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RESEARCH LETTERS

High Discovery Rate of Duodenal and Gastric Eosinophilia in Patients With Unexplained Moderate–Severe Abdominal Symptoms: A Prospective US Multisite Study

Eosinophilic gastrointestinal (GI) diseases, including eosinophilic gastritis (EoG) and eosinophilic duodenitis (EoD), are chronic inflammatory conditions characterized by GI tissue eosinophilia and persistent, often debilitating, GI symptoms.[1] Although considered rare, emerging evidence suggests that the prevalence of eosinophilic GI diseases is increasing in the United States, and may be more prevalent than previously thought.[1,2] Notably, diagnosis requires an adequate biopsy protocol, as disease is often patchy,[3] and the diagnosis may be overlooked if eosinophils are not counted.[4]

The aim of this prospective, multicenter study was to investigate the discovery rate of gastric and duodenal eosinophilia among patients in secondary GI care with moderate–severe unexplained abdominal symptoms. Abdominal symptoms were measured using the Total Symptom Score (TSS), a previously developed daily symptom questionnaire measuring 8 GI symptoms with a score range of 0–80.[5] For comparison, and to better characterize normal levels, we performed the same assessments in a group of healthy, asymptomatic controls in a separate study.

These 2 multicenter prospective studies were conducted in centers across the United States. In 1 study, patients with ≥6 months of symptoms (abdominal pain, abdominal cramping, early satiety, bloating, nausea, vomiting, diarrhea, and loss of appetite) and a TSS ≥10 were recruited from 20 centers. In the other study, asymptomatic controls (TSS ≤1) were recruited by advertisement from 4 of the 20 centers. Patients or controls who met respective symptom-severity criteria via a daily patient-reported questionnaire[5] underwent esophagogastroduodenoscopy (EGD) with systematic collection of gastroduodenal biopsies. No consensus guidelines exist for diagnosis of EoG/EoD but, based on expert input and criteria used in randomized studies, we used thresholds of ≥30 eosinophils per high-powered field (eos/hpf) in ≥5 gastric hpfs and ≥30 eos/hpf in ≥3 duodenal hpfs.[5] A primary objective of these studies was to determine the proportion of patients and controls who met prespecified histologic criteria for EoG/EoD. See Supplementary Material for additional details.

Of the 556 patients screened, 405 met symptom criteria and underwent EGD with biopsies, and 181 (45%) met histologic criteria for EoG/EoD. The rate of EoG/EoD was 43% (152 of 353) after removing patients with active *Helicobacter pylori* infection (Figure 1*A*, Supplementary Table 1). Mean (SD) TSS was 31 (11) and 30 (12) for EoG/EoD and EoG- or EoD-negative, respectively, and mean (SD) TSS for controls was 0.1 (0.2) (Figure 1*B*).

In the EoG/EoD group (n = 152), 10 had EoG only (7%), 114 had EoD only (75%), and 28 had both EoG and EoD (18%) (Figure 1*C* and *D*). There were 201 EoG- or EoD-negative patients who met symptom criteria and underwent EGD, were negative for *H pylori*, but did not meet histologic criteria for EoG/EoD (<30 eos/hpf). Of 33 evaluable asymptomatic, healthy controls, 2 (6%) met histologic criteria for EoG/EoD. The age- and sex-adjusted odds ratio for EoG/EoD in symptomatic patients vs controls was 11.0 (95% CI, 2.6–47.6).

Combining all symptomatic patients, gastric eosinophils did not correlate with TSS (Pearson $r = 0.08$, $P = .11$), but correlated with early satiety ($r = 0.11$, $P = .03$), and duodenal eosinophils did not correlate with TTS ($r = 0.06$, $P = .24$), but correlated with diarrhea ($r = 0.13$, $P = .009$). Among EoG/EoD alone, gastric eosinophils correlated with vomiting only ($r = 0.16$, $P = .049$). We hypothesize that other factors may contribute to symptom severity which warrant further study.

In the EoG/EoD group (n = 152), 102 (67%) had received a clinical diagnosis of gastroesophageal reflux disease (GERD), 84 (55%) had received a diagnosis of irritable bowel syndrome (IBS), 26 (17%) had received a diagnosis of functional dyspepsia, and 145 (95%) had a history of receiving at least 1 of these diagnoses. Seven patients (5%) with EoG/EoD had received a diagnosis of eosinophilic esophagitis previously.

Overall, 47% (72 of 152) of the EoG/EoD cohort and 43% (87 of 201) of the symptomatic patients without EoG/EoD had a history of an atopic condition (most frequently asthma and allergic rhinitis), vs 15% of controls (5 of 33) ($P < .001$ vs EoG/EoD cohort; $P = .002$ vs symptomatic patients without EoG/EoD cohort). Median peripheral blood eosinophil counts were 180 cells/μL (interquartile range, 110–260 cells/μL) in patients with EoG/EoD, 110 cells/μL (interquartile range, 70–160 cells//μL) in EoG- or EoD-negative patients, and 70 cells/μL (interquartile range, 50–150 cells/μL) in controls ($P < .0001$ for EoG/EoD vs EoG- or EoD-negative or controls). Similar proportions of patients reported worsening of their GI symptoms with certain foods (73% of patients with EoG/EoD, 82% of EoG- or EoD-negative patients) or avoided specific foods (57% of

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Abbreviations used in this paper: **DGBI, disorder of gut–brain interactions; EGD, esophagogastroduodenoscopy; EoD, eosinophilic duodenitis; EoG, eosinophilic gastritis; eos/hpf, eosinophils per high-powered field; GERD, gastroesophageal reflux disease; GI, gastrointestinal; IBS, irritable bowel syndrome; TSS, Total Symptom Score.**

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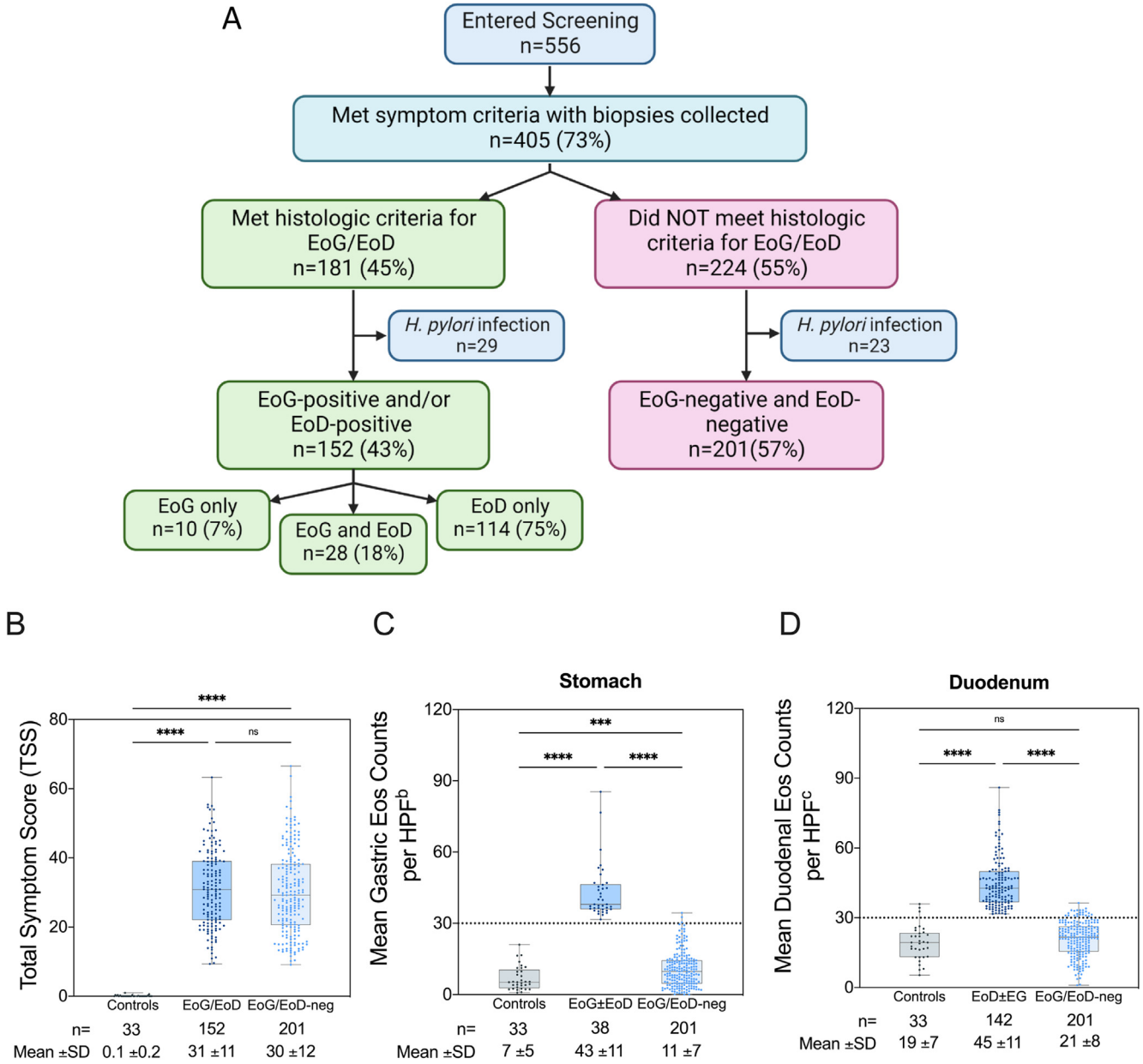

Figure 1. Patient histologic and symptom assessment. (*A*) Study flow chart and discovery rate of EoG/EoD from the symptomatic patient cohort. [a]Histologic criteria is defined as ≥30 eos/hpf in 5 gastric hpfs and/or ≥30 eos/hpf in 3 duodenal hpfs. (*B*) Mean TSS for patients with EoG/EoD, histologically EoG/EoD-negative (EoG/EoD-neg) patients, and healthy controls. (*C*) Mean gastric eosinophil counts per high-powered field (HPF) in patients with EoG (with or without EoD [EoG±EoD]), without EoG/EoD (EoG/EoD-neg), and controls. [b]These include mean across 5 highest HPFs for gastric eosinophil counts. (*D*) Mean duodenal eosinophil count per HPF in patients with EoD (with or without EoG [EoD±EoG]), without EoG/EoD (EoG/EoD-neg), and controls. [c]These include mean across 3 highest HPFs for duodenal eosinophil counts. (*B–D*) All subjects were negative for *Helicobacter pylori*. *Boxes* indicate 25th and 75th percentiles; *center line* indicates median. Welch's unpaired *t* test. **P* < .05; ***P* < .01; ****P* < .001; *****P* <.0001; ns, not significant.

patients with EoG/EoD, 62% of EoG/EoD-negative patients). Of 116 patients on a proton pump inhibitor, the EoG/EoD discovery rate was 48% (56 of 116) vs 41% (96 of 237) in the 237 patients not on a proton pump inhibitor ($P = .17$).

Current guidelines discourage systematic biopsies in the diagnostic workup of patients with chronic gastroduodenal symptoms, but detecting or ruling out EoG/EoD has not been a major consideration.[6] This large, prospective, multicenter, observational study suggests that gastric and duodenal eosinophilia may be more common than previously reported among US patients with chronic abdominal symptoms, including those with a prior diagnosis of a disorder of gut–brain interactions (DGBI). Forty-three percent of patients with moderate–severe symptoms met the

histologic criteria for EoG/EoD. Ninety-three percent of patients with EoG/EoD had duodenal involvement with or without the presence of gastric involvement, indicating that EoD is more common than EoG when using these histologic criteria. Mean eosinophil counts from our healthy control group (7 gastric and 19 duodenal eos/hpf) suggest the use of a cutoff threshold of ≥30 eos/hpf used in clinical trials is conservative (Figure 1*C* and *D*) although further analyses are warranted to determine a cutoff range that is specific for real-world EoG/EoD diagnosis.[5,7]

Patients with chronic, unexplained abdominal symptoms are frequently diagnosed with a DGBI due to the absence of an identifiable underlying organic cause. Among patients with unexplained dyspepsia who have a normal EGD, a meta-analysis of case-control studies reported eosinophil degranulation was a consistent biomarker of disease.[8] Duodenal tissue eosinophilia has also been associated with a substantially increased risk of new-onset GERD.[9] Most patients found to have EoG/EoD in this study had received a previous diagnosis of dyspepsia, IBS, and/or GERD, but cause and effect cannot be determined. Although the current study suggests increased duodenal and gastric eosinophils might be a useful biomarker, evaluation of anti-eosinophil therapies in terms of symptom management is outside the scope of these studies. It is possible the eosinophils are not inducing symptoms and are incidental as tissue-resident cells.[10] Eosinophils are also involved in tissue repair, and it is conceivable that they play a protective role in the mucosa against food or microbial antigens.[10]

This study had several limitations, one of which was that the control group was collected as part of a separate clinical protocol. However, this drawback is mitigated by the fact that all of the control subjects were enrolled at the same clinical sites as the symptomatic patients. Historical diagnoses of DGBIs and GERD were based on medical records, not necessarily on established diagnostic criteria. Biopsies were collected from the second and third parts of the duodenum only, so eosinophilia of the duodenal bulb could have been missed. Symptomatic patients were older than controls and a higher proportion of patients were female.

In summary, in patients with at least a 6-month history of moderate–severe chronic, unexplained abdominal symptoms, we observed a high rate of increased duodenal and gastric eosinophilia, at levels used consistently in the diagnosis of EoG and EoD. Most of these subjects had a previous diagnosis of functional dyspepsia, IBS, and/or GERD. The precise role of eosinophils in symptomatic patients previously presumed to have a DGBI or GERD remains to be elucidated; however, these findings suggest that gastroduodenal eosinophilia may be more common than previously recognized.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.12.015.

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Conflicts of interest

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Data Availability

Data available from Allakos Inc on request.

Supplementary Methods

We conducted a prospective study of patients with chronic GI symptoms (patients) from February 2020 through August 2020 at 20 sites in the United States, and a prospective study of healthy, asymptomatic subjects (controls) from June 2020 through January 2021 at 4 of the same sites.

Institutional Review Boards at each center approved the study protocols. All study subjects provided written informed consent and received compensation for their participation.

Symptomatic patients included in this study were aged 18–80 years with at least a 6-month history of symptoms (eg, abdominal pain, nausea, vomiting, diarrhea, early satiety, bloating, and abdominal cramping) without an identified cause and unresponsive to dietary and/or pharmacologic interventions, or with symptoms and a clinical diagnosis of IBS and/or functional dyspepsia. Patients with a known history of EoE were allowed in the study.

Patients entering screening were further assessed using the electronic EoG/EoD patient-reported outcome questionnaire.[5] A minimum of 4 completed questionnaires per week was required. Screened patients with a daily mean individual symptom score $\geq$3 for any of the 7 symptoms listed above, with the addition of loss of appetite (score range, 0–10), and a TSS $\geq$10 (score range, 0–80) for 2 of the 3 weeks of screening were included in the study and underwent EGD with gastric and duodenal biopsies for histopathologic detection of EoG/EoD.

Healthy subjects (controls) were aged 18–80 years, had a mean daily individual symptom score of $\leq$1 on all symptoms assessed by the patient-reported outcome questionnaire over 2 weeks of screening, and were deemed healthy by the investigator based on absence of prescription medications and significant acute or chronic comorbidities. Controls taking proton pump inhibitors or antihistamines or with any pathology detected by endoscopy or histologic analysis were excluded.

Patients and controls who met their respective symptom criteria (as above) underwent EGD with standardized and identical endoscopy, biopsy, and histopathology protocols. Eight gastric biopsies (4 each from separate areas of the gastric corpus and antrum) and 4 duodenal biopsies (2 each from the second and third portions of the duodenum) were collected. As many as 2 additional gastric and/or duodenal biopsies could be collected from any areas of interest at the discretion of the endoscopist. As many as 4 esophageal biopsies (2 distal and 2 mid/proximal) were collected from patients with a history of EoE or patients found to have esophageal abnormalities on EGD. Biopsies were embedded in paraffin and 5-μm-thick sections were prepared for staining. A minimum of 5 nonoverlapping hpfs were evaluated for each biopsy. Eosinophils were identified by H&E staining.

Two independent central pathologists blinded to subjects' demographic, clinical, and endoscopic information performed the histologic analyses. A third pathologist evaluated a random subset of study patients and controls, also in a blinded fashion, to ensure the reliability of counts. Each biopsy specimen was examined at low magnification first (40$\times$ and 100$\times$) to evaluate for proper orientation and presence of incidental findings that were criteria for exclusion (eg, *H pylori* infection, celiac disease, or neoplasia). A minimum of 5 nonoverlapping hpfs were evaluated for each biopsy.

The primary objectives of the studies were to evaluate the proportion of subjects who met the prespecified histologic criteria for EoG/EoD (as below) in at least 5 hpfs in the gastric mucosa and/or in at least 3 hpfs in the duodenal mucosa. Patients with *H pylori* present in biopsy samples were excluded. The criteria for EoG and/or EoD diagnosis were $\geq$30 eos/hpf in 5 or more gastric and/or 3 or more duodenal hpfs, respectively. The histologic criteria were based on randomized trials following US Food and Drug Administration guidance.[5] Additional post-hoc analyses were conducted among 2 symptomatic cohorts: EoG/EoD (positive by histology for EoG/EoD) and EoG/EoD-negative (negative by histology for EoG/EoD), and a control cohort (asymptomatic, healthy subjects).

Previous diagnoses of IBS, GERD, functional dyspepsia, and/or eosinophilic esophagitis, as well as medications, were collected from medical records.

The total study duration for each subject was approximately 40 days, comprising a screening period of up to 35 days before EGD, an EGD performed on day 1, and a follow-up phone call on day 4.

Summary statistics were computed to describe subject characteristics and eosinophil counts. To obtain mean eosinophil cell counts per hpf, the 5 highest counts from gastric hpfs and the 3 highest counts from duodenal hpfs were averaged. For all binary end points, the number and percent of subjects were calculated, along with 95% CI values. Continuous data were summarized using the number of subjects with nonmissing observations, mean, 95% CIs for the mean, median, SD, minimum value, and maximum value. Categorical data were summarized using the frequency count and percentage of subjects in each category. Subjects with missing values did not contribute to the denominator for percentage calculations unless specified otherwise. Statistical comparisons were made with unpaired t tests. Linear regressions with age and sex as covariates were performed for eosinophil count comparisons. The Pearson correlation coefficient was computed to determine the linear correlation between total and individual symptom scores and eosinophil counts in the stomach and duodenum.

Supplementary Table 1. Characteristics of Symptomatic Patients With and Without Eosinophilic Gastritis or Eosinophilic Duodenitis and Controls

Characteristic[a]	Patients with EoG/EoD (n = 152)	EoG/EoD-negative patients (n = 201)	*P* value[b]	Controls (n = 33)
Age, *y*, mean (range)	45 (19–78)	44 (18–76)	.234	34 (18–51)
Sex, female, n (%)	113 (74)	151 (75)	.902	13 (39)
Race, White, n (%)	135 (89)	182 (91)	.599	33 (100)
Weight, *kg,* median	84	80	.115	80
GI symptoms, mean no. of years	10	9	.127	—
Symptoms reported during screening, no. of subjects (%)				
Abdominal pain	151 (99)	200 (100)	1.000	0
Nausea	139 (91)	185 (92)	.847	0
Vomiting	80 (53)	88 (44)	.107	0
Diarrhea	144 (95)	179 (89)	.081	0
Early satiety	152 (100)	199 (99)	.508	0
Loss of appetite	147 (97)	194 (97)	1.000	0
Bloating	152 (100)	200 (100)	1.000	0
Abdominal cramping	151 (99)	201 (100)	.431	0