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ORIGINAL ARTICLE

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건강한 20대 성인에서 *Helicobacter pylori* 감염과 십이지장의 위화생

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Helicobacter pylori Infection and Duodenal Gastric Metaplasia in Healthy Young Adults

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Background/Aims: Duodenal ulcers occur relatively frequently in adolescents, like in adults, and may relate to *Helicobacter pylori* infection and duodenal gastric metaplasia (DGM). This study investigated the association between *H. pylori* infection and DGM in healthy adults aged 20-29.
Methods: Between 1995 and 2005, endoscopic biopsies of the duodenum, antrum and body were taken from healthy, young volunteers, who were first-year medical students, faculty staff, residents, and research assistants of Gyeongsang National University in Jinju, Korea. Urease tests were performed and the extent of DGM and histopathological grades according to the Updated Sydney System were determined.
Results: In total, 662 subjects were enrolled (429 males and 233 females). The median age was 22.3 years. The overall incidence of DGM was 11.5% but DGM was more frequent in males (15.4%) than in females (4.3%) ($p<0.0001$). While *H. pylori* positivity rates changed significantly during the 1995-2005 period ($p<0.01$), the incidences of DGM did not. DGM was observed in 7.2% and 14.9% of subjects who were and were not colonized with *H. pylori*, respectively. DGM was also associated with less severe chronic gastritis and the absence of active gastritis in both the antrum and body, and the absence of follicles in the antrum ($p<0.05$).
Conclusions: These findings suggested that DGM is not rare in healthy young adults and is unrelated to gastric *H. pylori* infection. **(Korean J Gastroenterol 2013;61:191-195)**

Key Words: *Helicobacter pylori*; Metaplasia; Adult

INTRODUCTION

Helicobacter pylori was first discovered to be a cause of active chronic gastritis by Warren and Marshall in 1983.[1] It is now widely accepted that *H. pylori* is the main pathogen of peptic ulcer diseases and is more strongly associated with duodenal ulcers than with gastric ulcers.[2] Duodenal ulcers have been shown to occur relatively frequently in both adults and adolescents.[3] This may reflect the fact that primary *H. pylori* infection generally occurs during early infancy, with most

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adults eventually becoming *H. pylori* carriers.[4] During active duodenitis, small surface areas of duodenal villi can start to develop duodenal gastric metaplasia (DGM).[5,6] While the exact pathogenesis of DGM is not known, it is frequently found in patients with duodenal ulcers.[7] To determine whether DGM in healthy adults was associated with *H. pylori* infection, and whether the prevalences of *H. pylori* infection and DGM change concomitantly over time, we analyzed endoscopic biopsies of the duodenum, antrum and body that were taken over the 11-year period of 1995-2005 from healthy adults who were working at a South Korean medical school.

SUBJECTS AND METHODS

Between 1995-2005, a number of first-year medical students, faculty members, residents and research assistants working in the Department of Pediatrics, Gyeongsang National University Hospital (GNUH; Jinju, Korea) volunteered to undergo gastroduodenal endoscopy. Biopsies from the duodenum, antrum and body were taken and pathology slides were made at the Departments of Microbiology and Pathology of GNUH. The biopsies were taken so that the subjects could determine whether they had any gastroduodenal histopathology, including DGM. To ensure that the present study only included healthy young adults, subjects over the age of 30 years and who had underlying diseases such as diabetes, tuberculosis, hypertension, hepatitis, and malignancy were excluded.

The gastric endoscopic biopsies were first subjected to urease tests, which were performed in the endoscopy room. On the basis of the rapidity of the color change, the subjects were graded into grades 0 (negative, no color change), 1 (color change observed between 24 and 48 hours), 2 (color change between 6 and 24 hours), and 3 (color change within 6 hours). For histological analyses, three biopsy specimens, one each from the gastric antrum, gastric body and duodenum, were stained with hematoxylin-eosin and alcian blue periodic acid-Schiff, pH 2.5. The histological results were interpreted according to the updated Sydney system.[8] The extent of DGM was arbitrarily graded as follows: absent, DGM not observed; mild, DGM observed in less than 5% of the mucosal length; moderate, DGM observed in 5-50% of the mucosal length; marked, DGM observed in more than 50% of the mucosal length.[9] All of the histopathological slides that were reviewed were prepared and donated by the GNUH (which is a member of the National Biobank of Korea) after its Institutional Review Board reviewed the research protocols (GNUHIRB-2009-007).

The Wilcoxon rank sum test was used for two-group comparisons and the Kruskal-Wallis test for multiple-group comparisons. Statistical significance was set at a p-value of < 0.05 (SPSS software version 12.0; SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline demographic characteristics of the study groups

In total, 662 volunteers were enrolled. Duodenal bulb urease test results were only available for 263 volunteers, and gastric body histological data were only available for 641 volunteers. However, antral and body urease test results and duodenal and antral histology data were available for all subjects. The volunteers consisted of 233 females (35.2%) and 429 males (64.8%). The median age of the whole group was 22.3 years (range, 19.9-29.9 years), while the median ages of the males and females were 21.9 and 22.5 years, respectively. The gender distributions and median ages did not change significantly over the duration of the study period.

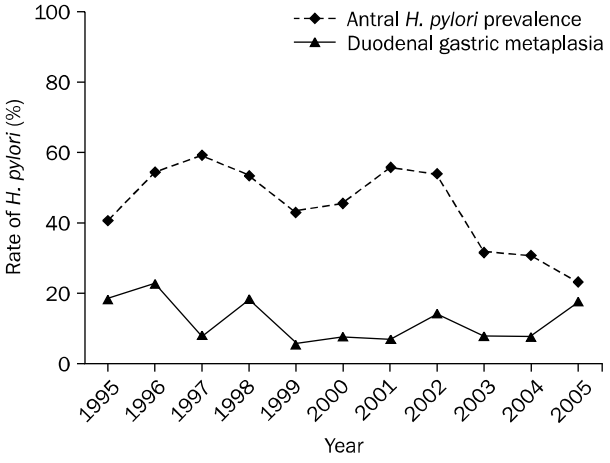

Fig. 1. Rates of *Helicobacter pylori* positivity in the gastric antrum and duodenal gastric metaplasia throughout an 11-year study period (1995-2005). *H. pylori* positivity (as determined by histologic degree of *H. pylori* density) decreased significantly over the 11-year period ($p < 0.05$) but the incidence of duodenal metaplasia did not change ($p=0.085$).

2. Incidence and extent of DGM in subjects divided according to year and gender

Fig. 1 depicts the incidence of DGM over the 11 study years, which did not change significantly (p=0.085). The incidences of DGM in males, females, and all subjects were 15.4%, 4.3%, and 11.5%, respectively. The difference between males and females in terms of DGM incidence was markedly statistically significant (p=0.0001).

With regard to the extent of DGM, as shown in Fig. 2, marked DGM was never observed: of the 76 subjects with DGM, it was mild in 11.8% and moderate in 88.2%. Active duodenitis was only observed in one subject with DGM.

3. Histopathological data and urease test results of subjects divided according to the extent of DGM

The histological findings of the duodenum, gastric antrum, and gastric body of the subjects after they were divided according to their DGM extent were evaluated. Gastric atrophy was never observed, while intestinal metaplasia was observed in seven of the 662 subjects (1.1%; one case each in 1995, 1996, 1997, 2001, 2003, 2004 and 2005). Six of the seven cases with intestinal metaplasia did not exhibit DGM, while the remaining case exhibited only mild DGM. With regard to the association of DGM with histological parameters, namely chronic and active inflammation, significant associations were not observed for the duodenum: although 77.6% of the subjects with DGM also had moderate chronic duodenitis, this did not achieve statistical significance. However, for the gastric antrum, the subjects with mild, moderate, and marked chronic gastritis had DGM rates of 16.0%, 7.9%, and 5.3%, respectively (p=0.0006). Thus, mild chronic gastritis was associated with a high incidence of DGM, and the incidence of DGM dropped as the chronic gastritis became more severe. This trend was also observed for the gastric body: the subjects with mild, moderate, and marked chronic gastritis had DGM rates of 15.0, 6.0, and 0%, respectively (p=0.0016). With regard to active gastritis, for the antrum and the body, the absence of active gastritis was associated with a DGM incidence of 69.7% (p=0.0003) and 85.1% ($p < 0.001$), respectively. In terms of *H. pylori* colonization in the antrum, 7.2% and 14.9% of the subjects with and without *H. pylori* colonization had DGM, respectively (p=0.0055). Antral *H. pylori* positivity (as determined by histologic degree of *H. pylori* density) decreased significantly over the 11-year period ($p < 0.05$) (Fig. 1). Similarly, in the body, 6.3% and 14.3% of the subjects with and without *H. pylori* colonization had DGM, respectively (p=0.0047).

Urease tests using duodenal bulb biopsies were only performed in 263 of the subjects, while urease tests using gastric antrum and gastric body biopsies were performed in all subjects. For the duodenum, gastric antrum and gastric body samples, the urease-positive rates were 37.3%, 64.2% and

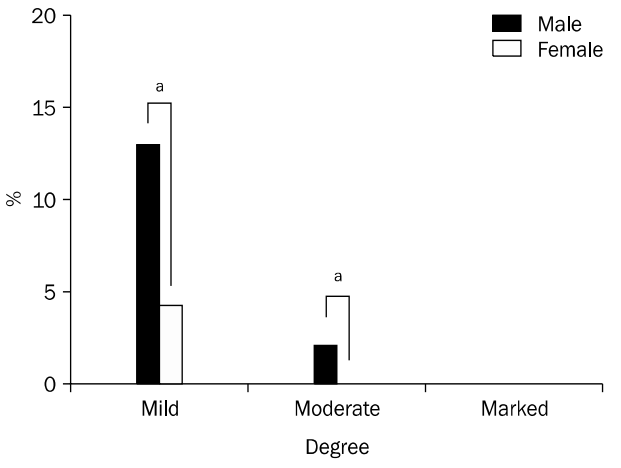

Fig. 2. Degree of duodenal gastric metaplasia in healthy, young subjects divided by gender. [a]$p < 0.0001$: males differed significantly from females in their incidences of mild and moderate duodenal gastric metaplasia.

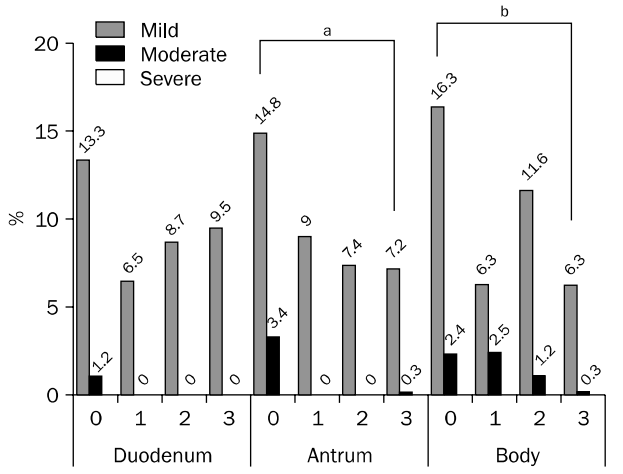

Fig. 3. The duodenal, antral and body urease grade data of the subjects, who are divided according to both the degree and presence/absence of duodenal gastric metaplasia. Urease test results are expressed as grade 0 (no change of color), grade 1 (color change between 24-48 hours), grade 2 (color change between 6-24 hours), and grade 3 (color change within 6 hours). Significant differences: [a]p=0.0002; [b]p=0.0003.

68.4%, respectively. The rate of *H. pylori* infection (urease-test positivity) in the antrum differed significantly throughout the study period ($p < 0.001$), as did the degree of chronic and active gastritis in the antrum ($p < 0.001$) and the degree of active gastritis in the body ($p=0.022$). For all three areas, urease-negative volunteers had higher incidences of DGM than urease-positive volunteers. For both the gastric antrum and body, the higher the urease test grade was, the lower the frequency of DGM (Fig. 3).

DISCUSSION

While DGM is often observed in patients with duodenal ulcers, it is also seen in healthy people.[10] The incidence of DGM may also be influenced by age since DGM is seen significantly more frequently in adult patients than in patients under the age of 17 years.[11] It is also more frequently observed in children over the age of 12 years than in children under the age of 8 years.[12] One study of 116 normal asymptomatic adults with a mean age of 46 years revealed that the prevalence of DGM was 22%.[13] In the present study, which involved a large population of healthy young adults, the incidence of DGM was 11.5%. Gastric atrophy was never observed and the incidence of intestinal metaplasia was very low. However, our study may underestimate the real prevalence of DGM in this group because only one duodenal biopsy specimen per person was used.

In the present study, DGM was more common in males than in females. This has been reported previously,[11,14] although boys and girls do not differ in the prevalence of DGM.[15] These observations suggest that factors operating during the transition from adolescence to adulthood may contribute to the pathogenesis of DGM.

H. pylori is strongly associated with duodenal ulcer disease.[2] Moreover, it has been shown that patients with recurrent duodenal ulcer disease have higher incidences of not only *H. pylori* but also DGM,[16] and duodenal *H. pylori* infections are always observed in the areas of DGM, although the reverse is not always true.[16] On the basis of these observations, it has been hypothesized that *H. pylori* infection and DGM are linked in the pathogenic mechanism that generates duodenal ulcers, as follows.[17] First, when *H. pylori* colonizes the gastric antrum, it induces the hypersecretion of gastric acid, which in turn leads to excessive levels of hyperchloric acid in the duodenum and the generation of DGM. *H. pylori* then colonizes the DGM, which provokes even stronger inflammatory reactions that result in active duodenitis. This impairs the bicarbonate secretion of the duodenum, which leaves the duodenum vulnerable to acid and pepsin and results in the development of a duodenal ulcer. Supporting the possibility that both *H. pylori* and acid drive the development of DGM is a study showing that when ulcer healing was induced by *H. pylori* eradication and/or acid suppression, each strategy alone reduced the DGM by 42-43%, whereas the two strategies together reduced DGM by 66%.[18] However, several reports have cast doubt on the notion that *H. pylori* infection is related to DGM prevalence while gastric pH is related to the extent of DGM. One study showed that, compared to patients with normal duodenum, *H. pylori* infection is more common in patients with duodenal inflammation, which is a prerequisite of duodenal ulcer development, whereas patients with DGM had similar levels of *H. pylori* infection.[19] Thus, active duodenitis, but not DGM, is significantly associated with *H. pylori* infection. In addition, a study of *H. pylori*-positive patients with a duodenal ulcer or nonulcer dyspepsia failed to detect a significant correlation between gastric pH and the extent of DGM.[20] Moreover, another study has shown that the prevalence and/or severity of DGM is related not to *H. pylori* infection but rather to the aging process.[9] Finally, several studies have found that *H. pylori* eradication and acid reduction have highly variable effects on DGM,[21,22] and a study of duodenal ulcer patients 6 months after *H. pylori* eradication revealed that they still had significantly more extensive DGM than healthy controls.[10] In relation to these observations, the present study showed that although the incidence of *H. pylori* infection had dropped significantly over the 11-year study period, the incidence of DGM did not change. Moreover, the histological presence of *H. pylori* was not associated with a higher incidence and extent of DGM, nor was DGM significantly associated with the degree of chronic gastritis, active gastritis, or urease-test grade. These observations are in agreement with a previous report.[10]

This study suffered from several limitations. First, since the acidity of the gastric juice or the serum gastrin levels were not measured, it was not possible to examine how the hypersecretion of gastric acid relates to the development of DGM. Second, we could not explain why the male volunteers had a significantly higher incidence of DGM. However, it is con-

sistent with previous studies showing that males have a higher prevalence of duodenal ulcers than females.[23] Despite these limitations, the present study is useful because most previous studies examining the relationship between *H. pylori* infection and DGM employed biopsies obtained from patients undergoing surgery or endoscopy due to gastrointestinal symptoms and/or older adults. In contrast, the present study employed biopsies taken from healthy young adults without upper gastrointestinal symptoms over a period of 11 years. As a result, it was possible to examine how the incidence of DGM was related to *H. pylori* infection prevalence over time.

In conclusion, the incidence of DGM was higher in *H. pylori*-negative volunteers than in *H. pylori*-positive volunteers. It was also more common in males than in females. There is inverse relationship between DGM and severe chronic gastritis, active gastritis, or follicles. These findings suggest that DGM is not rare in healthy young adults and is unrelated to gastric *H. pylori* infection. Additional studies examining the incidence of DGM and *H. pylori* infection in all age groups are needed.

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