Original Article

Association of Duodenal Eosinophilia and Non-ulcer Dyspepsia Presented at GI Clinic, Rajavithi Hospital

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ABSTRACT

Background: The pathophysiologic mechanism involved in non-ulcer dyspepsia (NUD) is largely unknown. One hypothesis concerns eosinophilia-mediated hypersensitivity. A Swedish study reported that NUD was associated with duodenal eosinophilia. In Thailand, data on duodenal eosinophilia in Thai NUD patients has not been documented.

Aim: To evaluate an association between duodenal eosinophilia and NUD in Thai patients.

Patients and Methods: Thirty-five NUD patients and 7 control subjects underwent gastroduodenoscopy with biopsy specimens each from the body of stomach, antrum, duodenal bulb and second part duodenum. Eosinophilic counts were assessed for each biopsy specimen by summation of microscopic counting over 5 high-power fields. Another biopsy specimen from the gastric antrum was also obtained for the rapid urease test.

Results: Thirty-five patients were enrolled in the NUD group, 10 males (28.5%) and 25 females (71.5%), with a median age of 46 (20-69) years. There were 7 subjects in the control group, 2 males (28.6%) and 5 females (71.4%) with a median age of 65 (33-75) years. There were 2 subjects with gastric ulcer, 3 subjects with erosive gastritis and 2 subjects with severe hemorrhagic gastritis. Over 90% of NUD patients had intermittent dyspeptic symptom(s) for more than 12 weeks. Most patients in both groups had mild to moderately severe of epigastric pain, abdominal bloating and postprandial fullness. *Helicobacter pylori* infection was found in 28.6% to 45.2%, with no correlation to any dyspeptic symptoms. The median duodenal eosinophilic counts in the NUD group and in the control group were 7.5 (0-34) cells/5 HPF and 8.0 (4-21) cells/5 HPF, respectively. The difference was no statistical significance.

Conclusion: In this study, there was no association between duodenal eosinophilia and NUD in Thai patients.

Key words : Non-ulcer dyspepsia, *Helicobacter pylori*, duodenal eosinophilia

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INTRODUCTION

Dyspepsia is among the most common GI disorders, and is characterized by pain or discomfort centered in the upper abdomen. It is prevalent in more than one-fourth of the general population worldwide and is a frequent reason for medical consultation. One-half to two-thirds of dyspeptic patients demonstrate no focal or structural cause at endoscopy, and are labeled as having functional dyspepsia or non-ulcer dyspepsia (NUD). However, the pathophysiologic processes underlying the functional dyspeptic symptoms are poorly understood. Previous studies have shown that many factors may be responsible for functional dyspeptic symptoms, including visceral hypersensitivity[1,2], *Helicobacter pylori (H. pylori)* infection[3], and gastric motor dysfunction[4-6], which includes delayed solid gastric emptying, antral hypomotility and impaired gastric accommodation.

Talley *et al*. recently reported duodenal hypersensitivity to balloon distention in this disorder[7], and the observation of abnormal duodenogastric reflex responses suggested that the duodenum might be the key to unlock the underlying pathophysiology. A previous case-control study reported a significant number of eosinophils detected in the duodenum of patients with non-ulcer dyspepsia[8], implying that duodenal eosinophilia could be a positive pathologic marker for the diagnosis of non-ulcer dyspepsia. However, in Thailand, there is no data regarding this issue. The objectives of this study are (1) to compare the degree of eosinophilia in the stomach and in the duodenum, and (2) to find any correlation between degree of eosinophilia and *H. pylori* infection, in adult Thai patients with non-ulcer dyspepsia.

MATERIALS AND METHODS

Study subjects

From January 2008 to April 2009 patients with and without dyspepsia who underwent outpatient esophagogastroduodenoscopy (EGD) for any reasons at the GI Clinic, Rajavithi Hospital, Bangkok, were asked to complete questionnaires on age, symptom details, underlying diseases and current medications.

At the upper endoscopic examination, a rapid urease test (Pronto dry® test) for *H. pylori*, and gastric and duodenal mucosal biopsies were collected. To look out for parasitic infestation, complete blood count (CBC) and at least 2 stool samples were examined in all patients.

Inclusion criteria were clinical symptoms compatible with functional dyspepsia by Rome III criteria, age ≥18 years, and normal upper endoscopy. Exclusion criteria for the NUD group were: 1) subjects with underlying severe medical condition(s) which would make participation in the study unsafe or impractical, 2) patients with history of atopy, 3) patients taking medications which may affect the results of Pronto dry® test, such as proton-pump inhibitors, NSAIDs or antibiotics within 2 weeks prior to the study, 4) patients taking corticosteroids and antiparasite within 1 month prior to the study, 5) pregnancy, 6) age less than 18 years or greater than 75 years, 7) patients positive for parasite(s) from the stool examination, 8) presence of esophagitis, gastric atrophy, erosions, ulcers, gastroduodenal mass or other lesions on endoscopy, 9) patients with eosinophilia (eosinophil count > 500 cells/mm^3), 10) subjects with underlying medical condition(s) which could potentially have eosinophilia or eosinophilic infiltrate in the gastrointestinal tract, including eosinophilic gastroenteritis, hypereosinophilic syndrome, connective tissue diseases (e.g. Churg-Strauss vasculitis, rheumatoid arthritis, eosinophilic fasciitis), and neoplasia such as lymphoma, gastric and lung carcinoma, 11) anemia, 12) inability to understand or to provide written informed consent. Exclusion criteria for the control group were similar to the NUD group, except for the endoscopic findings.

The study was approved by the Ethics Committee of Rajavithi Hospital. All patients gave written, informed consent to participate in the study.

Study design

Abdominal symptom questionnaire

Patients were asked to complete a questionnaire on age, underlying diseases, current medications and symptoms, including severity scoring of the following symptoms: epigastric pain, early satiety, bloating, nausea, vomiting, heartburn, abdominal pain with alteration of defecation, and postprandial fullness, using a ten-point Likert scale.

Esophagogastroduodenoscopy and *H. pylori* status

Upper endoscopic examination was routinely performed at the GI unit, Department of Medicine, Rajavithi Hospital. Endoscopy calibration was conducted before the study.

H. pylori infection was defined as a positive rapid

urease test (Pronto dry® test) or a positive histological finding.

Histopathology

At endoscopy, biopsy specimens were taken from the stomach (body, antrum) and the duodenum (duodenal bulb, second part of duodenum). Biopsy specimens were fixed in formalin and routinely processed to paraffin wax. Sections were cut and stained with H & E and the silver stain (for *H. pylori*). For pathology, the presence and grade of acute and chronic inflammation, gastric metaplasia, and pathogens, were recorded.

Eosinophils were quantified by counting the number per high-power field, HPF (magnification 40X); 5 high-power fields being selected randomly in each section. The sums of the 5-field counts were then calculated.

Statistic analysis

Data were presented as median values because of a skewed distribution of the entire data. The primary outcome, the association between subject status (non-ulcer dyspepsia patient VS control) and eosinophil counts in tissue specimen, was assessed using logistic regression (case/control status) as the binary response variable. Univariate models (only the eosinophil counts as the predictor variable) and multiple predictor variable models, including age, sex, and *H. pylori* status as covariates, were assessed. Statistical comparisons between the two groups were performed with Pearson Chi-Square and Fisher's exact test. A significant difference was defined as *p*-value below 0.05.

RESULTS

Forty-two patients were enrolled in this study. There were 35 patients in the NUD group, 10 males (28.5%) and 25 females (71.5), with a median age of 46 (20-69) years. Most NUD patients had dyspeptic symptoms more than 12 weeks, which was statistically different from the control group. Other characteristics such as underlying disease(s), smoking, alcohol inges-

Table 1. Show the baseline characteristics of both groups.

Parameter	NUD (n = 35)	Control (n = 7)	*p*-value
Median age (range)	46 (20-69)	65 (33-75)	0.012*
Underlying disease (%)	16 (45.7%)	6 (85.7%)	0.096
Smoking (%)	2 (5.7%)	0 (0%)	1.000
Alcohol (%)	1 (2.9%)	0 (0%)	1.000
Drug (%)	23 (65.7%)	7 (100%)	0.067
Median BMI (kg/m^2) (range)	22.5 (16.2-37.4)	22.0 (19.3-25.8)	0.614
Median peripheral eosinophil count (cells/mm^3) (range)	132 (0-436)	72 (0-427)	0.826
Duration of symptom >12 weeks (%)	32 (91.4%)	3 (42.9%)	0.002*
Intermittent pain (%)	31 (88.6%)	4 (80%)	0.507

*Significant at level $p < 0.05$

Table 2. Show the symptoms of both groups.

Parameter	NUD (n = 35)	Control (n = 7)	*p*-value
Epigastric pain (%)	31 (88.6%)	4 (57.1%)	0.077
Abdominal bloating (%)	30 (85.7%)	3 (42.9%)	0.012*
Vomiting (%)	3 (8.6%)	1 (14.3%)	0.532
Heartburn (%)	6 (17.1%)	2 (28.6%)	0.482
Abdominal pain in other part of abdomen (%)	6 (17.1%)	1 (14.3%)	0.853
Postprandial fullness (%)	25 (71.4%)	3 (42.9%)	0.197
Satiation (%)	17 (48.6%)	1 (14.3%)	0.208

*Significant at level $p < 0.05$

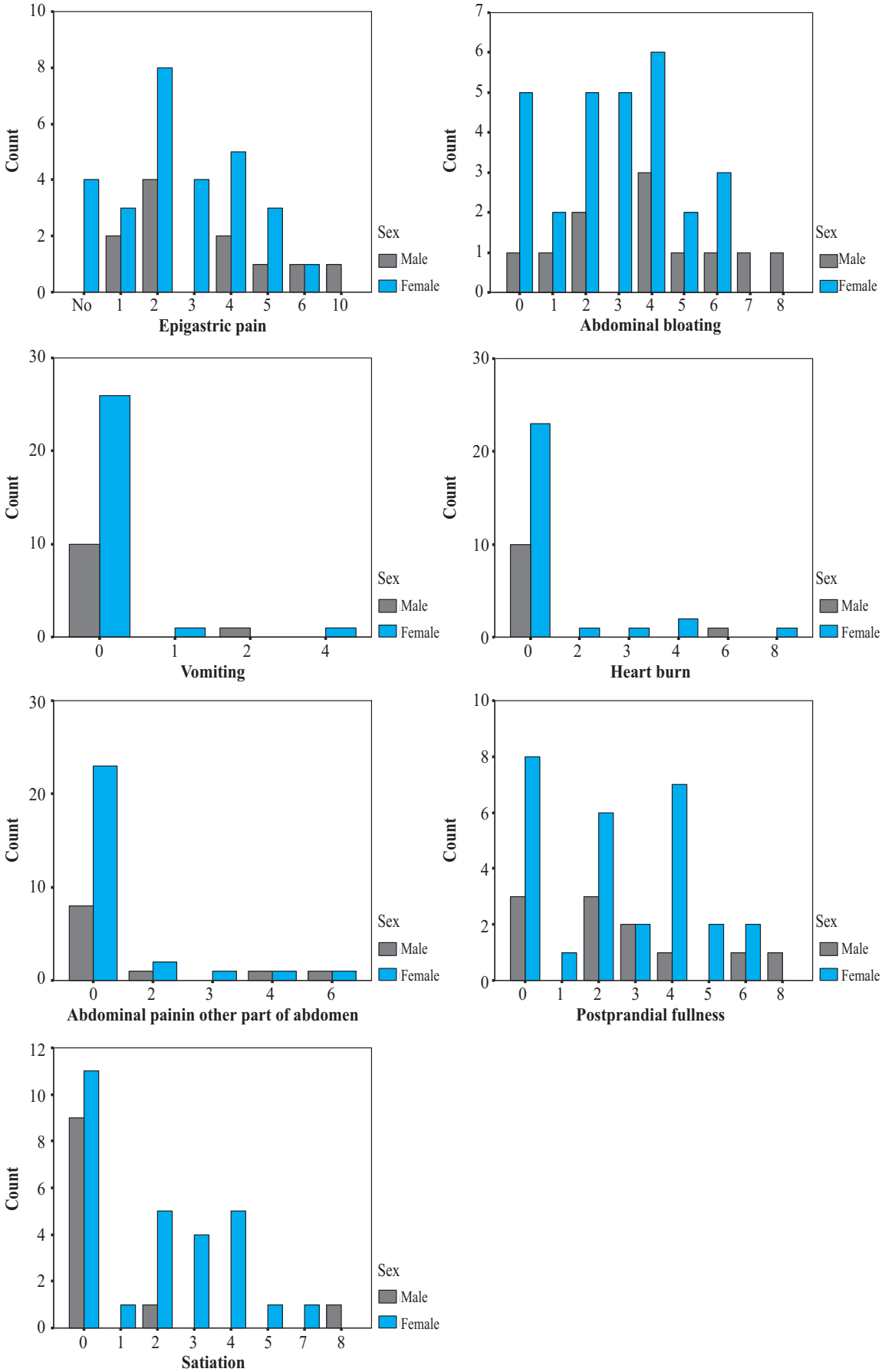

Figure 1. Symptom score (a ten-point Likert scale) in the NUD group

tion, median body mass index (BMI), median peripheral eosinophil count, and nature of dyspeptic pain, were comparable, as shown in Table 1.

The 7 patients in the control group had gastric ulcer (2), erosive gastritis (3) and severe hemorrhagic gastritis (2). There were 2 males (28.6%) and 5 females (71.4%) with a median age of 65 (33-75) years.

Symptom details (epigastric pain, vomiting, heartburn, abdominal pain in other parts of the abdomen, postprandial fullness and satiation) were similar in both groups, except for abdominal bloating which was significantly more often in the NUD group than in the control group (Table 2). The majority of NUD patients had epigastric pain, abdominal bloating and postprandial fullness. Symptoms severity was shown in Figure 1.

H. pylori was positive in 45.2% by rapid urease test and in 28.6% by findings in histopathology. H. pylori infection showed no correlation with any of the variables (data not shown).

In the NUD group, the median eosinophil count in the stomach and in the duodenum were 1.0 (range 0-16.5) and 7.5 (range 0-34) cells/5 HPF, respectively, as shown in Table 3, a similar finding as with the control group. Based on univariate analysis, the severity of the symptoms did not correlate with the number of eosinophil infiltrate (data not shown).

DISCUSSION

In the present study, dyspeptic patients exhibited various have many different presenting symptoms. The majority of patients had epigastric pain, abdominal bloating and postprandial fullness, but symptoms such as heartburn, vomiting and pain in other parts of the abdomen associated with changes in defecation were less common (<10%-20%). The median duration of symptoms before enrollment was over 12 weeks. The prevalence of *H. pylori* infection was 28.6%-45.2%, which was close to the reported prevalence in local studies in Chonburi (44%)[9] and in Northeastern Thailand (49% - 62%)[10,11], but higher than in a Western study (17%)[12]. This may be related to better sanitation in Western countries.

Interestingly, unlike in a previous study by Talley *et al*[8], we found that duodenal eosinophilia did not differ between the case and control groups. This could be due to other pathological diseases being chosen in the control group, thus affecting eosinophil accumulation in the stomach and duodenum with no difference being shown.

The duodenal eosinophil count in dyspeptic patients in this study were lower than in a previous study[8]. This could be due to many confounding factors, such as high prevalence of atopy and autoimmune diseases in Western countries, and parasitic infestation, which was not excluded in that study. Scanty data on the possible relevance of duodenal eosinophilia exists in the literature. Toukan *et al*[13] in a case-control study from Turkey, evaluated 31 cases with non-ulcer dyspepsia versus 32 healthy controls. They found a slight but significant increase in the eosinophil count in the duodenal bulb mucosa, but *H. pylori* status was not considered. In 59 pediatric cases with non-ulcer dyspepsia, 71% of enrolled patients were diagnosed with possible duodenal eosinophilia but atopy could have confounded these results[14]. Another study from Talley *et al*[8] reported the odds ratio for non-ulcer dyspepsia (VS asymptomatic controls) in subjects with high eosinophil counts in the duodenal bulb and in the second part duodenum of 11.7 and 7.3 respectively. However, in that study atopy and other causes of eosinophilia

Table 3. Median eosinophil count in gastric and duodenal biopsied specimen (cells/5 HPF).

Parameter	NUD (range) (n = 35)	Control (range) (n = 7)	*p*-value
Stomach	**1 (0-16.5)**	**2 (1-9)**	0.128
- Body of stomach	0 (0-17)	3 (0-4)	
- Antrum	2 (0-17)	1 (0-15)	
Duodenum	**7.5 (0-34)**	**8 (4-21)**	0.826
- Duodenal bulb	6 (0-28)	8 (2-25)	
- Second part duodenum	8 (0-49)	9 (0-17)	

*Significant at level $p < 0.05$

were not excluded. In our study, atopy and other possible causes of eosinophilia were excluded. There was a possibility that increased eosinophil numbers in non-ulcer dyspepsia were relevant, on account of the eosinophil-mast cell-nerve gut axis, but our study was not designed to evaluate this hypothesis.

There were limitations in our study. Firstly, there was no healthy control group as this was not accepted by the ethical committee of the institute. Secondly, as the eosinophil infiltrates were assessed by microscopic counting eosinophil degradation would lower the actual value of eosinophil count. Thirdly, there could be type II error because of small sample size.

Current therapy for non-ulcer dyspepsia is symptomatic and largely ineffective[15-17]. Another implication of our findings may be related to new targeted therapy. Several drugs can inhibit eosinophil production or eosinophil-derived products. In most subjects with eosinophilic esophagitis and eosinophilic gastroenteritis, corticosteroids are effective[18]. To our knowledge, no trials of corticosteroids have been conducted in non-ulcer dyspepsia patients

In conclusion, our study demonstrated a higher degree of eosinophilia in the duodenum than in the stomach in both groups of patients, but no causal relationship could be demonstrated.

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