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Comparison of *Helicobacter pylori* infection and gastric mucosal histological features of gastric ulcer patients with chronic gastritis patients

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Abstract

AIM: To compare *Helicobacter pylori* infection and gastric mucosal histological features of gastric ulcer patients with chronic gastritis patients in different age groups and from different biopsy sites.

METHODS: The biopsy specimens were taken from the antrum, corpus and upper angulus of gastric ulcer and chronic gastritis patients. Giemsa staining, improved Toluidine-blue staining and *H pylori*-specific antibody immune staining were performed as appropriate for the histological diagnosis of *H pylori* infection. Hematoxylin-eosin staining was used for the histological diagnosis of activity of *H pylori* infection, mucosal inflammation, glandular atrophy and intestinal metaplasia and scored into four grades according to the Updated Sydney System.

RESULTS: Total rate of *H pylori* infection, mucosal inflammation, activity of *H pylori* infection, glandular atrophy and intestinal metaplasia in 3 839 gastric ulcer patients (78.5%, 97.4%, 82.1%, 61.1% and 64.2%, respectively) were significantly higher than those in 4 102 chronic gastritis patients (55.0%, 90.3%, 56.2%, 36.8%, and 37.0%, respectively, $P<0.05$). The rate of *H pylori* colonization of chronic gastritis in <30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and >70 years age groups in antrum was 33.3%, 41.7%, 53.6%, 57.3%, 50.7%, 43.5%, respectively; in corpus, it was 32.6%, 41.9%, 53.8%, 60.2%, 58.0%, 54.8%, respectively; in angulus, it was 32.4%, 42.1%, 51.6%, 54.5%, 49.7%, 43.5%, respectively. The rate of *H pylori* colonization of gastric ulcer in <30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and >70 years age groups in antrum was 60.5%, 79.9%, 80.9%, 66.8%, 59.6%, 45.6%, respectively; in corpus, it was 59.7%, 79.6%, 83.6%, 80.1%, 70.6%, 59.1%, respectively; in angulus, it was 61.3%, 77.8%, 75.3%, 68.8%, 59.7%, 45.8%, respectively. The rate of *H pylori* colonization at antrum was similar to corpus and angulus in patients, below 50 years, with chronic gastritis and in patients, below 40 years, with gastric ulcer. In the other age- groups, the rate of *H pylori* colonization was highest in corpus, lower in antrum and lowest in angulus (all $P<0.05$). The rates of glandular atrophy and intestinal metaplasia were higher and earlier in *H pylori*-positive patients than those without *H pylori* infection (both $P<0.01$). In comparison of gastric ulcer patients with chronic gastritis patients, the rate of glandular atrophy and intestinal metaplasia was higher in *H pylori*-positive patients with gastric ulcer than in *H pylori*-positive patients with chronic gastritis (both $P<0.01$); the rate of glandular atrophy and intestinal metaplasia were also higher in *H pylori*-negative patients with gastric ulcer than in *H pylori*-negative patients with chronic gastritis (both $P<0.01$). Both glandular atrophy and intestinal metaplasia were much more commonly identified in the angulus than in the antrum, lowest in corpus (all $P<0.01$).

CONCLUSION: Rate of *H pylori* infection, glandular atrophy and intestinal metaplasia in gastric ulcer were higher than in chronic gastritis in all-different age -groups. Distribution of *H pylori* colonization is pangastric in the younger patients. It is highest in corpus, lower in antrum and lowest in angulus in the older age groups. Progression of glandular atrophy and intestinal metaplasia seem to have a key role in the distribution of *H pylori* colonization. *H pylori* appears to be the most important risk factor for the development of glandular atrophy and intestinal metaplasia, but it is not the only risk.

Key words: *Helicobacter pylori* infection; Gastric ulcer; Glandular atrophy; Intestinal metaplasia

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INTRODUCTION

For more than a century, peptic ulcer disease has been a major cause of morbidity and mortality. The pathophysiology of peptic ulcer disease has centered on an imbalance between aggressive and protective factors in the stomach[1]. Twenty years have elapsed since Marshall and Warren's discovery of the link between *Helicobacter pylori* (*H pylori*) infection and peptic ulcer disease[2]. Now, there is much evidence to support the idea that *H pylori* infection is a pre-requisite for duodenal and gastric ulcers[3,4]. As to the patterns of gastritis associated with peptic ulcers, long before the discovery of *H pylori*, they were known to be different from duodenal ulcer and gastric ulcers. Duodenal ulcer is associated with an antrum-predominant gastritis, whereas gastric ulcer is associated with diffuse or a corpus-predominant gastritis[5,6]. Although much about the relationship between *H pylori* and gastritis of peptic ulcer has been found, there is no study, to our knowledge ,which compares *H pylori* infection and gastric mucosal histological features of gastric ulcer patients with chronic gastritis in different age -groups. Therefore, we undertook the present study.

MATERIALS AND METHODS

Patients

Patients were prospectively and consecutively selected from subjects, with present or past abdominal complaints, who underwent upper gastrointestinal endoscopy screening in Nippon Medical School Hospital from November 1994 to November 2003. They were not enrolled if they had concurrent illnesses or were on any medication other than antacids. None had taken H_2 receptor antagonists, proton pump inhibitors, bismuth, antibiotics, non-steroidal anti-inflammatory drugs, or corticosteroids within 2 mo of the examination. Ultimately, 7 941 patients were included in the study consisting of 3 839 patients with gastric ulcer, aged from 11 to 94 years (mean age 56.7±13.4), with 2 601 males and 1 238 females, and 4 102 patients with chronic gastritis, aged from 11 to 93 years (mean age 53.9±16.1), with 1 768 males and 2 334 females. All patients gave informed consent before their endoscopy and the study was approved by the Ethics Committee of Nippon Medical School.

Histological analysis

Biopsy specimens for histological diagnosis were obtained endoscopically from the greater curvature of the antrum, and the upper corpus and the lesser curvature of the lower corpus of the stomach in all cases. Biopsy specimens were fixed overnight in buffered formalin, embedded in paraffin, cut into 3-μm thick sections, and examined with hematoxylin-eosin staining, improved toluidine-blue staining, Giemsa staining and *H pylori*-specific antibody immune staining (Dako, USA). *H pylori* were identified as curved rods or coccoid forms by methods of modified toluidine-blue and confirmed by immunostaining, using anti-*H pylori* antibody. Histologically, *H pylori* infection was considered negative if *H pylori* were absent from all biopsy sites; *H pylori* infection was considered positive if at least one of the histology tests was positive[7,8]. Lymphocytes and plasmocytes infiltration indicate chronic inflammation of *H pylori* and polymorphonuclear (PMN) cell infiltration stand for activity of *H pylori* infection. It was scored based on the density of inflammatory cells in both lamina propria and glandular epithelium. The histological glandular atrophy was identified when the gastric glands were correspondingly decreased in amount and/or widely separated. In order to avoid the observative variation, in the antral and supra-angular specimens, only cases with preserved muscularis mucosa were taken as evidence for histological glandular atrophy, in which, the lower layer of glands almost touched the muscularis mucosa in normal mucosa. In the corpal specimens, the cases without muscularis mucosa were taken as negative for histological glandular atrophy if the fundic glands were compact and not separated. This is because muscularis mucosa was usually not included in the biopsy specimens of normal mucosa. In accordance with the Updated Sydney System, the degree of mucosal inflammation, activity of *H pylori* infection, glandular atrophy, and intestinal metaplasia were classified into four grades as follows: 0, none; 1, mild; 2, moderate and 3, severe.

Statistical analysis

The prevalence of *H pylori* infection, rates of inflammation, activity of *H pylori* infection, glandular atrophy and intestinal metaplasia were compared using the chi-square test for four-fold table. The difference of grades of mononuclear cell infiltration, polymorphonuclear cell infiltration, glandular atrophy, and intestinal metaplasia between groups were compared by Mann-Whitney *U*-test. *P* -values of <0.05 were considered to denote statistical significance.

RESULTS

Total H pylori infection and histological features in chronic gastritis and gastric ulcer patients

Rates of *H pylori* infection, mucosal inflammation, activity of *H pylori* infection, glandular atrophy and intestinal metaplasia in patients are shown in Table 1. They were scored in all 7 941 consecutive patients. However, glandular atrophy was not scored in 299 chronic gastritis patients and 545 gastric ulcer patients. The positivity of *H pylori* infection, mucosal inflammation, activity of *H pylori* infection, glandular atrophy and intestinal metaplasia in patients, with gastric ulcer, was all significantly higher than those of chronic gastritis patients (all $P<0.01$).

Table 1 ***H pylori*** **infection and histological features of** ***H pylori*** **infection in chronic gastritis and gastric ulcer patients (*n*, %)**

	H pylori	Mucosal inflammation	Activity	Glandular atrophy	Intestinal metaplasia
Chronic gastritis	55.0	90.3	56.2	36.8	37.0
Gastric ulcer	78.5[b]	97.4[b]	82.1[b]	61.1[b]	64.2[b]

[b]$P<0.01$ *vs* chronic gastritis.

H pylori infection and histological features in three biopsy sites of patients with chronic gastritis

Rate of *H pylori* infection, mucosal inflammation, activity

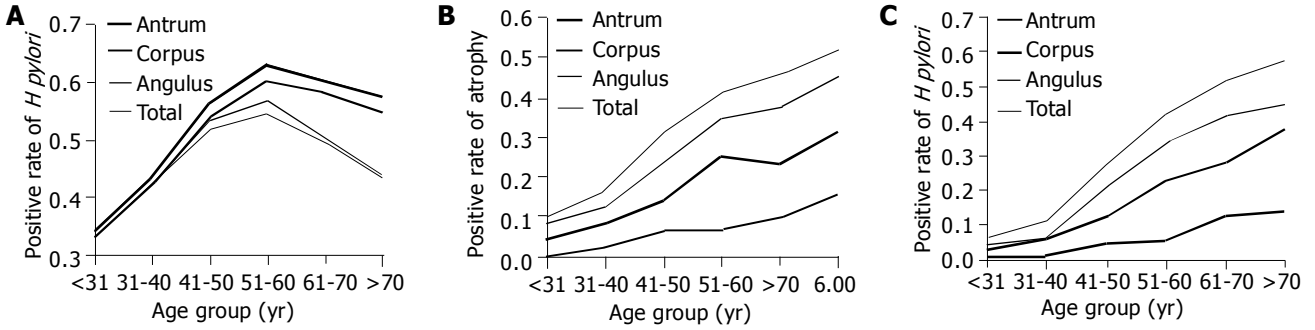

Figure 1 Distribution of *H pylori* infection, atrophy, intestinal metaplasia in three biopsy sites of different age-group patients with chronic gastritis. A: distribution of *H pylori* infection; B: distribution of atrophy; C: distribution of intestinal metaplasia.

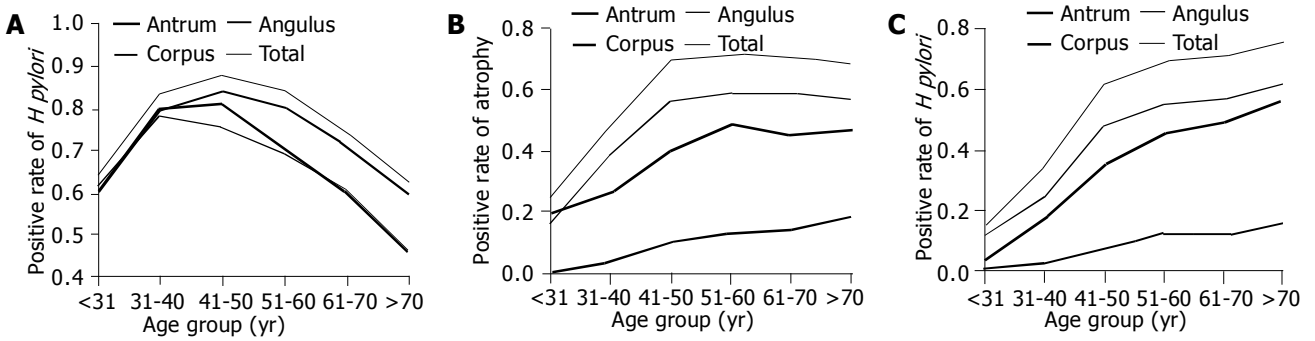

Figure 2 Distribution of *H pylori* infection, atrophy, intestinal metaplasia in three biopsy sites of different age-group patients with gastric ulcer. A: distribution of *H pylori* infection; B: distribution of atrophy; C: distribution of intestinal metaplasia.

of *H pylori* infection, glandular atrophy and intestinal metaplasia in three biopsy sites of different age-group patients with chronic gastritis are shown in Figure 1 A-C.

The distribution of *H pylori* colonization of chronic gastritis in <30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and >70 years age groups in antrum was 33.3%, 41.7%, 53.6%, 57.3%, 50.7%, 43.5%, respectively; in corpus it was 32.6%, 41.9%, 53.8%, 60.2%, 58.0%, 54.8%, respectively; in angulus it was 32.4%, 42.1%, 51.6%, 54.5%, 49.7%, 43.5%, respectively; overall it was 34.3%, 43.5%, 56.3%, 62.9%, 60.5%, 57.5%, respectively. Total rate of *H pylori* infection and activity of *H pylori* infection in 4 102 cases with chronic gastritis were significantly higher from <31 years to 51-60 years, respectively ($P<0.01$). No obvious difference was found between 51-60 years and 61-70 years; 61-70 years and >70 years. However, rates of *H pylori* infection and activity of *H pylori* infection of 51-60 years were significantly higher than that of >70 years ($P<0.05$). Comparing distribution and density of *H pylori* infection, we found that there was no significant difference among three biopsy sites in <31 years, in 31-40 years and 41-50 years groups. Rate of *H pylori* infection in 51-60 years, the corpus was significantly higher than that in angulus ($P<0.05$); in 61-70 years and >70 years groups, the rate was significantly higher in the corpus than in antrum and angulus ($P<0.01$).

The age-group distribution of mucosal inflammation in <31 years was significantly lower than that of the other age groups ($P<0.01$); both were significantly higher in 31-40 years and in 41-50 years than that in <31 years ($P<0.01$), lower than that in the other age groups ($P<0.01$). However, there was no difference between 51-60 years, 61-70 years and >70 years. In comparison of the mucosal inflammation among three biopsy sites, it was significantly lower from antrum, angulus to corpus in all age groups ($P<0.05$).

Total rate of glandular atrophy and intestinal metaplasia was significantly higher from <31 years to >70 years, respectively ($P<0.05$). In comparison to the rate of glandular atrophy and intestinal metaplasia among three biopsy sites, both of them were lowest in corpus ($P<0.05$), significantly higher in antrum ($P<0.01$), highest in angulus ($P<0.01$) in all age groups.

H pylori infection and histological features in three biopsy sites of patients with gastric ulcer

Distributions of *H pylori* infection, mucosal inflammation, activity of *H pylori* infection, glandular atrophy and intestinal metaplasia in three biopsy sites of different age- group patients, with gastric ulcer, are shown in Figure 2 A-C.

The distribution of *H pylori* colonization of gastric ulcer in <30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and >70 years age groups in antrum was 60.5%, 79.9%, 80.9%, 66.8%, 59.6%, 45.6%, respectively; in corpus it was 59.7%, 79.6%, 83.6%, 80.1%, 70.6%, 59.1%, respectively; in angulus it was 61.3%, 77.8%, 75.3%, 68.8%, 59.7%, 45.8%, respectively; overall it was 63.9%, 83.4%, 87.8%, 84.1%, 74.7%, 62.8%, respectively. Total distribution of *H pylori* infection and activity of *H pylori* infection in 3 839 cases, with gastric ulcer, was highest in

41-50 years ($P<0.05$); no obvious difference was found between 31-40 years and 51-60 years; <31 years and >70 years. Total rate of *H pylori* infection and activity of *H pylori* infection in 61-70 years was significantly higher than in <31 years and >70 years ($P<0.01$). However, it was significantly lower than in 31-40 years and 51-60 years. Comparing distribution and density of *H pylori* infection, we found that there was no significant difference among three biopsy sites in <31 years, 31-40 years and 41-50 years. In comparison of distribution of *H pylori* infection, there was no significant difference among three biopsy sites in <31 years and 31-40 years, respectively; however, in a further study, we had found the density of *H pylori* in antrum was significantly higher than in corpus of both age groups ($P<0.05$). Rate of *H pylori* in corpus was significantly higher than in angulus in 41-50 years ($P<0.05$). It was highest among three biopsy sites in the other age groups (all $P<0.01$).

Rate of mucosal inflammation in <31 years was significantly lower than that of the other age groups ($P<0.01$); there was no difference among the other age groups. Rate of mucosal inflammation was significantly lower in corpus than in antrum and angulus in >70 years ($P<0.05$); there was no difference among three biopsy sites in the other age groups.

Total rate of glandular atrophy was highest in >70 years ($P<0.01$), lower in 31-40 years ($P<0.01$), lowest in <31 years ($P<0.01$). There was no difference in 41-70 years, in which all of the rates were higher than in <31 years and 31-40 years ($P<0.01$). Rate of glandular atrophy among three biopsy sites was lowest in corpus ($P<0.05$), there was no difference between antrum and angulus in <31 years. However, the rate was significantly higher in antrum ($P<0.01$), highest in angulus in the other age groups ($P<0.01$).

Total rate of intestinal metaplasia was significantly higher from <31 years to >70 years ($P<0.01$), except between 51-60 years and 61-70 years in which there was no significant difference. Rate of intestinal metaplasia among three biopsy sites was lowest in corpus, higher in antrum, highest in angulus in all age groups ($P<0.01$).

Glandular atrophy and intestinal metaplasia in different age groups with and without H pylori infection

Distributions of glandular atrophy and intestinal metaplasia in different age groups with and without *H pylori* infection were shown in Tables 2 and 3. Rate of glandular atrophy and intestinal metaplasia was significantly higher in *H pylori*-positive patients than in *H pylori*-negative patients in all age groups, regardless of patients with chronic gastritis or gastric ulcer ($P<0.01$). Comparing distribution of glandular atrophy and intestinal metaplasia between chronic gastritis and gastric ulcer in <31 years, *H pylori*-positive patients with *H pylori*-positive patients, *H pylori*-negative patients with *H pylori*-negative patients, we found both *H pylori*-positive and *H pylori*-negative patients had no significant difference even though the rate was a little higher in gastric ulcer patients; in the other age groups both rates were significantly higher in gastric ulcer patients ($P<0.01$).

Table 2 Atrophy and intestinal metaplasia in different age groups of patients with chronic gastritis with and without *H pylori* infection (*n*, %)

	<31 yr	31-40 yr	41-50 yr	51-60 yr	61-70 yr	>70 yr
Cases	423	515	647	929	885	703
Atrophy						
H pylori-positive	25.4	30.2	54.0	56.4	63.6	66.3
H pylori-negative	2.5	5.6	8.7	16.1	27.2	34.5
Intestinal metaplasia						
H pylori-positive	15.9	20.1	41.5	53.9	62.8	68.3
H pylori-negative	1.8	4.5	9.9	21.7	34.9	43.1

Table 3 Atrophy and intestinal metaplasia in different age groups of patients with gastric ulcer with and without *H pylori* infection (*n*, %)

	<31 yr	31-40 yr	41-50 yr	51-60 yr	61-70 yr	>70 yr
Cases	119	343	745	1 098	940	594
Atrophy						
H pylori-positive	34.8	54.4	65.2	66.3	67.8	75.1
H pylori-negative	4.7	13.7	36.4	46.5	51.9	57.6
Intestinal metaplasia						
H pylori-positive	21.1	37.8	63.6	71.0	75.1	81.0
H pylori-negative	4.7	15.8	47.3	57.1	58.8	65.6

DISCUSSION

H pylori are important human pathogens, responsible for most peptic ulcer diseases, gastritis, gastric adenocarcinomas and gastric mucosa-associated lymphoid lymphoma, even in the pathogenesis of some extragastric diseases. In most persons, *H pylori* infection is largely restricted to the gastric antrum, in other hosts they develop a more widespread, infection that involves the body of the stomach and sometimes the antrum as well[9-13]. *H pylori* occupy a unique niche, extremely acidic environment. The urease of *H pylori* is essential for its colonization and survival at extremely low pH, to ensure cytoplasmic homeostasis during large pH changes that occur during feeding. *H pylori* can use molecular hydrogen as energy source; thus, its growth depends to some extent on the hydrogen excreted. In our results, the distribution of *H pylori* colonization at antrum was similar to corpus in patients with chronic gastritis before 50 years and in patients with gastric ulcer before 40 years. These results suggest the distribution of *H pylori* infection is pangastric in the younger patients. In the other age groups, the rate of *H pylori* colonization was highest in corpus, lower in antrum and lowest in angulus. Progression of glandular atrophy and intestinal metaplasia seems to have a key role in the distribution of *H pylori* colonization in these areas. In the younger there were not much glandular atrophy and intestinal metaplasia in the stomach, group which is beneficial for *H pylori* colonization, therefore *H pylori* even colonized, however, colonization of the lumen of gastric glands by *H pylori* eventually led to gastritis, glandular atrophy, and intestinal metaplasia, especially in angulus and antrum, but in the corpus it was very mild. Glandular atrophy and intestinal metaplasia in the angulus and antrum may result in decreased acid output as a consequence of diminished gastrin release[14,15], therefore *H pylori* gradually decreased during the development of glandular atrophy and intestinal metaplasia in the angulus and antrum but not in corpus in the older

age group. Logan and colleagues showed that potent acid suppression with a proton pump inhibitor resulted in a proximal shift of *H pylori* in the stomach[16]. This shift was accompanied by increased colonization of *H pylori* in the corpus, decreased in the antrum. Besides acids, environmental and host factors might also affect the distribution of *H pylori* in the stomach[17]. El-Omar and colleagues reported that the genetic make up of the host might also have a role. Polymorphism in the IL-1β gene cluster, which has both pro-inflammatory and potent acid suppressive effects, is associated with an augmented cytokine response to *H pylori* infection that greatly increases the risk of gastric atrophy, gastric ulcer, and gastric cancer[18,19].

It has long been known that patients with gastric ulcers have pangastritis affecting both the antrum and body, in contrast to patients with duodenal ulcers, who have antral-predominant gastritis. It is clear that the severity of the underlying pathology is a significant factor to ulcer formation. The more severe the gastritis, the more likely it is that decreased mucosal defense will allow acid-induced damage. Thus, it has been observed that gastric ulcers occur in the areas of most severe gastritis[20,21]. Our results are in accordance with this hypothesis, showing mucosal inflammation of gastric ulcer is a diffuse gastritis, but mucosal inflammation of chronic gastritis is an antrum-predominant gastritis. Moreover, inflammation of gastric ulcer is more severe than that of chronic gastritis. We also found infection with *H pylori* was nearly always accompanied by mononuclear cell infiltration in the lamina propria with neutrophilic cell and eosinophilic cell invasion of the lamina propria and epithelium. The regular epithelial gland structure was disrupted, and overlying mucus was decreased. Mucosal inflammation is thought to be mediated by direct contact between *H pylori* and the gastric epithelium, which induces IL-8 production, and by several *H pylori* products, including urease, ammonia manufactured by urease activity, and VacA protein[22-24].

Prior to the identification of *H pylori* as the major cause of gastritis, the decline in the ability to secrete gastric acid due to atrophic change of gastric mucosa was considered a consequence of aging[25]. The discovery of *H pylori* has led to a reassessment of the importance of aging and studies have focused on the long-term effects of *H pylori* infection and its role in the development of atrophic gastritis. Recently, it was suggested that *H pylori* infection is apparently a much more important factor than age per se in the chronological changes of the gastric mucosa leading to the development of atrophy[26]. Our present data clearly showed that the rate of glandular atrophy and intestinal metaplasia increased with age, in patients with chronic gastritis or gastric ulcer, and in patients with or without *H pylori* infection. However, the rate of glandular atrophy and intestinal metaplasia was higher and they occurred earlier in *H pylori*-positive patients with chronic gastritis; in contrast, it was very low in those without *H pylori* infection. They were high in *H pylori*-positive patients with gastric ulcer, but also very high in those without *H pylori* infection. Comparing gastric ulcer patients with chronic gastritis patients, we found the rates of glandular atrophy and intestinal metaplasia were higher in *H pylori*-positive patients with gastric ulcer than in *H pylori*-positive patients with chronic gastritis; they were also higher in *H pylori*-negative patients with gastric ulcer than in *H pylori*-negative patients with chronic gastritis. It suggests that even *H pylori* appear to be the most important risk factor for development of glandular atrophy and intestinal metaplasia, but it is not the only risk. Other identified risk factors include cigarette smoking, bile reflux, NSAID use, high salt intake, and autoimmune gastritis and yet unrecognized genetic factors may also play a part[27-30].

It is believed for a long time that atrophic gastritis extends from the antrum to the body with advancing age. Satoh indicated that *H pylori* infection was usually associated with antral atrophic gastritis and intestinal metaplasia[31,32]. Contrast to this concept, we found by an analysis of 4 102 cases with chronic gastritis and 3 839 cases with gastric ulcer, that both glandular atrophy and intestinal metaplasia were much more commonly identified in the angulus than in the antrum, lowest in corpus regardless of the different density of *H pylori* colonization, different ages or diseases. Though it remains to be further confirmed whether the real histological origin of glandular atrophy or intestinal metaplasia develops first from the angulus or not, we should take this fact into consideration in the evaluation of biopsy. There are two possible explanations for the apparent ability of *H pylori* to induce a more intense inflammatory response at angulus; either the bacteria are metabolizing and proliferating maximally because the local environment is at their pH optimum, or they are generating more inflammatory products, under which they can maximize adhesion, growth, and release of inflammatory products and induce maximal cytokine production via signal transduction. These areas of peak inflammatory response are the preferential sites for ulceration or development of glandular atrophy and intestinal metaplasia[33].

In conclusion, rates of *H pylori* infection, atrophy and intestinal metaplasia in gastric ulcer were higher than those in chronic gastritis. Distribution of *H pylori* colonization is pangastric in the younger patients; however, the rate of *H pylori* colonization is highest in corpus, lower in antrum and lowest in angulus in the older age groups. Progression of atrophy and intestinal metaplasia seems to have a key role in the distribution of *H pylori* colonization.

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