field. The crude and adjusted (for age and sex) odds of esophageal eosinophilia for patients with active CD were compared to those without CD. Sensitivity analyses were performed using more stringent case definitions and by estimating the associations between CD and reflux esophagitis, and CD and Barrett's esophagus (BE).

Results—Of 292,621 patients in the source population, 88,517 with both esophageal and duodenal biopsies were studied. 4,101 (4.6%) met criteria for EoE and 1,203 (1.4%) met criteria for CD. Odds of EoE were 26% higher in patients with CD than patients without CD (aOR: 1.26, 95% confidence interval [CI]: 0.98 – 1.60). The magnitude of association varied according to EoE case definition (Table 3), but all definitions showed a weak, positive association between the two conditions. There was no association between CD and reflux esophagitis (aOR 0.95, 95% CI: 0.85 – 1.07) or BE (aOR 0.89, 95% CI: 0.69 – 1.14) and CD.

Conclusions—There is a weak increase in EoE in patients with CD. This association strengthened with increasingly stringent definitions of EoE, and was not observed for other esophageal conditions. In patients with CD, concomitant EoE should be considered in the correct clinical setting.

Keywords

eosinophilic esophagitis; celiac disease; epidemiology; prevalence; pathology

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune and antigen-mediated disease characterized by clinical symptoms of esophageal dysfunction and eosinophilic infiltration of ≥15 eosinophils per high power field (eos/hpf), in the absence of other contributing causes of eosinophilia.[1, 2] EoE affects both adults and children at a prevalence of 50-100/100,000 and has been increasing in incidence at a rate of 10/100,000 per year.[3-5] Atopic conditions such as asthma and allergic rhinitis are strongly associated with EoE,[6] and both aeroallergens and food antigens contribute to the pathogenesis.[7-9] As a result, there has been a focus on the utility of food elimination diets in achieving clinicopathologic improvement,[10-13] and milk and wheat have been identified as common triggers of disease.[13, 14]

Similar to EoE, celiac disease is an immune-mediated condition. Celiac disease is triggered by gluten in genetically predisposed individuals,[15, 16] and because wheat can also trigger EoE, several studies have investigated the relation between the two diseases.[17-20] The results, however, are conflicting. One study reported that the prevalence of EoE in celiac disease was nine times higher than in the general population.[17] Other studies have reported prevalence of EoE in patients with celiac disease ranging between 1.2% and 4.4%, [19-22] and one investigation indicated no association between the two conditions.[23] It is possible that selection bias or a lack of a suitable comparator group may explain the contradictory

findings of these previously conducted studies and additional investigation into the relationship between EoE and celiac disease is warranted.

The primary aim of the study was to determine the relationship between EoE and celiac disease among patients with concomitant esophageal and duodenal biopsies using a large pathology database. We hypothesized that there would be no significant relationship between these conditions and that the previously reported associations may be attributable to selection bias.

Methods

Study Design and Data Source

This was a cross-sectional study of all patients with esophageal and duodenal biopsy specimens in a U.S national pathology database, examined between January 1, 2009 and June 30, 2012 by pathologists at Miraca Life Sciences. Miraca Life Sciences is a specialized pathology laboratory serving outpatient endoscopy centers throughout the United States. They review samples from 43 states, Washington DC, and Puerto Rico, with central specimen processing in 1 of 3 laboratories (Irving, TX; Phoenix, AZ; and Boston, MA). Each laboratory follows identical sectioning and staining procedures. An experienced group of 41 subspecialty trained gastrointestinal pathologists reviews the slides. All biopsy reports are deposited into a central database, which also includes information about patient age, sex, and indication for esophagogastroduodenoscopy (EGD). Uniformity among pathologists is maximized through a standardized approach to specimen handling and a pre-determined set of diagnostic criteria and terminology for biopsy reading. Consensus is maintained and updated through an extensive quality assurance process that includes a 1% to 2% random review of cases. Details about this methodology have been previously published.[24-26] The study was approved by both the University of North Carolina and the Miraca Life Sciences Institutional review boards.

Study Population

A de-identified database of unique patients with esophageal and duodenal biopsy specimens was generated for this study. We initially started with 320,319 patients who had esophageal biopsies, of whom 90,994 also had concomitant duodenal biopsies. We then excluded those who had a clinical history of EoE or celiac disease but no corresponding histologic evidence of active disease at the time of biopsy, since we could not confirm their case status. In addition, we also excluded subjects with duodenal intraepithelial lymphocytosis but without other features of celiac disease.

PPI use prior to endoscopy was unknown in this dataset. Therefore, we were unable to assess for or exclude PPI-responsive esophageal eosinophilia. In our primary analysis, patients were defined as having esophageal eosinophilia if there were ≥15 eos/hpf (400x magnification; area per hpf = 0.237 mm^2). In sensitivity analysis, the severity of eosinophilia was evaluated in further detail by categorizing the density in ranges of eos/hpf (empirically defined as ≥50 or ≥100 eos/hpf) and documenting the presence of eosinophilic microabscesses (defined as clusters of ≥4 contiguous eosinophils).[27] These patients were

then further categorized into EoE case definitions by creating several increasingly stringent, proxy definitions for EoE based on the presence of factors consistent with EoE diagnosis (see sensitivity analysis section, below).

Cases of celiac disease were defined by duodenal biopsies with a Marsh score of 3. Pathologic findings for these lesions included villous atrophy (3a: partial; 3b: subtotal villous atrophy, 3c: total villous atrophy or flat mucosa), with a concurrent increase in the ratio of intraepithelial lymphocytes (IEL) to enterocyte (EC) with > 40 IEL/100EC.[28, 29] Although less advanced Marsh scores can represent subtler histologic forms of celiac disease, given the lower specificity of these lesions for celiac disease, only Marsh class 3 was included in our case definition, as has been described previously in this data set.[30-32]

Clinical characteristics of patients were identified based on upper gastrointestinal symptoms or conditions that were noted as the indication for endoscopy (i.e. suspected EoE, dysphagia symptoms, reflux symptoms or GERD [defined as a report of heartburn, regurgitation, or reflux], suspected celiac disease, nausea and/or vomiting, weight loss or failure to thrive, diarrhea, abdominal pain or dyspepsia, chest pain, and screening or follow-up of a known diagnosis of Barrett's esophagus). We also recorded the presence of other conditions noted on histologic examination such as reflux esophagitis (defined as a mixed active/chronic inflammatory pattern with squamous papillomatosis and basal hyperplasia), intestinal metaplasia (Barrett's esophagus), eosinophilic gastroenteritis, and any known history of inflammatory bowel disease for use in sensitivity analyses (see below).

Statistical Analysis

Primary analysis—We described the distribution of demographic characteristics for the overall study population, those with esophageal eosinophilia, and those with celiac disease. We then used generalized linear models to estimate whether, among those with both esophageal and duodenal biopsies, there was an increased odds of concomitant esophageal eosinophilia in patients meeting diagnostic criteria for celiac disease relative to those without the diagnosis of celiac disease. Crude and adjusted analyses (adjusted for age and sex) were performed. We evaluated whether there was an interaction with age or effect modification by age. We also produced stratum-specific estimates for adult (age ≥18 years) and pediatric subgroups.

Sensitivity analyses—We performed several *a priori* sensitivity analyses. First, we examined the association between celiac disease and increasing levels of esophageal eosinophilia on biopsy (nested categories of ≥15, ≥50, and ≥100 eos/hpf). A second analysis was performed to examine the association between celiac disease and our EoE case definitions, which incorporated additional information on histopathology observations and clinical indication for endoscopy. We selected increasingly stringent and specific definitions[24-26] including: ≥15 eos/hpf and documentation of dysphagia; ≥15 eos/hpf, dysphagia, exclusion of patients with clinical or histologic data suggesting alternative explanations for the eosinophilia (reflux/heartburn symptoms, reflux esophagitis, Barrett's esophageal on biopsy, inflammatory bowel disease, and eosinophilic gastroenteritis), and the presence of eosinophilic microabscesses in the esophageal epithelium.

The final sensitivity analysis performed was to examine any association between celiac disease and other esophageal disorders such as Barrett's esophagus and reflux esophagitis. Because our study population was restricted to those patients with esophageal and duodenal biopsies, we wanted to determine if any relationship between EoE and celiac disease was confounded by underlying factors that predisposed this group to having biopsies obtained from both locations. If this was the case, then we hypothesized that we would see an association between celiac disease and Barrett's esophagus or reflux esophagitis.

Results

Patient characteristics

We identified 88,517 patients who had both esophageal and duodenal biopsies and whom also met the inclusion criteria. The mean age in the group was 51.1 years with 38.2% male (Table 1). The most common indication for upper endoscopy was abdominal pain/dyspepsia (52.1%), followed by heartburn (43.4%), dysphagia/odynophagia (16.5%), and diarrhea (13.4%). The mean of the maximum eosinophil count was 2.9 eos/hpf, and 1.1% had microabscesses.

There were 4,101 (4.6%) patients who met criteria for esophageal eosinophilia defined as ≥ 15 eos/hpf. The mean age was lower at 39.6 years with higher percentage of males 57.2% compared to the study population (Table 1). In this group, 36.8% had dysphagia, and the mean eosinophil count was 36.6 eos/hpf with 22.7% having eosinophil microabscesses.

A total of 1,203 (1.4%) patients met criteria for celiac disease. There was no major difference in age between those with and without celiac disease (49.6 vs. 51.1 years), and the groups had similar sex distributions (Table 2). Common symptoms and endoscopy indications in the celiac disease group were abdominal pain/dyspepsia (38.9%), heartburn (35.7%) and diarrhea (15.9%).

Relationship between esophageal eosinophilia, EoE, and celiac disease

There were 72 subjects with celiac disease who had concomitant esophageal eosinophilia with ≥ 15 eos/hpf (6.0%) compared with 4,029 in the non-celiac group (5.6%). This corresponds to 26% higher odds of esophageal eosinophilia, adjusted for age and sex, among patients with celiac disease when compared to patients without celiac disease (aOR: 1.26, 95% confidence interval [CI]: 0.98 – 1.60) (Table 3). We found no statistically significant evidence of interaction with age (p=0.20 for interaction term). However, stratum-specific estimates were suggestive of an association between esophageal eosinophilia and celiac disease in adults (age ≥18) (aOR 1.35 (95% CI 1.04 – 1.73) but not in children (aOR 0.94 (95% CI 0.42 –2.07).

On sensitivity analysis, the magnitude of the association varied according to EoE case definition (Table 3), but all definitions were suggestive of a weak, positive association. For example, the odds when defining EoE as ≥ 50 eos/hpf, was 58% higher for those patients with concomitant celiac disease (aOR: 1.58, 95% CI: 1.04 – 2.41). In contrast to these findings, there was no association between celiac disease and either reflux esophagitis (aOR 0.95, 95% CI: 0.85 – 1.07) or Barrett's esophagus (aOR 0.89, 95% CI: 0.69 – 1.14).

Discussion

Multiple and varied food antigens have been implicated in the pathogenesis of EoE, similar to the role gluten plays in celiac disease. Based on this, there is a question of whether the two conditions are associated. In the present study, which examined subjects with paired esophageal and duodenal biopsies in a large pathology database, we found that the odds of esophageal eosinophilia and our constructed case definitions of EoE were mildly increased in patients with celiac disease compared to those without celiac disease. This association generally became stronger when more stringent definitions of EoE were applied. There was no association between celiac disease and either reflux esophagitis or Barrett's esophagus, indicating that the association between esophageal eosinophilia and celiac could not likely be explained by selection bias.

Previous literature on the relationship between EoE and celiac disease has been conflicting. Most of these studies were conducted in the pediatric population and prevalence of EoE in pediatric celiac disease patients has ranged from 3.2% - 4.4%.[19-21] However, examining prevalence of EoE among celiac disease without a comparator group that has undergone upper endoscopy may lead to erroneous assumptions about the increased prevalence of EoE in this group. For example, one study estimated 6.5% of patients undergoing upper endoscopy for any reason would have EoE.[33] Another pediatric study found 6 cases of celiac disease out of the 17 with EoE in children referred for upper endoscopy in Italy.[18] When treated with a gluten free diet, the children had both symptomatic and histologic improvement of EoE, suggesting a possible shared pathogenic trigger between the two diseases. On the contrary, there was no histologic improvement in another small cohort of pediatric patients treated with a gluten free diet.[21] A retrospective, population-based review from 2004-2008 of both adults and children found an association between EoE and celiac disease only in children (defined as < 19 years of age).[22] Here the standardized incidence ratio (SIR) for EoE within the pediatric celiac disease cohort was 48.4 (95% CI = 9.73, 141.41) and the SIR for celiac disease in the EoE cohort was 75.1 (95% CI = 15.08, 219.28). A study by Thompson et al. of 666 patients of all ages with celiac disease identified EoE in 14 patients and an overall age- and sex-adjusted SIR of 16.[34] In contrast, no association between EoE and celiac disease was found in a population-based cohort of randomly selected adults undergoing upper endoscopy.[24] Similarly, a study by Lucendo and colleagues did not find increased HLA DQ2 and DQ8 (implicated in patients with celiac disease) in subjects with EoE when compared to controls.[35] Thus, the literature on this topic has been contradictory and confusing, likely because of variable study designs, inclusion criteria, and comparator groups, as well as relatively small sample sizes. It is not surprising that a recent systematic review examining the association between EoE and celiac disease found no clear association between the two conditions and concluded that there was a lack of robust studies for summarizing the realtionship.[36]

Therefore, there are a number of strengths to our study. To our knowledge, this is the largest investigation of the association between EoE and celiac disease. In restricting our study population to those patients with both esophageal and duodenal biopsies, we addressed the potential selection bias introduced in previously conducted studies. Notwithstanding, aside from pediatric gastroenterology practices where biopsies of the esophagus, stomach, and

duodenum are routinely obtained, there would typically need to be a rationale, either clinically or endoscopically, for an adult patient to have both esophageal and duodenal biopsies obtained. In using a comparator group of patents with both esophageal and duodenal biopsies, any observed association could be confounded by factors contributing to the need for biopsies from both locations. However, by restricting the sample to those with endoscopy and biopsies, we removed the possible confounding effect of endoscopy (with duodenal and esophageal biopsies) on the observed association. The potential that the association between the two different diseases represents an artifact of confounding bias has been previously discussed.[37] We adjusted on age and sex, both possible confounders in the association between celiac and EoE, but other, unmeasured factors that we could not account for may have also contributed. If this was the case, we would hypothesize that celiac disease would also be associated with other esophageal conditions. However, we found no increase in odds of either Barrett's esophagus or reflux esophagitis in patients with celiac disease. These null results lend credence to the idea that the association between EoE and celiac disease is not spurious. Finally, the *a priori* sensitivity analyses, where more restrictive case definitions of EoE were applied, generally showed a stronger relation with celiac disease.

There are also limitations to consider with the design of this current study. First, the retrospective design limits the amount of data available. In addition, because the study is cross-sectional, we are only able to comment on the association between the two diseases and not on causality. Third, clinical information was limited to the data provided on the endoscopy report and pathology requisition. Therefore, the diagnosis of esophageal eosinophilia and celiac disease was primarily based on established histopathologic features and description of clinical features of patients may be incomplete. Because we do not have full data about endoscopic findings, we also cannot comment on the specific indications for esophageal biopsy. Also, there were no data on PPI use before endoscopy, thus we could not preclude the possibility that some cases could represent patients with PPI-responsive esophageal eosinophilia.

In summary, this large, retrospective, cross-sectional study found that the odds of esophageal eosinophilia were 26% higher among patients with celiac disease as compared to patients without celiac disease, and that the odds tended to increase with more stringent EoE case definitions. This weak, but persistent association builds on the discrepant results previously reported in the literature in smaller studies and offers a reduced potential for selection bias with the use of comparison groups. While this association is not strong enough to recommend obtaining esophageal biopsies in all celiac disease patients to assess for EoE, certain esophageal symptoms, such as dysphagia, chest discomfort, or heartburn, in a patient with celiac disease should raise the question of EoE as a possible cause. In patients identified to have both EoE and celiac disease, mechanistic studies are required to determine whether the two conditions truly share a similar pathogenesis.

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Table 1

Demographic characteristics, clinical symptoms, and histological features of study population

	Study population (n = 88,517)	Esophageal eosinophilia[a] (n = 4,101)
Demographic characteristic		
Age (yrs) mean ± SD	51.1 ± 18.2	39.6 ± 17.6
Male n (%)	33,786 (38.2)	2,347 (57.2)
Clinical symptoms/EGD indications[b] – n (%)		
Dysphagia/odynophagia	14,558 (16.5)	1,510 (36.8)
Heartburn	38,470 (43.4)	1,562 (38.1)
Chest pain	3,091 (3.5)	126 (3.1)
Abdominal pain/dyspepsia	46,132 (52.1)	1,843 (44.9)
Nausea/vomiting	10,826 (12.2)	474 (11.6)
Weight loss	5,059 (5.7)	145 (3.5)
Diarrhea	11,864 (13.4)	533 (13.0)
Histological features		
Maximum eosinophil count, mean ± SD	2.9 ± 11.9[c]	36.6 ± 23.9
Eosinophil microabscesses n (%)	929 (1.1)	929 (22.7)

[a] Patients with esophageal eosinophilia on esophageal biopsy with a minimum count of ≥ 15 eos/hpf and with an EoE pathology code

[b] Multiple indications could be listed for each procedure

[c] Includes 52,393 patients with normal or documented number of esophageal eosinophils on biopsy

Table 2

Demographic characteristics, clinical symptoms, histological features and presence of reflux esophagitis or Barrett's esophagus by celiac disease status[a]

	Celiac disease status[b]		
	Yes (n = 1,203)	**No (n = 87,314)**	**p[a]**
Demographic characteristic			
Age (yrs) mean ± SD	49.6 ± 18.7	51.1 ± 18.2	<0.01
Male n (%)	471 (39.2)	33,315 (38.2)	0.48
Clinical symptoms/EGD indications – n (%)			
Dysphagia/odynophagia	186 (15.5)	14,372 (16.5)	0.35
Heartburn	429 (35.7)	38,041 (43.6)	<0.01
Chest pain	30 (2.5)	3,061 (3.5)	0.06
Abdominal pain/dyspepsia	468 (38.9)	45,664 (52.3)	<0.01
Nausea/vomiting	123 (10.2)	10,703 (12.3)	0.03
Weight loss	75 (6.2)	4,984 (5.7)	0.43
Diarrhea	191 (15.9)	11,673 (13.4)	0.01
Histological features			
Maximum eosinophil count, mean ± SD	3.9 (13.9)[c]	2.9 ± 11.8[d]	0.02
Eosinophil microabscesses n (%)	18 (1.5)	911 (1.0)	0.13
≥15 eos/hpf n (%)	72 (6.0)	4,029 (5.6)	0.02
Reflux esophagitis – n (%)	446 (37.1)	33,418 (38.3)	0.40
Barrett's esophagus – n(%)	69 (5.7)	5,773 (6.6)	0.22

[a] p values for significant difference in distribution of proportions and p value for difference in mean age and eosinophil count

[b] Characterized by severe/diffuse villous blunting with intraepithelial lymphocytosis

[c] Includes 712 patients with documented number of esophageal eosinophils on biopsy

[d] Includes 51,681 patients with documented number of esophageal eosinophils on biopsy

Table 3

Association between esophageal eosinophilia and CD with increasingly restrictive definitions of EoE

EoE definition	(n)	EoE with CD on biopsy (n)	OR (95% CI)	aOR** (95% CI)
No EoE	84,416	1,131	Referent	Referent
EoE as defined by:				
≥15 eos/hpf	4,101	72	1.32 (1.04, 1.67)	1.26 (0.98, 1.60)
≥15 eos/hpf and dysphagia	1,406	23	1.23 (0.81, 1.86)	1.18 (0.78, 1.80)
≥15 eos/hpf, eosinophilic microabscesses, and exclusion of competing conditions*	230	4	1.30 (0.49, 3.51)	1.25 (0.46, 3.37)
≥50 eos/hpf)	1,050	23	1.65 (1.09, 2.50)	1.58 (1.04, 2.41)
≥100 eos/hpf)	227	5	1.66 (0.68, 4.03)	1.57 (0.64, 3.82)

* Competing conditions included reflux/heartburn symptoms, RE, BE, IBD, and eosinophilic gastroenteritis

** Adjusted for age, sex