



Does the Location and Prevalence of Gastric Intestinal Metaplasia Change in Patients with Functional Dyspepsia

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Abstract

Gastric intestinal metaplasia plays a significant role in the pathogenesis of intestinal gastric cancer. **Objective:** A retrospective analysis of demographic characteristics, site of involvement, and incidence was performed involving patients who underwent endoscopy who had biopsy-diagnosed intestinal metaplasia. **Materials and Methods:** The study included 720 patients with functional dyspepsia retrospectively from among 6160 patients who underwent upper endoscopy in Celal Bayar University, Faculty of Medicine, Gastroenterology Department, between 2014 and 2020. **Results:** Intestinal metaplasia was detected at the antrum, corpus, and angulus in 59.94%, 13.47%, and 28.57% of the cases, respectively. Antral lesions were significantly more prevalent ($P < 0.05$). Of the patients with IM, 63.5% had HP positivity, with a significant association between IM positivity and HP positivity ($P < 0.05$). There was a significant difference between patients with or without a history of chronic PPI use in terms of the prevalence of intestinal metaplasia ($P < 0.05$). **Conclusion:** These results suggest that the endoscopic follow-up of patients with IM requires additional attention to the lesser curvature of the antrum as well as the gastric angulus.

Subject Areas

Biochemistry

Keywords

Gastric Intestinal Metaplasia, Helicobacter Pylori, Gastritis, Functional Dyspepsia

1. Introduction

Gastric cancer is a major public health problem that is the fifth most frequent cancer type and the third leading cause of cancer-related deaths globally [1]. The acknowledged gastric carcinogenesis cascade proposed by Correa is considered initiated by *Helicobacter pylori* (HP) infection, followed by stages of superficial gastritis, chronic atrophic gastritis, intestinal metaplasia (IM), dysplasia, and gastric cancer [2]. Herein, IM represents an intermediate step that may lead to the development of intestinal type gastric adenocarcinoma.

In 1994, HP was declared a primary carcinogen by the World Health Organization. Chronic HP infection is known to be closely related to the development of atrophic gastritis and IM. Thus, the role of HP treatment in the carcinogenesis cascade remains an active area of research, particularly in terms of the potential reversibility of atrophy and metaplasia.

IM plays a major role in the pathogenesis of intestinal-type gastric cancer as suggested by studies such as those of Gomez *et al.* that showed a six-fold increased risk of gastric cancer in patients with IM compared to the general population [3] [4].

Thus, the presence of IM is an obvious risk factor for the development of gastric cancer, and early identification of IM represents the single most important step in the follow-up of patients with a risk of gastric cancer [5]. Previous studies have shown that eradication of HP may prevent the development of gastric cancer by alleviating atrophic gastritis [6]. Furthermore, a meta-analysis found that oxyntic atrophy plays a role in the pathogenesis of gastric cancer [7] [8].

Several recent studies also reported that long-term use of PPIs may be a risk factor for the pathogenesis of gastric cancer [9]. It has been proposed that the suppression of gastric acidity may lead to hypergastrinemia via a negative feedback mechanism, resulting in an increased risk of gastric cancer [8]. Additionally, investigations into the role of gastric metaplasia in the pathogenesis of gastric cancer suggested that it may occur as a long-term consequence of atrophic gastritis [10].

Gastric cancer screening is associated with reduced mortality by allowing timely diagnosis and treatment of the condition [11].

Patients with chronic atrophic gastritis or IM have an increased risk of gastric adenocarcinoma. Since atrophy and IM exhibit an irregular distribution pattern in the stomach, the more recently published guidelines, an international biopsy protocol has been developed to detect atrophic and metaplastic changes by obtaining 2 antral (one from the lesser and greater curvature), 2 corpus, and 1 incisura angularis samples. The antral biopsy samples should be obtained 2 - 3 cm from the pylorus, while corpus biopsy samples should be 8 cm from the cardia. In the presence of additional lesions, target biopsies should also be performed [2]. Regular follow-up is not recommended if limited (mild or moderate) atrophy is present. However, in patients with IM confined to a single area who have a family history of gastric cancer, incomplete IM or *Helicobacter pylori* infec-

tion, endoscopic follow-up with chromo-endoscopy and biopsy is recommended. Endoscopic follow-up examinations every three years are also recommended for patients with severe atrophic gastritis.

HP eradication may improve atrophic gastritis and reduce the risk of gastric cancer. However, in patients with intestinal metaplasia, HP eradication does not alleviate intestinal metaplasia, although it may slow down the process of neoplastic transformation. Therefore, HP eradication is recommended [2].

In this retrospective analysis, patients undergoing endoscopy due to dyspeptic complaints who were found to have biopsy-diagnosed IM were compared to patients without this condition in terms of demographic characteristics, site of involvement, and incidence. Furthermore, patients with longer-term (≥ 3 months) use of PPIs were compared with no such use of PPIs regarding intestinal metaplasia. Additionally, the association between HP positivity and IM was investigated using the most recent Sydney grading system.

This study was conducted on 720 patients whose biopsies were taken according to Sydney classification by scanning 6120 patients and diagnosed by the same endoscopist and pathologist.

2. Materials and Methods

The study included 720 patients with functional dyspeptia retrospectively from among 6160 patients who underwent upper endoscopy in Celal Bayar University, Faculty of Medicine, Gastroenterology Department, between January 2014 and April 2020.

Of these, 5540 subjects were excluded due to reasons previous history of esophageal or gastric surgery, diagnosis of gastric cancer, alarm symptoms, HP eradication treatment within the past 2 months, use of antibiotics, and inadequate number (*i.e.* ≥ 5) of sampling sites (Figure 1).

Signed consent was obtained from all subjects in the endoscopy unit before the endoscopic procedure. After 8 - 12 hours of fasting, local oropharyngeal sedation was performed using 2% Xylocaine spray, and intravenous midazolam (0.07 - 0.1 mg/kg) was administered immediately prior to the procedure. A gastroscope with an endoscopic video information system was used in the process of the esophagogastroduodenoscopy (EGD) (NBI system using video endoscopes [GIF-H260; Olympus], video processor [Evis Lucera CV 260 SL; Olympus], and lighting unit [Evis Lucerna CLV 260 SL; Olympus]).

A total of 5 gastric biopsy samples were from the following sites: antrum anterior wall, antrum posterior wall, corpus anterior wall, corpus posterior wall, and gastric angulus. Biopsy materials were fixed in 10% formaldehyde solution and were sent to the pathology laboratory, where tissue sections with 4 to 6 μm thickness were prepared from paraffin blocks and stained with hematoxylin and eosin. Then the presence of HP was examined histologically, and the samples were assessed by experienced gastroenterology pathologists to check for gastric atrophy and intestinal metaplasia using the Sydney grading system. HP positivity

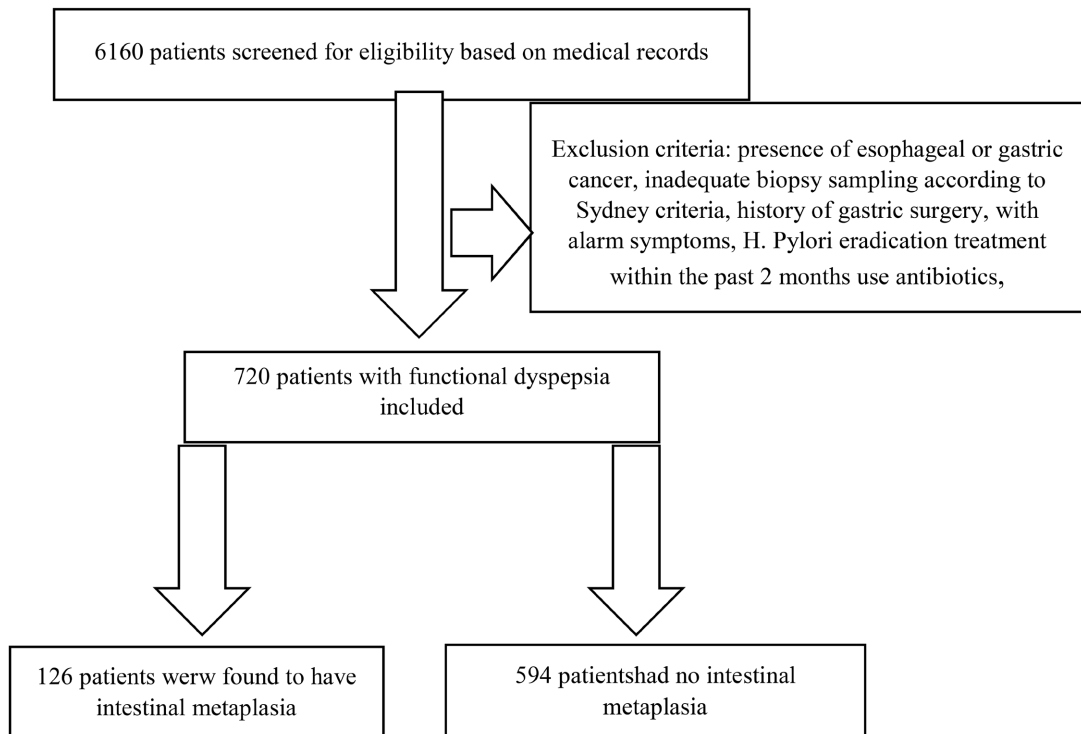


Figure 1. The study design.

was also checked via Giemsa staining. Association between HP infection, chronic proton pump inhibitor (PPI) use exceeding 3 months, and intestinal metaplasia was evaluated.

The study was carried out with the approval of the Institutional Ethical Review Board of Celal Bayar University Medical Center (approval no: 19858. 29/04/2019). The study protocol conforms to the ethical guidelines of the Declaration of Helsinki.

Statistical analyses

Statistical tests were performed using the Statistical Package for the Social Sciences (SPSS) version 25.0. The IM prevalence across age groups was compared with Kolmogorov Smirnov test and the chi-square test was used to analyze categorical variables, and a value of $P < 0.05$ was regarded as significant.

3. Results

720 patients were included in the study. 126 (17.55%) patients to have intestinal metaplasia. The mean age was 54.31 years, with a range of 18 to 89 years. Of the 126 patients with intestinal metaplasia, 70 (56%) were male and 56 were female (44%) (**Table 1**).

There were no statistically significant differences between genders. 54 (43%) of the patients with IM were aged 60 years or older, while 72 (57%) were less than 60 years of age. There was no significant difference in IM patients aged over 60 and less than 60 years of age ($P > 0.05$).

We investigated the relation of patients with intestinal metaplasia with ana-

tomical involvement site, PPI use and *H. pylori* (Table 2).

Intestinal metaplasia was detected at the antrum, corpus, and angulus in 59.94%, 13.47%, and 28.57% of the cases, respectively. Antral lesions were significantly more prevalent ($P < 0.05$).

Of the patients with IM, 63.5% had HP positivity, with a significant association between IM positivity and HP positivity ($P < 0.05$). There was a significant difference between patients with or without a history of chronic PPI use in terms of the prevalence of intestinal metaplasia ($P < 0.05$).

Additionally, the distribution of IM in anatomical gastric sites exhibited significant variations (Table 3).

Table 1. The relation of IM to age and gender.

	Intestinal metaplasia (+) n: 126	Male (%) / Female (%)	P
Age			
<60	72	38 (54) / 34 (61)	
≥60	54	32 (46) / 22 (39)	
Gender	126	70 (56) / 56 (44)	$P > 0.05$

Table 2. Involvement site of intestinal metaplasia and its relationship with PPI and *H. pylori*.

n:126	Intestinal Metaplasia				P
	(+)	%	(-)	%	
Antrum	73	59.94	53	40.06	$<0.05 \approx$
Korpus	17	13.49	109	86.51	$<0.05^*$
Incisura angularis	36	28.57	90	71.43	$<0.05^*$
Helicobacter Pylori (+) (n 126)	80	63.50	46	36.50	$<0.05 \approx$
PPI (n 126)	114	90.48	12	9.52	$<0.05 \approx$

*Intestinal Metaplasia (-) was significantly higher than Intestinal Metaplasia (+); \approx Intestinal Metaplasia (+) was significantly higher than Intestinal Metaplasia (-); & Intestinal Metaplasia (+) was significantly higher than Intestinal Metaplasia (-) in Antrum than Korpus and Insisura Angularis.

Table 3. Distribution of intestinal metaplasia among anatomical sublocations.

	Antrum (n: 73),			P	Korpus (n :17),			P
	Anterior Wall (%),	Posterior Wall (%)	The Whole Wall (%),		Leser Cruvatura (%)	Graeter Cruvatura (%)	The Whole Wall (%)	
IM+	38 (52.05)	10 (13.7)	25 (34.25)	$<0.05^*$	1 (5.88)	6 (35.29)	10 (58.83)	$<0.05 \approx$

*Intestinal Metaplasia (+) was significantly higher than Intestinal Metaplasia (-) in the anterior wall than the other wall. \approx Intestinal Metaplasia (+) was significantly higher than Intestinal Metaplasia (-) in the whole wall than the other wall. In Korpus and insisura angularis, intestinal Metaplasia (-) was significantly higher than Intestinal Metaplasia (+) and in Antrum, *H. Pylori* (+) patients and PPI user patients intestinal Metaplasia (+) was significantly higher than Intestinal Metaplasia (-).

4. Discussion

Previous studies have shown a strong association between HP infection, facilitation of IM pathogenesis by HP infection, and the precancerous nature of IM when it is comorbid with HP infection [12].

A high prevalence of IM has been noted in HP-positive patients with gastritis. However, IM prevalence may vary between countries or between different geographical regions within a country. Generally, the differences in prevalence correspond to the incidence of gastric cancer [13].

In a study by Fontham *et al.*, a 4.7-fold incidence of IM was found in HP-positive patients compared to HP-negative subjects, which was consistent with our findings showing a significantly higher prevalence of IM in HP-positive subjects [14].

The reported incidence of IM in the study by Craanen *et al.* was 10% and 32% among patients aged ≤ 50 years and >50 years, respectively, showing an increased risk of IM with age [15]. In our study, 43% of IM patients were over 60 years of age. Although intestinal metaplasia was seen more in the elderly population, it was not statistically significant.

Seventy-three percent of the patients in Craanen *et al.*'s study was positive for HP, confirming the important role of HP in the pathogenesis of IM [15].

Our findings are in line with those reported by Adım *et al.* and Craanen *et al.*, with a significant difference in IM frequency between HP-positive and HP-negative patients ($P < 0.05$).

In the study by Genta *et al.*, involving 810,821 patients, 8.4% of the patients had IM, with an increased likelihood of IM among male subjects and the elderly. They found the rate of IM at the age of 18 as 2% and over the age of 75 at 14%. The lesser curvature of the antrum has been reported to be more frequently involved in HP colonization [16].

In our study, intestinal metaplasia rates were high in our elderly and male patients

The difference observed between gastric sites in terms of HP colonization frequency may be related to the more rapid contraction wave in the greater curvature compared to the lesser curvature, implying a slower flow of gastric liquid in the lesser curvature leading to a relative stasis of the gastric content and HP colonization [17].

In our study, the pathological examination of the samples obtained from an-gulus and antrum biopsies are also supportive of this notion.

In the study by Eriksson *et al.*, the overall prevalence of intestinal metaplasia was 19%. Intestinal metaplasia was found most frequently in the antrum and in the angulus [18].

In a study by Akpolat *et al.*, IM was found to be present in 14% and 44% of the patients < 50 and ≥ 50 years of age, respectively. In that study, patients between 20 and 29 years of age had the lowest rate of IM (11%), while those between 70 and 79 years of age had the highest rate (83%), showing an age-related increase

in IM incidence [19].

Adim *et al.* detected the presence of IM in 10.2% of their patients less than 50 years of age compared to 12.7% of patients over 50 years of age [17]. Again, in our study, patients aged 50 or over had a significantly higher IM risk compared to younger patients.

In the study by Mao *et al.*, the reported incidence of intestinal metaplasia in gastric angulus, antrum, and lesser curvature, and corpus was 28.5, 20.24%, and 25.48%, respectively. Intestinal metaplasia was more severe in the lesser curvature and angulus compared to the greater curvature, and HP-positive patients had more severe inflammation in the lesser curvature [2].

In our study, the respective incidences of intestinal metaplasia in the antrum, angulus, and corpus were 59.94%, 28.57%, and 13.49%. The most common site of involvement in the antrum was the anterior wall (52.05%).

HP eradication has been reported to alleviate gastric atrophy and inflammation, although a delayed improvement of gastric atrophy was also shown in patients who receive treatment with PPIs or other acid blockers [19].

Annibale *et al.* showed an increased rate of improvement in gastric atrophy through HP eradication in patients with normal serum gastrin levels, although gastric atrophy persisted in those with high serum gastrin [20].

In an experimental mouse model, Chen *et al.* showed associations of hypergastrinemia with gastric atrophy, metaplasia, and cancer development [21].

Additionally, long-term use of PPIs in patients infected with HP was found to worsen atrophic gastritis in the gastric corpus [22]. In our study, a significant difference in the incidence of intestinal metaplasia was found between patients with a history of chronic use of PPIs vs. those without such use ($P < 0.05$).

5. Conclusions

HP-positive patients with atrophic gastritis should undergo HP eradication to prevent and reduce the likelihood of progression to intestinal metaplasia. Patients for whom long-term PPI treatment is planned should be followed up regarding the development of gastric atrophy and intestinal metaplasia.

Additionally, Sydney grading system should always be followed and biopsy sampling from a minimum of 5 sites should be performed in the follow-up of patients with intestinal metaplasia.

Informed Consent

Endoscopic approval form was obtained from all our patients before endoscopy. It is stated in this consent form that the data can be used in studies.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and

materials which may negatively affect the evaluation process of this study.

Authorship Contributions

Idea/Concept: Tahir Buran, Elmas Kasap; Design: Tahir Buran; Control/ Supervision: Tahir Buran, Elmas Kasap; Data Collection and/or Processing: Tahir Buran, Elmas Kasap; Analysis and/or Interpretation: Tahir Buran, Semin Ayhan; Literature Review; Tahir Buran; Writing the Article: Tahir Buran; Critical Review: Elmas Kasap, Semin Ayhan, Tahir Buran; References and Funding: Tahir Buran; Materials: Tahir Buran, Elmas Kasap.

English language check and correction. Manuscript has been “spellchecked”.

Conflicts of Interest

The authors declare no conflicts of interest.

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