Annals of Diagnostic Pathology 40 (2019) 40–44

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Clinicopathological features of duodenal bulb biopsies and their relationship with upper gastrointestinal diseases

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ARTICLE INFO

Keywords:
Gastric metaplasia
Gastric heterotopia
Chronic atrophic gastritis
Gastric fundic polyps
Gastroesophageal reflux disease

ABSTRACT

Aim: To assess the prevalence of the lesions in duodenal bulb mucosa and the relationship between duodenal lesions and upper gastrointestinal diseases, including helicobacter pylori infection.

Methods: Clinical, endoscopic and pathological data of the cases with duodenal bulb and gastric mucosal biopsy from January 2005 to May 2017 were analyzed retrospectively.

Results: A total of 3540 patients were enrolled. The biopsy from protuberant lesions with endoscopic morphology are mostly duodenal gastric heterotopia or adenoma. The biopsy from duodenal ulcers are often observed in inflammatory changes and gastric metaplasia.

Patients with gastric heterotopia had a significantly lower prevalence of chronic atrophic gastritis, intestinal metaplasia, and gastric ulcer; and much higher prevalence of gastroesophageal reflux disease and gastric fundic polyps.

Patients with gastric metaplasia had been positively associated with gastroesophageal reflux disease, and negatively associated with gastric fundic polyps.

There were positive correlation between helicobacter pylori infection and duodenal active inflammation, Brunner gland hyperplasia, gastric metaplasia and duodenal ulcer. However, Patients with gastric heterotopia in bulb had been negatively associated with helicobacter pylori infection.

Conclusions: The mucosa lesions in duodenal bulb were associated with concurrent gastric fundic gland polyps, gastroesophageal reflux disease, duodenal ulcer, and helicobacter pylori infection.

1. Introduction

Duodenal bulb is the first stop of the acidic alimentary bolus in the stomach passing through small intestinal mucosa. The effects of gastric acid and microorganisms in the stomach on duodenal mucosa are inevitable. Duodenitis, duodenal ulcer (DU), hyperplasia of Brunner's glands, duodenal gastric foveolar metaplasia (DGM), and duodenal gastric heterotopia (DGH) are more common in duodenal mucosal lesions. Duodenal bulb was a frequently occurring part of DGM [1], which was due to the frequent exposure of duodenal bulb mucosa to acidic alimentary bolus, an adaptive change in the intestinal epithelium induced by physical, chemical, and inflammatory factors. DGH could occur in any part of the digestive tract. It might even occur outside the gastrointestinal tract. Most scholars believed that DGH was a congenital and acquired disease [2]. Also, the incidence was similar to that of DGM, and it was related to *Helicobacter pylori* infection and DU [3,4]. Although the incidence of duodenal malignancy was relatively low, it could seriously affect life and health and therefore, it could not be ignored. In this study, the endoscopic biopsy specimens of duodenal bulb for > 10 years were analyzed in Large Center for Digestive Disease Research. Also, the incidence; clinical, endoscopic, and pathological features of duodenal mucosal lesions; and their relationship with other lesions of the upper digestive tract and the possible pathogenesis were discussed.

2. Patients and methods

This study was approved by the Ethics Committee of the Peking University Third Hospital, and informed consent was acquired in accordance with the Declaration of Helsinki.

2.1. Clinical information

Patients undergoing endoscopy at the endoscopy center of the Peking University Third Hospital from January 2005 to May 2017 were selected for the study. Patients who had abnormal manifestations of the

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https://doi.org/10.1016/j.anndiagpath.2019.02.006

endoscopic biopsy of duodenal bulb and whose biopsies of duodenal bulb and/or gastric mucosa were taken for histopathological examination were enrolled.

2.2. Exclusion criteria

The exclusion criteria were as follows: (1) patients with malignant tumor of esophagus and stomach; (2) patients with a history of upper digestive tract surgery; and (3) patients whose biopsy tissues were too superficial to judge the nature of the disease.

2.3. Methods

The biopsy tissues were fixed in 10% formalin solution, embedded in paraffin, and cut into continuous slices (5 μm), after Hematoxylin and Eosin staining (for histopathology analysis) and Warthin–Starry silver staining (for Helicobacter pylori infection analysis) were performed. The histological evaluation was conducted by experienced digestive pathology specialists.

2.4. Diagnostic criteria for histopathology

The diagnostic criteria were as follows (Fig. 1):

(1) Duodenitis: Lymphocytic and plasma cell infiltration was more in the lamina propria and/or epithelium of duodenal mucosa. If neutrophil infiltration occurred, it was active duodenitis.

(2) DGH: The structure of the gastric gland was evident in the duodenal mucosa, which consisted of parietal and chief cells with/without gastric columnar mucous epithelial cells on the surface.

(3) DGM: Duodenal villus epithelial cells were replaced by gastric foveolar epithelial cells, and no gastric gland was found.

(4) Hyperplasia of Brunner's glands: Proliferation of Brunner's glands was seen in duodenal lamina propria; when the proliferation was obvious. Protuberant lesions and other changes were under endoscopy. Hence, it was the adenoma of Brunner's glands.

(5) Histological examination of the gastric mucosa and the evaluation and grading of *H. pylori* were conducted according to the standard of Sydney gastritis classification [5].

(6) Malignant tumors diagnosed according to the diagnostic criteria of the World Health Organization.

2.5. Statistical analysis

The SPSS18.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as x ± s. The *t*-test was used for the comparison between groups. Enumeration data were expressed as the number of cases and (or) percentage. The chi-square test was used, and a P value < 0.01 indicated a statistically significant difference.

3. Results

3.1. General information

Over the past 10 years, 105,960 patients underwent upper digestive endoscopy in the hospital. Of these, 3821 patients underwent duodenal mucosal biopsy. The malignant tumors of the esophagus and stomach were removed in 67 patients, 16 patients had the history of upper digestive tract surgery, and the duodenal bulb mucosa in 198 patients was too superficial. Therefore, a total of 3540 patients met the inclusion criteria and were enrolled, including 2050 males (male-to-female ratio = 1.38:1). The age of enrolled patients ranged from 20 to 96 years (56.17 ± 15.49 years). The general information of patients and the detection of common lesions in the duodenal bulb are shown in Table 1. A total of 518 patients had DU (duodenal bulb deformation not included), and lesions were obtained near the ulcer in 440 patients. The detection rates of males with DU and DGM were significantly higher than those of females.

If 10 years old was used as an age group, a significant difference in age composition was observed among different duodenal lesions ($\chi^2 = 140.692$, $P = 0.000$). As shown in Fig. 2, the detection trends of different diseases were not the same with the increase in age. The detection rates of simple duodenitis, hyperplasia of Brunner's glands, and duodenal bulb ulcer decreased with age, while the detection rates of DGH, DGM, and duodenal tumor lesion increased with age.

3.2. Morphological characteristics of benign duodenal lesions under endoscopy

Mucosal protuberance, erosive lesions, ulcer, erythema, leukoplakia, and edema were observed in the benign duodenal lesions under endoscopy. The pathological findings corresponding to biopsies are shown in Table 2. Protuberant lesions were mostly seen in DGH and adenoma [odds ratio (OR) = 25.15 and 5.92, respectively]. The biopsy

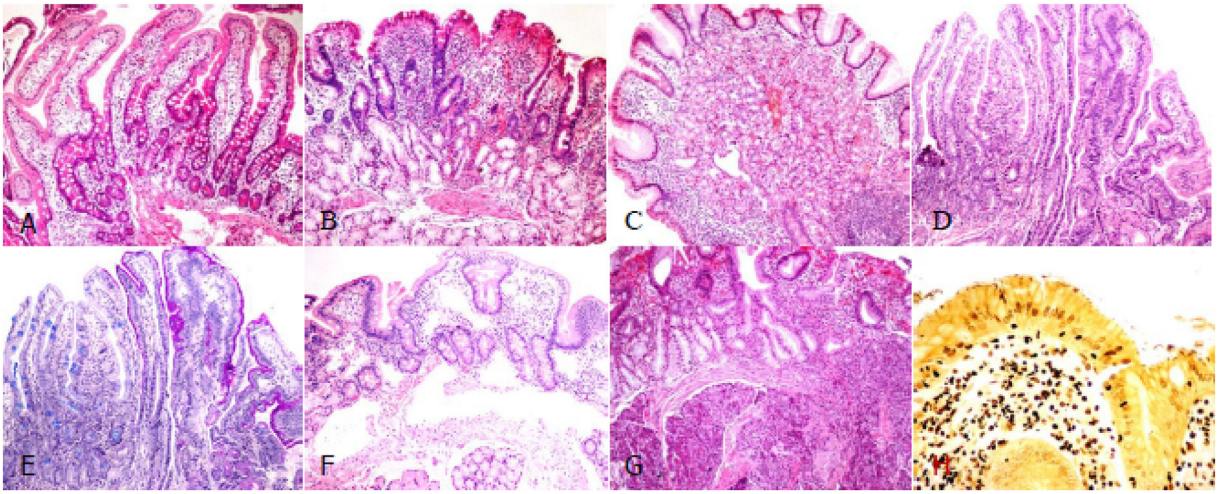

Fig. 1. (A) Duodenitis. (B) Hyperplasia of Brunner's glands. (C) Duodenal gastric heterotopia. (D) Duodenal gastric foveolar metaplasia. (E) Duodenal gastric foveolar metaplasia. Foveolar metaplasia in right portion is amaranth by the period-acid Schiff/Alcian blue stain. (F). Lymphangiectasia. (G) Heterotopic pancreas (A to G, original magnification ×10). (H) Helicobacter pylori is black on the surface of foveolar metaplasia by Warthin–Starry silver staining (original magnification ×40).

Table 1
Demographics and prevalence of the most common histopathologic diagnoses in duodenal bulb n (%).

	Number (%)	Age (x ± s)	Sex (male, %)	Sex *P*-value
Total	3540	56.17 ± 15.49	2050 (57.9)	0.699
Duodenitis	1103 (31.2)	54.23 ± 16.17	646 (58.6)	0.025
Brunner gland hyperplasia	877 (24.8)	54.15 ± 16.18	505 (57.6)	0.861
Gastric heterotopia	1051 (29.7)	59.00 ± 13.91[a]	580 (55.2)	0.117
Gastric metaplasia	656 (18.5)	57.38 ± 14.72[a]	412 (62.8)	0.019
Duodenal ulcer	518 (14.6)	53.68 ± 17.40	366 (70.7)	< 0.001
Malignant	61 (1.7)	57.38 ± 14.72[a]	36 (59.0)	0.862
Adenoma	46 (1.3)	57.63 ± 12.61	31 (67.4)	0.195
lymphangiectasia	6 (0.17)	46.67 ± 12.04	4 (66.7)	1.0[b]
Heterotopic pancreas	5 (0.14)	46.80 ± 18.94	2 (40)	0.656[b]

[a] vs Duodenitis: P = 0.000.
[b] Fisher exact test.

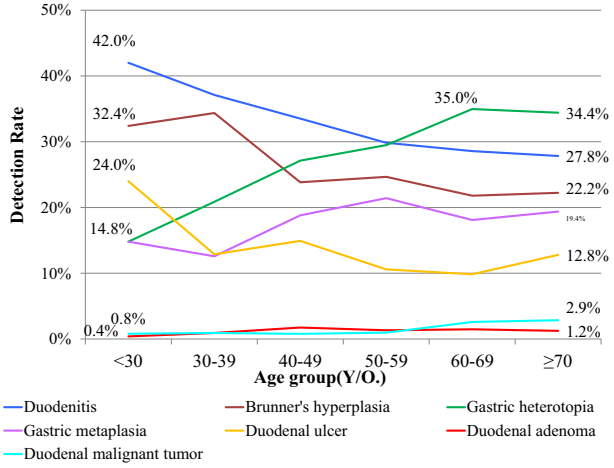

Fig. 2. The variation tendency of duodenal bulb lesions with age.

pathology of ulcers in 440 patients was mostly inflammation and DGM (OR = 2.31 and 2.11, respectively), while erosion and changes in mucosal color were mostly seen in duodenal inflammation and hyperplasia of Brunner's glands. Among six patients with lymphangiectasia, protuberance was observed in four patients under endoscopy, abnormal color was observed in two patients, and protrusion was observed in the heterotopic pancreas of five patients.

3.3. Histological changes in the gastric mucosa

The biopsies of the duodenal bulb and gastric mucosa were obtained from a total of 3388 patients. The main lesions of duodenal bulb and their corresponding gastric mucosal lesions are shown in Table 3.

As shown in Table 3, DGH positively correlated with the incidence of fundic gland polyp and gastroesophageal reflux disease (GERD) (OR = 3.29 and 1.31, respectively), but it negatively correlated with the incidence of chronic atrophic gastritis, DGM, and gastric ulcer (OR = 0.66, 0.58, and 0.46, respectively). DGM in the duodenal bulb positively correlated with GERD, but it negatively correlated with the fundic gland polyp (OR = 1.37 and 0.67, respectively).

A total of 43 patients with duodenal adenoma undergoing gastric biopsy were identified at the same time. The detection rate was 3.6% in 337 patients with dysplasia in the stomach, which was significantly higher than that in patients without dysplasia in the stomach [OR = 3.60, 95% confidence interval (CI): 1.83–7.07].

The incidences of atrophic gastritis, dysplasia, and fundic gland polyp in patients with DU were lower and negatively correlated (OR = 0.78, 0.60, and 0.30, respectively). More patients developed a gastric ulcer at the same time, and they were positively correlated (OR = 4.03). Among patients with DU, 41 had DGH (OR = 0.171, 95% CI: 0.123–0.238) and 145 had DGM (OR = 1.956, 95% CI: 1.576–2.427).

Among patients with DU, 131 patients had GERD (26.04, 131/503). The detection rate of GERD in this study was 26.71% (905/3388), with no significant difference (OR = 0.96, 95% CI: 0.774–1.191). The relationship between duodenal mucosal lesions and other lesions of the upper digestive tract is shown in Fig. 2.

3.4. Malignant tumor

A malignant tumor of the duodenum was detected in 61 patients (detection rate was 1.7%, including 41 patients with adenocarcinoma, 10 with carcinoid, and 10 with lymphoma). The detection rate was only 0.06% (61/105960) in the whole endoscopic population.

Further, 50 patients with malignant tumor of the duodenum underwent gastric mucosal biopsy at the same time. Of these, 14 patients had a malignant tumor in the stomach, 25 had chronic superficial gastritis, 11 had chronic atrophic gastritis accompanied by intestinal metaplasia, and 4 had mild dysplasia. No significant difference in the incidence was found among patients with malignant tumor in the duodenum, patients with/without atrophic gastritis in the stomach (1.3% vs 0.95%, $\chi^2 = 0.585$, $P = 0.444$), and patients with/without dysplasia (1.2% vs 1.0%, Fisher's exact test $P = 0.776$).

3.5. H. pylori infection

A total of 783 patients (22.8%) were *H. pylori* positive; this number was significantly lower than that of *H. pylori*–positive patients ($P = 0.000$). Further, 186 patients were *H. pylori* positive; of these DGM occurred in 111 patients. The detection rate of *H. pylori* in patients with DGM in the duodenal bulb was significantly higher than those without DGM ($\chi^2 = 179.721$, $P < 0.001$). The relationship between the detection of different duodenal lesions and *H. pylori* is shown in Table 4. The active inflammation of duodenum, hyperplasia of Brunner's glands,

Table 2
Relationship between major morphological changes by endoscopy and corresponding histological changes in duodenal bulb [Number (%)/OR , 95% Confidence interval].

Endoscopy features	Number	Duodenitis N = 1103	Brunner gland hyperplasia N = 877	Gastric heterotopia N = 1051	Gastric metaplasia N = 656	Adenoma N = 46
Protuberate	2276	455 (20.0)	525 (23.1)	1012 (44.5)	427 (18.8)	42 (1.8)
		0.24 (0.20–0.28)	0.78 (0.66–0.91)	25.15 (18.09–34.96)	1.04 (0.87–1.25)	5.92 (2.12–16.55)
Ulcer	440	212 (48.2)	112 (25.5)	22 (5.0)	132 (30)	0
		2.31 (1.89–2.82)	1.04 (0.83–1.31)	0.11 (0.07–0.16)	2.11 (1.68–2.64)	
Erosion	267	141 (52.8)	86 (32.2)	5 (1.9)	46(17.2)	1 (0.37)
		2.69 (2.10–3.46)	1.49 (1.14–1.95)	0.04 (0.02–0.10)	0.91 (0.65–1.26)	
Change in color	496	295 (59.5)	154 (31.0)	12 (2.4)	51 (10.3)	3 (0.6)
		4.06 (3.34–4.94)	1.45 (1.17–1.78)	0.05 (0.03–0.09)	0.46 (0.34–0.62)	

Table 3
The relationship between gastric pathology and duodenal lesions (%)/OR , 95% Confidence interval].

Bulb lesions	N	CAG 849	IM 1000	Dysplasia 337	GFP 337	GU 241	GERD 905
Duodenitis	850	278 (32.7) 1. 76 (1.41–1.99)	316 (37.2) 1.60 (1.36–1.89)	105 (1.24) 1.40 (1.10–1.79)	55 (6.5) 0.55 (0.41–0.75)	104 (12.2) 2.44 (1.87–3.19)	200 (23.5) 0.80 (0.67–0.96)
Brunner gland hyperplasia	852	195 (22.9) 0.85 (0.71–1.03)	240 (28.2) 0.89 (0.75–1.05)	76 (8.9) 0.84 (0.64–1.10)	70 (8.2) 0.76 (0.58–1.002)	50 (5.9) 0.77 (0.56–1.06)	218 (25.6) 0.93 (0.78–1.11)
Gastric heterotopia	1026	204 (19.9) 0.66 (0.55–0.79)	225 (21.9) 0.58 (0.49–0.68)	106 (10.3) 0.94 (0.73–1.20)	187 (18.2) 3.29 (2.61–4.13)	42 (4.1) 0.46 (0.33–0.65)	313 (30.5) 1.31 (1.12–1.54)
Gastric metaplasia	640	157 (24.5) 0.97(0.79–1.78)	183 (28.6) 0.94 (0.78–1.14)	61 (9.5) 0.88 (0.67–1.19)	47 (7.3) 0.67(0.49–0.93)	51 (8.0) 1.16 (0.85–1.61)	204 (31.9) 1.37 (1.13–1.65)
Adenoma	43	19(44.2) 2.40 (1.31–4.40)	23 (53.5) 2.79 (1.52–5.10)	12 (27.9) 3.60 (1.83–7.07)	12 (27.9) 3.60 (1.83–7.07)	5 (11.6) 1.73 (0.68–4.44)	6 (14.0) 0.44 (0.19–1.05)
Duodenal ulcer	503	107 (21.2) 0.78 (0.62–0.98)	143 (28.4) 0.94 (0.76–1.16)	33 (6.6) 0.60 (0.41–0.87)	18 (3.6) 0.30 (0.18–0.49)	91 (18.1) 4.03 (3.04–5.33)	131 (26.0) 0.96 (0.77–1.19)

Abbreviations: CAG, chronic atrophic gastritis; IM, intestinal metaplasia; GFP, gastric fundic gland polyp; GU, gastric ulcer; GERD, gastroesophageal reflux disease.

Table 4
The relationship between H. pylori and duodenal lesions.

Duodenal lesions	H. pylori (%)	OR (95% CI)
Inactive duodenitis (n = 725)	183 (25.2)	0.79 (0.656–0.953)
Active duodenitis (n = 659)	369 (56.0)	7.12 (5.907–8.570)
Brunner gland hyperplasia (n = 852)	247 (29.0)	1.56 (1.31–1.862)
Gastric heterotopia (n = 1026)	26 (2.5)	0.057 (0.038–0.085)
Gastric metaplasia (n = 640)	193 (30.2)	1.62 (1.334–1.957)
Adenoma (n = 43)	1 (2.3)	0.08 (0.01–0.579)
Malignant (n = 50)	13 (26)	1.19 (0.632–2.259)
Duodenal ulcer (n = 503)	263 (52.3)	4.984 (4.084–6.082)

Abbreviations: OR, odd rate; CI, confidence interval.

DGM, and DU positively correlated with *H. pylori* infection, whereas DGH negatively correlated with *H. pylori* infection.

4. Discussion

Different lesions could be seen by mucosal biopsy for patients with an abnormal change in the duodenal bulb under endoscopy. The detection rate of DGH in protuberant lesions under endoscopy was higher, followed by hyperplasia of Brunner's glands and DGM. However, ulcer, erosion, and abnormal color were common in duodenitis.

In this study, the average age of onset of various diseases in the duodenum was about 50 years, but the detection trends of different lesions with age were different. The detection rate of simple inflammatory lesions decreased with age, whereas the detection rates of metaplastic and tumor lesions increased, but no related report was available.

In this study, the detection rate of DGH in the duodenum was 29.7%, which was higher than that in other studies (0.5%–14.3%) [2,6]. The high detection rate might be related to the study population treated in the third-grade class-A hospitals rather than the general population. It was more common in males than in females, which was similar to the results reported in other studies [7,8].

This study showed that the incidence of DGH was associated with gastric disease, which negatively correlated with chronic atrophic gastritis and intestinal metaplasia and positively correlated with fundic gland polyp. The incidence of DGH was related to the high output of gastric acid. Patients with atrophic gastritis and intestinal metaplasia were mostly in a low-acid state. It negatively correlated with the incidence of DGH. From another point of view, it was proved that the incidence of DGH was related to the level of gastric acid. Conlon et al. [9] conducted immunohistochemistry staining and confirmed that the mucin expression profile of DGH was similar to that of gastric mucosa. They believed that a similarity existed between the fundic gland polyps and DGH at the protein level. The long-term use of proton pump inhibitors (PPIs) was one of the factors causing fundic gland polyps [10-12]. Velázquez-Dohorn et al. conducted a retrospective study on patients in Mexico and found that the detection rate of fundic gland polyps in patients with gastric polyps increased from 28.6% in 2016 to 78.3% in 2000. This study suggested that the increase in the incidence of fundic gland polyps was associated with the long-term use of PPI and HP eradication therapy [13].

Most studies suggested that DGH was a congenital and heterotopic change. However, the detection rate of DGH in the present study positively correlated with age, which conformed to the law of inheritance of acquired diseases. Lessels et al. [14] believed that the incidence of DGH was determined by two factors: congenital and reactive. The latter might be a part of mucosal changes caused by injury of duodenum. Genta et al. [7] suggested that protuberant DGH might be the result of PPI-induced hypergastrinemia causing the hyperplasia of microfocal lesions in gastric mucosa, leading to an etiological hypothesis based on the interaction between congenital and reactive hyperplasia. However, the lack of a survey on drug use in the present study was not enough to make inferences about the relationship between PPI and the disease. In this study, DGH positively correlated with GERD (OR = 1.31) because most patients with GERD needed to take PPI for a long time, directly indicating that the incidence of DGH was associated with the use of PPI.

In this study, DGM in the duodenal bulb was common in males. The detection rate was 18.5%, and DGM positively correlated with DU and GERD. However, Hashimoto et al. [15] analyzed the duodenal bulb in surgical specimens of gastric cancer from 18 patients. They found that the detection rate of foveolar epithelial cells, chief cells, and parietal cells was 94%, 78%, and 50%, respectively. The high detection rates might be related to the small sample size in the study. A study [16] showed that high acid output to the duodenum had an important role in DGM. The detection rate of GM [17] in patients with functional heartburn was significantly higher than the rate in the asymptomatic control group (33.3% vs 12%, $P < 0.05$). Voutilainen et al. [18] continuously studied 1255 patients undergoing endoscopy. They found that *H. pylori* infection (OR = 1.6, 95% CI: 1.1–2.1) and duodenal villous atrophy (OR = 12.7, 95% CI: 4.4–36.5) were independent risk factors for DGM, whereas atrophic gastritis was a protective factor (OR = 0.5, 95% CI: 0.3–0.8). Veijola et al. [4] analyzed the endoscopic findings in 1030 adult patients with indigestion. They found that DGM was associated with high acid output in the stomach, but it negatively correlated with the proximal gastric ulcer and severe gastric atrophy. This study showed no significant correlation between DGM, atrophic gastritis, and gastric ulcer. Expanded sample size was needed in further studies.

At present, a large number of studies in China and other countries have confirmed that *H. pylori* infection was closely related to the incidence of DU and associated with many diseases of the intestine and other systems. In the present study, active inflammation of the duodenum, hyperplasia of Brunner's glands, DGM, and DU was positively related to *H. pylori* infection. *H. pylori* thalli in the duodenal bulb were

mostly located in the metaplastic gastric epithelium, which might be related to the local microenvironment suitable for the survival of *H. pylori* colonization in DGM mucosa [4,19]. The greater the degree of DGM, the higher the recurrence rate of DU ($P = 0.021$) [20]. The detection rate of DGM in patients receiving long-term H_2RA treatment was low [21]. A few studies [22-24] suggested that DGH and DGM were associated with the incidence of adenocarcinoma of duodenum; also, GNAS and/or KRAS mutations were found. Therefore, clinical attention should be given to such diseases.

In this study, the detection rate of hyperplasia of Brunner's glands was high (24.8%). It involved the Brunner's glands in the lamina propria. Under endoscopy, the surface of mucosa was usually uneven and the size was small, with no definite clinical significance. The large-size hyperplasia of Brunner's glands /adenoma could cause obstruction, and even adenocarcinoma was occasionally seen [6,25,26]. In this study, hyperplasia of Brunner's glands negatively correlated with chronic atrophic gastritis and intestinal metaplasia. It was speculated that hyperplasia of Brunner's glands might also be a reactive change after mucosal injury.

The incidence of primary small intestinal tumors was low. In this study, the detection rate of the duodenal adenoma and malignant tumors was 1.3% and 1.7%, respectively. The actual detection rate in the endoscopic population was lower, considering the inclusion criteria of this study (0.06%). Terada [6] investigated the detection rate of the duodenal adenoma in 615 consecutive patients under endoscopy. They found that the detection rate was only 0.4%, whereas the detection rate of malignant tumors was 7.8%, which were not high. In this study, the detection rate of duodenal adenoma in patients with dysplasia in the stomach was significantly higher than that in patients without dysplasia in the stomach, indicating a certain correlation between the incidence of the precancerous lesions of digestive tract and the incidence of tumors.

This study had certain limitations. (1) This study was performed on patients treated in the endoscopy center of third-grade class-A hospitals; they were mostly symptomatic or miscellaneous, with a higher average age. (2) An endoscopic duodenal mucosal biopsy was performed in the case of changes found under endoscopy, but a continuous biopsy was not performed in all patients. Also, a selection bias existed in the population. (3) Due to the retrospective study, it was lack of the data on the history of medication used by patients. Especially, proton pump inhibitor and H2 receptor antagonist affect gastric mucosa and duodenal mucosa protectively. On the other hand, non-steroidal anti-inflammatory drugs and low dose aspirin induce gastrointestinal mucosal injury.

In conclusion, among the benign lesions of the duodenum, the incidence of gastric metaplasia/heterotopia in the duodenum bulb positively correlated with age. DGH positively correlated with gastroesophageal reflux disease and fundic gland polyp, but negatively correlated with atrophic gastritis. DGM positively correlated with gastroesophageal reflux disease and DU. The inflammatory lesion of the duodenum positively correlated with *H. pylori* infection. The incidence of duodenal adenoma correlated with the incidence of dysplasia of the stomach. Hence, it was presumed that the incidence of a disease in the digestive tract was not caused by a single factor. It had some correlations with the lesions of other parts of the digestive tract and other organs.

Acknowledgments

We gratefully acknowledge Prof. Lin Sanren for his instructive advice and useful suggestions on our research. We also thank the members of the Department of Gastroenterology, Peking University Third Hospital for their support.

Declaration of conflict of interest

All of the authors declared that they have no potential conflicts of interest to disclose.

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