



Effect of Esophagogastroduodenoscopy Volume and Gastric/Esophageal Pathology on the Rate of Lymphocytic Duodenitis Reporting in Children and Adolescents

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Avicenna J Med 2022;12:169–173.

Abstract

Background It is not clear if the increase in the number of esophagogastroduodenoscopies (EGDs) performed has any significant effect on the rate of lymphocytic duodenitis (LD) reporting in children and adolescents and whether it correlates with abnormal gastric and/or esophageal pathology.”

Methods We performed a single-center retrospective study using the Mayo Clinic electronic health record and pathology database. We reviewed all EGD procedures performed in children and adolescents (<18 years) between January 1, 2000, and December 31, 2018, and identified two groups, the LD group and matched age and sex control group (normal duodenal biopsies). We evaluated the correlation of LD rate with the yearly number of EGDs performed and the presence of abnormal gastric and/or esophageal pathology.

Results Of 11,870 EGDs performed, we identified 338 (3%) individuals with LD and 390 (3%) randomly selected controls, with a mean (SD) age of 9.6 (5.3) and 11.7 (5.0) years, respectively. Based on logistic regression analysis, abnormal gastric histology was associated with the presence of LD when compared with controls (odds ratio, 2.85; 95% CI, 2.05–3.97; $P < 0.001$). The rate of LD-positive biopsies per year was highly correlated with the number of EGDs performed ($\rho = 0.931$; 95% CI, 0.826–0.974; $P < 0.001$).

Conclusion The rate of LD reporting is correlated with the number of EGDs performed and is more likely seen in children and adolescents with abnormal gastric histology.

Keywords

- esophagitis
- gastritis
- histologic changes

article published online
December 5, 2022

DOI <https://doi.org/10.1055/s-0042-175388>.
ISSN 2231-0770.

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What is Known

- LD is a common finding on duodenal biopsy in children and adolescents.
- The clinical significance of LD in the absence of celiac or Crohn's disease is not clear.

What is New

- The increase in the number of EGDs performed on children and adolescents is associated with an increase in the rate of LD reporting.
- LD is more commonly seen in children and adolescents with abnormal gastric pathology.

Introduction

The field of pediatric gastroenterology and hepatology has evolved substantially over the last two decades. As a result, more gastrointestinal (GI) procedures, such as esophagogastroduodenoscopy (EGD), considering the standard diagnostic test to evaluate children and adolescents with GI complaints, are being performed. The increase in GI procedures performed in children and adolescents has resulted in reporting many histologic findings with unclear clinical significance, such as chronic gastritis and lymphocytic duodenosis (LD).^{1–3} LD is defined as an increased number of (>25) intraepithelial lymphocytes with intact villous architecture per 100 epithelial cells.^{4–7} It is not clear if the increase in the number of EGDs performed has any significant effect on the rate of reporting these histologic findings, including LD, in children and adolescents.

Previous studies have shown that LD is associated with chronic gastritis due to *Helicobacter pylori*, celiac disease (CD), inflammatory bowel disease, and other autoimmune diseases.^{8,9} However, it is not clear if LD is associated with concurrent abnormal gastric and esophageal pathology, such as gastritis and/or esophagitis. While in adults the presenting symptoms will likely impact a decision to biopsy the esophagus, stomach, and small bowel (duodenum), it has been a long-standing practice in children and adolescents to biopsy the esophagus, stomach, and small bowel in all diagnostic EGDs. This different approach in children and adolescents allows assessment of 1) the correlation between the number of EGDs performed and the rate of LD reporting and 2) the association of LD with abnormal gastric and esophageal pathology.

Methods

We performed a single-center retrospective study using the Mayo Clinic electronic health record and pathology database, reviewing all EGD procedures performed in children and adolescents (<18 years) from January 1, 2000, through December 31, 2018. Pathology reports were reviewed by a study member (J.D.) to identify individuals with LD on their first diagnostic EGD (LD group), before reviewing their clinical notes and laboratory results. We selected age- and sex-matched children and adolescents who underwent EGD

with normal duodenal biopsies during the same period (control group).

All slides for both groups were initially reviewed and reported by experienced GI pathologists who were trained to review adult and pediatric GI biopsies. These pathologists were not blinded to the patient's clinical information. Clinical diagnoses and documentation of proton pump inhibitor (PPI) exposure within 3 months from EGD were reviewed and compared between the two groups.

We excluded individuals with known GI diagnoses, such as CD, Crohn's disease, and *H. pylori*. The number of EGDs performed in the LD and control groups were tabulated for each year from 2000 through 2018. A linear graph was generated to graphically explore a change in counts over the time period (→Fig. 1). The correlation between the number of EGDs per year and the percentage of LD-positive biopsies was assessed using Pearson's correlation coefficient. Logistic regression analysis assessed the association of gastric or esophageal histologic abnormalities with the presence of LD. A type I error rate of 0.05 was used to assess statistical significance. Analyses were performed using SAS v9.4 M6 (SAS Institute Inc).

Results

During the study period, 15,979 EGDs were performed in 11,870 children and adolescents. Of those, 6,008 (51%) were female and 5,862 (49%) male. Three hundred thirty-eight (3%) individuals had LD identified on their first diagnostic EGD and were included in the study, comprising the LD group. Three hundred ninety (3%) individuals were randomly selected as the control group. The mean (SD) age was 9.6 (5.3) years at the time of small bowel biopsy in the LD group, and 198 (59%) were female. In the control group, the mean (SD) age at the time of small bowel biopsy was 11.7 (5.0) years, and 237 (61%) were female (→Table 1).

The frequency of EGD procedures and LD findings were similar between males and females. Counts of EGD procedures and percentage of LD from 2000 through 2018 are shown in →Fig. 1A and B, respectively. The number of LD-positive biopsies per year was highly correlated with the number of EGD procedures performed yearly ($\rho = 0.931$; 95% CI, 0.826–0.974; $P < 0.001$). Beginning in 2010, the percentage of LD found on EGD began to increase, and this coincided with an increase in the number of EGDs performed each year.

When comparing previous exposure to PPIs between the two groups, we found that PPI use (44% vs. 29%, $P < 0.001$) was more common in the LD group (→Table 1). In the LD group with abnormal gastric histology, 119 of 138 (86%) were taking PPIs at the time of EGD. In the LD group, the median (range) of follow-up was 2.7 (0.0–190.9) months. The most common diagnoses in both groups were functional GI disorders, such as chronic abdominal pain, irritable bowel syndrome, and constipation. A comparison of clinical diagnoses between the two groups is summarized in →Table 2. During the follow-up period, none were diagnosed with CD, Crohn's disease, or *H. pylori*.

Of the 338 patients in the LD group, abnormal pathology was reported in 138 (41%) and 54 (16%) of gastric and

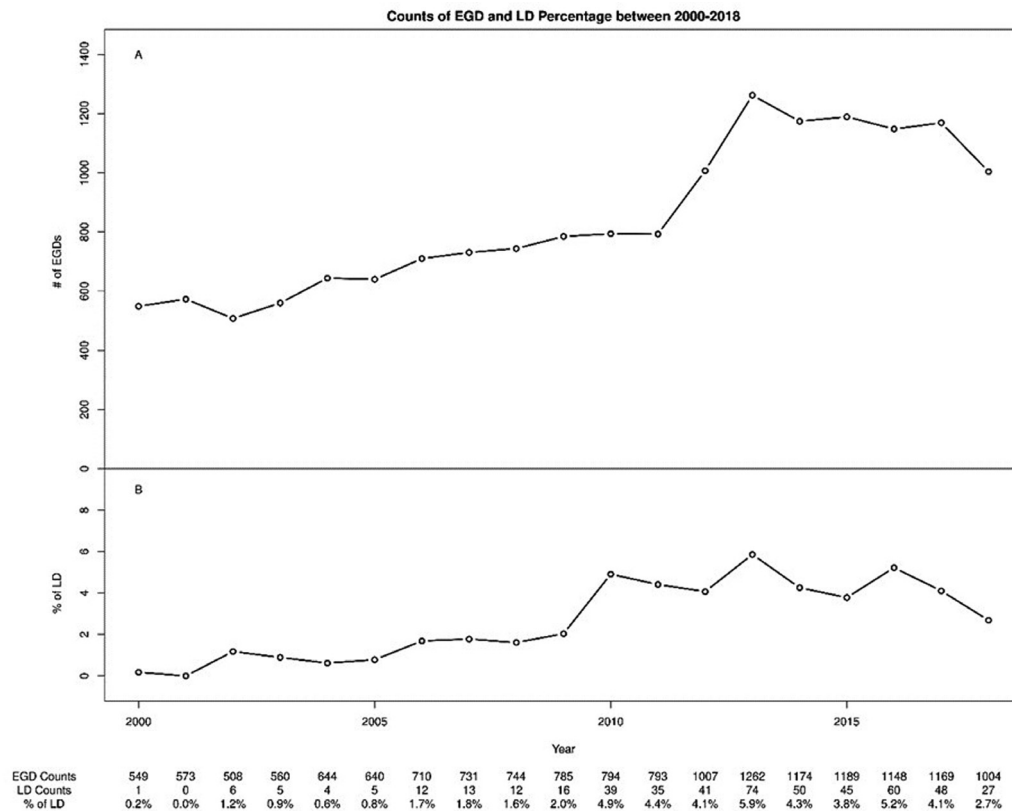


Fig. 1 Number of esophagogastroduodenoscopies performed and percentage of lymphocytic duodenosis between 2000 and 2018. (A) Number of EGDs performed. (B) Percentage of lymphocytic duodenosis. EGD, esophagogastroduodenoscopy; LD, lymphocytic duodenosis.

esophageal biopsies, respectively. In addition, abnormal gastric histologic findings included chronic gastritis in 95 (28%) and reactive gastropathy in 43 (13%). Meanwhile, abnormal esophageal histologic findings included reflux esophagitis in 33 (10%) and eosinophilic esophagitis (EOE) in 20 (6%) (►Table 1).

Of the 390 patients in the control group, abnormal pathology was reported in 76 (19%) and 45 (12%) gastric and esophageal biopsies, respectively. In addition, abnormal gastric histology included chronic gastritis in 45 (12%) and reactive gastropathy in 29 (7%). Abnormal esophageal histologic findings included reflux esophagitis in 26 (7%) and EOE in 18 (5%) (►Table 1).

Seventy-one patients in the LD group (21%) underwent a second EGD within a median (range) of 11.0 (0.0–146.0) months after their first EGD. Indication for a second EGD was persistent symptoms in 54 individuals and follow-up EGD in 17 (8 for EOE and 9 for gastroesophageal reflux disease). Of those, 58 of 71 (82%) had normal duodenal biopsies, and 13 (18%) had persistent LD on subsequent EGD. In the persistent symptom group (54 individuals) follow-up EGD showed LD resolution in 45 (83%) with a median (range) of 10.6 (1.4–146.0) months between the two EGDs. None were on gluten-free diets at the time of either their first or second EGD. Those with persistent symptoms were treated with standard PPIs or acetaminophen, and patients were diagnosed with functional GI disorders, such as chronic abdominal pain or functional dyspepsia, after follow-up EGD.

Based on logistic regression analysis, abnormal gastric histology was associated with the presence of LD (odds ratio, 2.85; 95% CI, 2.05–3.97; $P < 0.001$), while the presence of abnormal esophageal histology was not statistically significantly associated with LD (odds ratio, 1.46; 95% CI, 0.92–2.23; $P = 0.081$).

Discussion

Intraepithelial lymphocytes are a normal part of the small bowel's defense and surveillance system and respond to injury. LD is a common pathologic finding in children and adolescents undergoing EGD and is more common in those with CD, Crohn's disease, and *H. pylori*.¹⁰ Reporting of abnormal pathologic changes, such as reactive gastritis, chronic gastritis, and LD, is more commonly encountered. It is not clear if that is due to an increase in GI procedures, a change in pathology reporting practice, or a true increase in the prevalence of those histologic findings.

In our cohort, the rate of LD reporting increased over the study period. When we correlated the rate of LD reporting with the number of yearly EGDs performed, we found that the more EGDs performed, the more pathology reports with LD were encountered. We are not aware of any substantial change in our endoscopy practice or pathology reporting that could have affected these results. A previous study with a smaller cohort suggested that LD might be higher in the presence of esophagitis

Table 1 Characteristics of patients with abnormal gastric and esophageal biopsies

Patient characteristics	LD group (n = 338)	Control group (n = 390)	p-Value
Age at EGD, mean (SD), y	9.6 (5.3)	11.7 (5.0)	<0.001 ^a
Female sex	198 (59)	237 (61)	0.548 ^b
PPI exposure	150 (44)	113 (29)	<0.001 ^b
Abnormal gastric histology	138 (41)	76 (19)	<0.001 ^b
Chronic gastritis	95 (28)	45 (12)	
Reactive gastritis	43 (13)	29 (7)	
Lymphocytic gastritis ^c	0 (0)	1 (<1)	
Focal intestinal metaplasia	0 (0)	1 (<1)	
Abnormal esophageal histology	54 (16)	45 (12)	0.081 ^b
Reflux esophagitis	33 (10)	26 (7)	
EOE	20 (6)	18 (5)	
Candida esophagitis	0 (0)	1 (<1)	
Pancreatic acinar metaplasia	1 (<1)	0 (0)	

Abbreviations: EGD, esophagogastroduodenoscopy; EOE, eosinophilic esophagitis; LD, lymphocytic duodenosis; PPI, proton pump inhibitor.

^aEqual variance t-test.

^b χ^2 test.

^cA form of chronic gastritis with dense infiltration of foveolar epithelium by T lymphocytes.

Table 2 Final outcomes^a

Diagnosis	LD group (n = 338)	Control group (n = 390)	p-Value ^b
EOE	20 (6)	19 (5)	0.613
Reflux	57 (17)	45 (12)	0.664
Fructose malabsorption	12 (4)	23 (6)	0.082
Small bowel bacterial overgrowth	3 (1)	17 (4)	0.001
IBS	12 (4)	23 (6)	0.008
Rumination syndrome	0 (0)	8 (2)	0.004
Functional GI disorders	140 (41)	152 (39)	0.444
Lactose intolerance	20 (6)	39 (10)	0.014

Abbreviations: EOE, eosinophilic esophagitis; GI, gastrointestinal; IBS, irritable bowel syndrome; LD, lymphocytic duodenosis.

^aData are presented as No. (%) unless otherwise indicated.

^b χ^2 test.

and/or gastritis, but no statistical significance was found when compared with controls with normal biopsy.⁵ In our larger cohort, the LD rate was higher in both children and adolescents with esophagitis and gastritis but was only statistically significant in those with abnormal gastric biopsies, suggesting that LD can be a manifestation of a dispersed, nonspecific, immunoinflammatory response, as well as a normal host response to different triggers such as medications and infections. We believe that the presence of intraepithelial lymphocytes in the duodenum are a normal part of the small bowel defense mechanism and LD is more likely a transient reaction to pharmacologic, infectious, or environmental triggers. Many of the children with LD were diagnosed with functional GI disorders. It is not clear if the finding of LD should change the approach or the outcome of those cases when compared with children with functional diagnoses and normal SBB histology.

In our cohort, PPI use was more common in the LD group. Many children and adolescents with GI complaints are treated with PPI empirically before EGD.¹¹ It is not clear if the association between the rate of LD reporting and PPI use is due to the presence of gastritis or due to the direct effects of PPIs on the small bowel.¹² In both groups, functional GI diagnoses such as chronic abdominal pain and irritable bowel syndrome were more common.

The major limitation of our study was the retrospective nature of the available data. Because this was a single-center study and there was turnover among pathologists reviewing the data, we believe larger prospective studies with follow-up endoscopic assessment of LD cases are needed to clarify the association with PPI use and address long-term implications. Ideally, the pathology findings would be reviewed by a consistent team of pathologists to limit interobserver variation.

In conclusion, LD reporting is correlated with the number of EGDs performed and is more likely seen in children and adolescents with abnormal gastric histology.

Authors' Contributions

Study concept and design was conducted by I.A. and J.A. M.; data collection was conducted by J.D.; data analysis and interpretation were performed by all the authors; drafting of manuscript was done by J.A. and I.A.; critical revisions and final approval were duly done by all authors.

Funding

None.

Conflict of Interest

None declared.

Acknowledgment

We would like to thank the Scientific Publications staff at Mayo Clinic for copyediting support.

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