ORIGINAL ARTICLE

Duodenal eosinophilia is associated with symptomatic erosive gastro-oesophageal reflux disease, presence of co-morbidities, and ethnicity but not undifferentiated functional dyspepsia: A retrospective Malaysian study

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ABSTRACT

Background: Duodenal eosinophilia is postulated to play a key role in the pathogenesis of functional dyspepsia, a common condition responsible for considerable impairment of quality of life. Our objective was to evaluate the relative strength of the associations between duodenal eosinophilia, functional dyspepsia, symptomatic erosive gastroesophageal reflux disease (GERD), the presence of co-morbidities, and a number of other variables.

Methods: Eosinophil counts of archived endoscopic duodenal biopsies of 289 subjects were determined by a pathologist blinded to the clinical data. Duodenal eosinophilia was defined by a count of more than 15 per 5 high power fields. Clinical charts were reviewed by a gastroenterologist blinded to the histology review.

Results: In the study sample, the primary diagnosis was functional dyspepsia (undifferentiated by subtypes) in 45, symptomatic erosive GERD in 29, gall stone disease in 17, irritable bowel syndrome in 23, and an alternative or undetermined diagnosis in 175 subjects, respectively. On logistic regression analyses, eosinophil counts were positively associated with symptomatic erosive GERD (Odds Ratio, OR 1.03, 95% Confidence Interval, 95%CI: 1.00, 1.05; p=0.035) but not functional dyspepsia. Pre-defined duodenal eosinophilia was associated with symptomatic erosive gastro-oesophageal reflux disease (OR 3.36, 95%CI 1.18,-9.60; p=0.023), the presence of co-morbidities (OR 2.00, 95%CI 1.10, 3.62; p=0.022), and Chinese (as compared to Malay and Indian) ethnicity but not with either functional dyspepsia, irritable bowel syndrome, gallstone disease, Helicobacter pylori infection, or gender.

Conclusion: Duodenal eosinophilia was associated with symptomatic erosive GERD, the presence of co-morbidities, and Chinese ethnicity but not with undifferentiated functional dyspepsia.

KEYWORDS:
Duodenal eosinophilia, functional dyspepsia, GERD

INTRODUCTION

Functional dyspepsia is a common condition that is responsible for considerable impairment of quality of life.[1] The notion that microinflammation in the duodenum has a key role in the pathogenesis of functional dyspepsia has recently gained much traction.[2] It is postulated that duodenal microinflammation and the accompanying aberration of mucosal permeability are linked to activation of the immune system, visceral hypersensitivity, stimulation of afferent nerve endings, and altered gastroduodenal motor function.[2] Early evidence for this accrued from observations of a subtle increase in duodenal mucosal eosinophil counts in subjects with non-ulcer dyspepsia.[3] The association between duodenal eosinophilia and functional dyspepsia, however has not been uniformly consistent. Some have reported duodenal eosinophilia to be positively associated with functional dyspepsia as a whole[3-5] while others have reported an association with only subtypes of functional dyspepsia[6-9] or indeed no association at all.[10] The relevance of the association between duodenal eosinophilia and functional dyspepsia lies not only in its importance in elucidating the pathogenesis of functional dyspepsia but also in the potential applicability of duodenal eosinophilia as a diagnostic biomarker of functional dyspepsia. The objective of this retrospective study conducted on patients attending a Malaysian hospital was to investigate the strength of the associations between functional dyspepsia, duodenal eosinophilia, and a number of other variables, including age, gender, ethnicity, the presence of co-morbidities, other common gastrointestinal disorders, and *Helicobacter pylori* infection.

MATERIALS AND METHODS

Study Subjects

The study sample consisted of consecutive patients under the care of a single gastroenterologist (SMR) who underwent elective diagnostic oesophago-gastro-duodenoscopy (OGD) in 2019. It was routine practice for a random mucosal biopsy to be taken from the second part of the duodenum for histological examination as well as biopsies from the gastric antrum and body for the detection of *Helicobacter pylori*

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infection by the rapid urease test. Exclusions from routine biopsy included (i) patients in whom the OGD was performed in an emergency setting such as acute upper gastrointestinal bleeding, (ii) patients in whom the indication was primarily therapeutic such as in oesophageal stenting, duodenal stenting, or insertion of percutaneous endoscopic gastrostomy tubes, (iii) patients with a bleeding tendency, and (iv) patients on anti-platelet and/or anticoagulant drugs. A total of 464 patients underwent OGD during the study period and biopsies were taken from 289 subjects who constituted the study sample.

Histological Protocol

The duodenal biopsies of the 289 subjects were retrieved from the archives of the histopathology department and reviewed by a single pathologist who was blinded to the clinical information of the patients. All endoscopic duodenal biopsies in the study hospital were handled, processed, and examined using a standard protocol. The biopsy specimens were mounted directly from the biopsy forceps onto filter paper mucosal surface up and placed immediately in formalin preservative. After overnight processing, the tissue specimens were carefully embedded on edge, perpendicular to the mucosal surface, and sectioned at 3-micron thickness. Six sections were obtained after step sectioning and stained with haematoxylin and eosin. The number of eosinophils was counted in five random high-power fields (HPF) at ×40 magnification and field diameter of 0.55mm. Duodenal eosinophilia was defined as an eosinophil count of more than 15 per 5 (HPF) as proposed by Chaudhari et al.[11]

Clinical chart review and definition of diagnostic groups:

The clinical chart of each patient was reviewed by a gastroenterologist who was blinded to the results of the histology review. The information retrieved from the clinical charts included demographic details, the primary diagnosis, the presence of significant co-morbidities, and the presence of symptoms of anxiety or depression. The definition of significant co-morbidities included but was not confined to conditions such as diabetes, cardiac disease, respiratory disease, chronic kidney and liver disease, malignancy, and infection. The diagnosis of functional dyspepsia was made if the broad criteria of the Rome 4 classification were met including chronicity of upper abdominal symptoms, normal OGDS findings, absence of *Helicobacter pylori* infection, and no other obvious explanation for the symptoms.[12] Based on clinical and investigational findings, three other gastrointestinal disorders that permitted diagnosis with a high level of confidence included irritable bowel syndrome (IBS), symptomatic erosive gastro-oesophageal reflux disease (GERD), and gallstone disease. The diagnosis of IBS was based on the broad criteria of the Rome 4 classification.[12] Symptomatic erosive GERD was defined by the presence of convincing GERD symptoms and endoscopically identifiable erosive changes. Gall stone disease was defined by the presence of gall stones and clinical features that were convincingly attributable to the gall stones. Where symptoms overlapped, the primary diagnosis assigned to the subject was determined by which of the conditions was responsible for the predominant symptoms. When making direct comparisons of the eosinophil counts and rate of duodenal eosinophilia between groups, the IBS group was utilised as the control based on the findings of a previous study that duodenal eosinophilia was not a feature of IBS.[13]

Statistical methods

The Epi InfoTM version 7.2 statistical software package available from the Centres for Disease Control and Prevention (CDC) website was used in the statistical analyses. Differences in the rate of categorical variables between groups were tested by the chi-square test while differences in numerical variables were tested using the non-parametric Kruskal–Wallis test. Logistic regression analysis was used to examine the independent association between multiple explanatory variables and a dichotomous response variable. Association was expressed in terms of odds ratio (OR) and 95% confidence intervals (95%CI). All 289 subjects were included in the logistic regression analyses.

This retrospective study was approved by the hospital research and ethics committee and was conducted in accordance with the ethical standards laid down by the 1964 Helsinki Declaration.

RESULTS

Characteristics of the sample

Female subjects constituted 52.6% (152/289) of the sample. The median age of the sample was 48 years (range 15-88 years). Two hundred and forty (83.0%) of the subjects were Malaysian nationals, 3 subjects did not state their nationality while the remaining subjects were nationals of 24 different countries. In terms of ethnicity, the three largest groups consisted of Indians (n=102), Chinese (n=93), and Malays (n=56). Fourteen of the 102 ethnic Indians and 3 of the 93 ethnic Chinese were not Malaysian nationals.

The primary diagnosis was functional dyspepsia in 45 patients, symptomatic erosive GERD in 29 patients, gallstone disease in 17 patients, and IBS in 23 patients, respectively. The remaining 175 subjects consisted of patients with another primary diagnosis or in whom the primary diagnosis was undetermined. Twenty-seven patients were positive for *Helicobacter pylori* infection and 105 patients had significant co-morbidities. The demographic characteristics, the frequency of co-morbidities, the Helicobacter pylori infection rates, the rates of duodenal eosinophilia (as defined by a count of >15 per 5 HPF), and the absolute duodenal eosinophil counts in the various diagnostic groups are summarised in Table I. Comparison of the three diagnostic groups of functional dyspepsia, symptomatic erosive GERD, and gall stone disease, respectively, with the group of subjects with IBS (that served as a control) revealed that patients with symptomatic erosive GERD were significantly older and more likely to be male than patients with IBS (Table I). There was no statistically significant difference in these parameters between the functional dyspepsia and gall stone disease groups, respectively, and the control group of IBS subjects.

Comparison of eosinophil counts and rate of eosinophilia (>15 counts per HPF) between the diagnostic groups

The rate of eosinophilia as defined by >15 counts per HPF was significantly higher in the group with symptomatic erosive GERD than the IBS group (24/29 vs. 12/23, p=0.018, Table I).

Table I: Demographic characteristics, duodenal eosinophil counts, rates of H pylori infection and rates of co-morbidities in the diagnostic groups

Diagnostic group	Age in years	Gender: females n (%)	Ethnicity: n (%)	Co-morbidities n (%)	H. pylori infection n (%)	Duodenal eosinophilia[a] n (%)	Duodenal eosinophil count (per 5 high-power fields)
Functional dyspepsia (n=45)	39 (24-77)	34 (75.6)	Malay: 6 (13.3) Chinese: 14 (31.1) Indian: 18 (40.0) Other: 7 (15.6)	11 (24.4)	0 (0.0)	23 (51.1)	16 (3-58)
Symptomatic erosive GERD (n=29)	57 (26-88) *	13 (44.8) *	Malay: 7 (24.1): Chinese: 6 (20.7) Indian: 13 (44.8) Other: 3 (10.3)	16 (55.2)	2 (6.9)	2 (6.9)	20 (7-85) **
Gall stone disease (n=17)	47 (29-63)	12 (70.6)	Malay: 4 (23.5) Chinese: 6 (35.3) Indian: 5 (29.4) Other: 2 (11.8)	5 (29.4)	0 (0.0)	11 (64.7)	23 (5-55)
Irritable bowel syndrome (n=23)	44 (25-73)	18 (78.3)	Malay: 3 (13.0) Chinese: 9 (39.1) Indian: 6 (26.1)	7 (30.4)	0 (0.0)	12 (52.2)	18 (2-54)
Other or undetermined diagnoses (n=175)	50 (15-81)	75 (42.9)	Malay: 36 (20.6) Chinese: 58 (33.1) Indian: 60 (34.3) Other: 21 (12.0)	66 (37.7)	25 (14.3)	107 (61.1)	18 (1-75)

Data expressed as median (range) or n (%).
a Eosinophilia defined by a count >15 eosinophils per 5 high power fields.
*Significantly different compared to the irritable bowel syndrome group, *p<0.05.
** Significantly different compared to the irritable bowel syndrome group, p=0.052.

Table II: Logistic regression model of predictors of functional dyspepsia

	Odds ratio (95% confidence interval)	p value
Age	0.97 (0.95-1.00)	0.066
Female gender	3.22 (1.52-6.82)	0.002
Ethnicity: Chinese compared to Malay	1.50 (0.51-4.42)	0.461
Chinese compared to Indian	0.86 (0.39-1.93)	0.724
Chinese compared to Other	0.69 (0.24-2.00)	0.496
Presence of co-morbidities	0.82 (0.35-1.89)	0.635
Duodenal eosinophil count	1.00 (0.98-1.02)	0.878
Symptoms of anxiety or depression	2.38 (1.04-5.46)	0.041

Table III: Logistic regression model of predictors of symptomatic erosive GERD

	Odds ratio (95% confidence interval)	p value
Age	1.02 (0.99-1.06)	0.140
Female gender	0.85 (0.38-1.91)	0.699
Ethnicity: Chinese compared to Malay	0.37 (0.11-1.26)	0.111
Chinese compared to Indian	0.44 (0.15-1.24)	0.119
Chinese compared to Other	0.68 (0.16-2.98)	0.608
Presence of co-morbidities	1.46 (0.60-3.55)	0.400
Duodenal eosinophil count	1.03 (1.00-1.05)	0.035
Symptoms of anxiety or depression	0.41(0.09-1.84)	0.245

Table IV: Logistic regression model of predictors of duodenal eosinophilia (as defined by >15 cells per 5 high power fields)

	Odds ratio (95% confidence interval)	p value
Age	0.98 (0.96-1.00)	0.054
Female gender	0.83 (0.49-1.40)	0.484
Ethnicity: Chinese compared to Malay	3.17 (1.49-6.80)	0.003
Chinese compared to Indian	2.10 (1.14-4.01)	0.018
Chinese compared to Other	1.80 (0.80-4.07)	0.158
Presence of co-morbidities	2.00 (1.10-3.62)	0.022
Helicobacter pylori infection	0.73 (0.31-1.74)	0.484
Functional dyspepsia	0.66 (0.311– 1.41)	0.285
Irritable bowel syndrome	0.60 (0.23-1.53)	0.283
Gall stone disease	1.19 (0.40-3.53)	0.755
Symptomatic erosive GERD	3.36 (1.18-9.60)	0.023

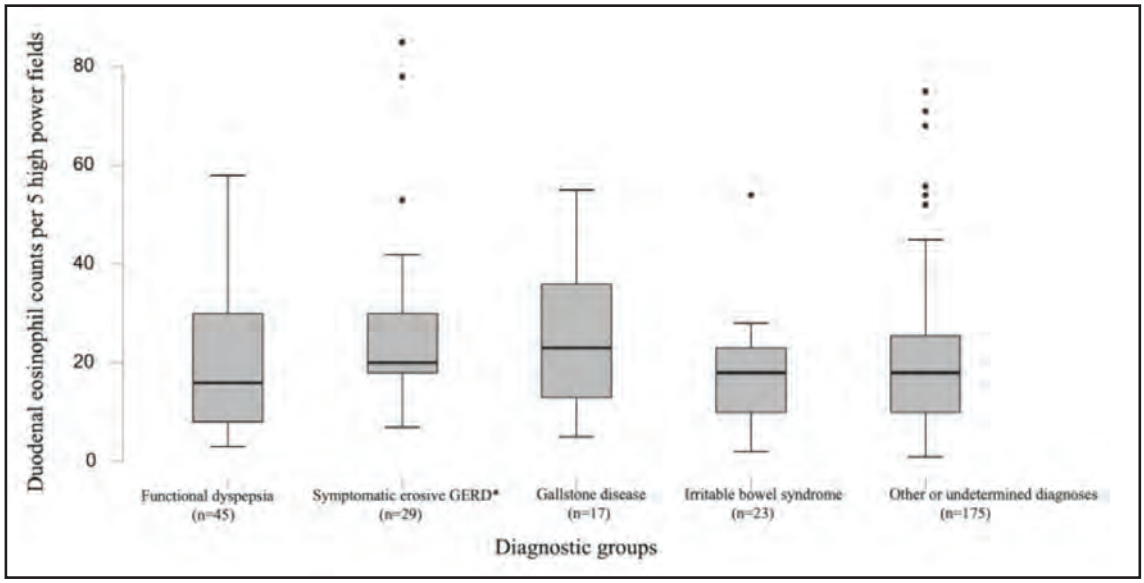

Fig. 1: Distribution of duodenal eosinophil counts in the diagnostic groups

The rates of eosinophilia in the functional dyspepsia and gall stone disease groups were not statistically significantly different from that of the IBS group (Table I). The distribution of the duodenal eosinophil counts in the diagnostic groups is shown in Figure 1. Comparison of the eosinophil counts of the functional dyspepsia, symptomatic erosive GERD, and gall stone disease groups, respectively, with that of the IBS group showed a difference that approached statistical difference only in the case of symptomatic erosive GERD group (Table I).

Logistic regression analyses

Logistic regression analysis with functional dyspepsia as the response variable revealed that functional dyspepsia was significantly predicted by female gender and the presence of symptoms of anxiety or depression but not by elevated duodenal eosinophil counts (Table II). Similar logistic regression analysis with symptomatic erosive GERD as the response variable revealed that symptomatic erosive GERD was independently associated with elevated duodenal eosinophil counts but not with any of the other variables (Table III). Logistic regression analysis with duodenal eosinophilia (>15 counts per HPF) as the response variable showed that duodenal eosinophilia was significantly predicted by the presence of co-morbidities and symptomatic erosive GERD but not by functional dyspepsia or *Helicobacter pylori* infection (Table IV). Duodenal eosinophilia was also associated with Chinese ethnicity as opposed to Malay or Indian ethnicity (Table IV).

DISCUSSION

The key finding of our study was that duodenal eosinophilia was independently associated with symptomatic erosive GERD and the presence of co-morbidities but not with undifferentiated functional dyspepsia. The relationship between symptomatic GERD and increased eosinophils in the duodenal mucosa was evident on two measures; the rate of duodenal eosinophilia (as defined by >15 counts per HPF) and the absolute duodenal eosinophil counts. In contrast, there was no detectable relationship between functional dyspepsia and eosinophils in the duodenal mucosa based on either of the two measures. In this context, it should be noted that normal ranges for duodenal eosinophil counts among healthy adults have not been clearly established. The cut-off value of eosinophils per HPF used to define duodenal eosinophilia in previous publications has been variable, ranging from 15 to 63 per HPF.[4,6,8,11] The arbitrary choice of 15 per HPF in our study as proposed by Chaudhari et al.,[11] was based on the premise that the degree of eosinophilia in conditions such as functional dyspepsia and GERD is likely to be subtle and a relatively lower cut-off would have greater sensitivity in detecting a positive signal. A number of studies have used a cut-off value of >22 counts per 5 HPF to define eosinophilia.[3,4,6] When we reanalysed our data using a cut-off value of >22 counts per 5 HPF, the association between duodenal eosinophilia and concomitant co-morbidities was preserved but the associations with symptomatic erosive GERD, ethnicity, and age were no longer detectable (data not shown).

The failure to find a relationship between functional dyspepsia and duodenal eosinophilic infiltration irrespective of whether it was measured in terms of absolute counts or rate of pre-defined eosinophilia is concordant with the findings of some studies[8-10] but not with others.[3-5] We are cognisant however of a limitation of our retrospective study that restricts the conclusions that can be drawn with regard to the relationship between duodenal eosinophilia and functional dyspepsia. This relates to the fact that while the diagnosis of functional dyspepsia per se was determined with a high level of confidence, the retrospective nature of the study precluded the precision needed to divide the group into the subtypes of epigastric pain syndrome and post-prandial distress syndrome, respectively, as prescribed by the Rome 4 classification.[12] In previous studies, duodenal eosinophilia was most frequently associated with the subtypes of patients with post-prandial distress and early satiety although it has

to be noted that even then the association with these two sets of symptoms was not consistent.[6-9] It may be that the number of subjects with post-prandial distress syndrome in our sample was small and our study was therefore not sufficiently powered to detect an association. Furthermore, in at least one other study, functional dyspepsia was not associated with total duodenal eosinophil counts but was positively associated with eosinophilic degranulation, the latter being a marker of eosinophil activation8. Hence, the absence of an association between functional dyspepsia and duodenal eosinophil counts in our study does not necessarily negate the role of duodenal eosinophils in the pathogenesis of functional dyspepsia.

The finding in our study of an independent association between symptomatic erosive GERD and elevated duodenal eosinophil counts is intriguing. The diagnosis of symptomatic GERD in our study was relatively robust as it was made on the basis of unequivocal endoscopic findings and compatible symptoms. This observation resonates with the findings of a recent study that duodenal eosinophilia in patients with functional dyspepsia predicted the development of GERD 10 years later.[14] The authors of that study postulate that subsets of GERD and functional dyspepsia may be part of the same disease spectrum and that duodenal eosinophilia could well be the link. Our finding lends credence to this hypothesis. Distinguishing with precision between the subtypes of functional dyspepsia and GERD on the basis of the history even with validated questionnaires can be challenging. It is quite conceivable that there is an overlap between patients with symptomatic erosive GERD in our study and subsets of patients with functional dyspepsia. The possibility that this explains the association between duodenal eosinophilia and patients labelled as symptomatic erosive GERD cannot be excluded.

Assigning subjects to the diagnostic groups in our study was predicated on the ability to make the diagnosis with a high degree of certainty from the available information. A substantial number of patients in our cohort would have had non-erosive GERD but we did not assign these subjects to a defined diagnostic group because of difficulties in distinguishing true non-erosive GERD from functional oesophageal disorders in the absence of routine ambulatory pH or impedance testing.

The independent association observed between the presence of co-morbidities and duodenal eosinophilia in our study is perhaps not surprising as there already exists a body of evidence linking systemic illness, abnormal intestinal permeability, and impaired intestinal barrier function.[15] The definition of significant co-morbidities was necessarily broad and included a multitude of illnesses as we wanted to investigate the relative impact of these conditions on duodenal eosinophil counts in comparison to the putative effect of functional dyspepsia.

Another notable observation of our study was that Chinese ethnicity was a more significant predictor of duodenal eosinophilia than Indian or Malay ethnicity. We are unaware of any other study that detected ethnic differences in duodenal mucosal eosinophil counts. The ethnic composition of our sample is not representative of that of Malaysia as a whole and is more a reflection of the local demography, health care seeking behaviour, and referral patterns. This does not however invalidate our observations of the observed association between ethnicity and duodenal eosinophilia. The quantifying of duodenal eosinophils on histological examination does not require sophisticated technology and has potential as a widely available marker of subsets of functional dyspepsia. However, our observation of the possible influence of co-morbidities, ethnicity, and even age on duodenal eosinophil counts suggests that the utility of duodenal eosinophilia alone as a diagnostic biomarker of functional dyspepsia is likely to be limited.

The fact that female gender and symptoms of anxiety or depression independently predicted the diagnosis of functional dyspepsia is consistent with the general experience and suggests that the population of patients with functional dyspepsia attending our institution is unlikely to be substantially different from that of other populations.[1]

An inherent limitation of a retrospective observational study such as ours is the absence of matched healthy controls. We mitigated this weakness in two ways. Firstly, by using the subset of patients with IBS as a compromise control group based on a previous report that duodenal eosinophilia was not a feature of IBS and secondly by using logistic regression analysis to adjust as far as was possible for confounding factors.[13] Another limitation relates to the sample size that is particularly relevant to the gall stone disease group that may not have been sufficiently powered to detect an association with duodenal eosinophilia. Other limitations include the inability to exclude eosinophilic oesophagitis in the absence of oesophageal biopsies and the inability to evaluate the impact of allergies as data on allergies was sketchy. It has been suggested that proton pump inhibitors suppress duodenal eosinophilia.[16] We did not specifically gather data on proton pump inhibitor usage among the subjects in our sample and can only speculate on whether this might have been a factor in not being able to detect an association between functional dyspepsia and duodenal eosinophilia. However, we have no reason to believe that proton pump inhibitor usage is lower in subjects with symptomatic erosive GERD than in functional dyspepsia patients.

CONCLUSION

In conclusion, duodenal eosinophilia in our study was associated with symptomatic erosive GERD, the presence of co-morbidities, and Chinese ethnicity but not with undifferentiated functional dyspepsia. Taken in conjunction with the results of other studies, our findings lend support to the hypothesis that subsets of GERD and functional dyspepsia may be part of the same disease spectrum of which duodenal eosinophilia is a common characteristic.

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