Most cases of chronic gastritis are due to *Helicobacter pylori* infection (1). However, the severity and extent of *H. pylori*-associated chronic gastritis varies among infected patients. Those with pan-gastritis or corpus-predominant gastritis may develop progressive atrophy with loss of pyloric and oxyntic glands (2).

The stomach is the main source of ghrelin, a 28–amino acid peptide that is an endogenous ligand for the growth hormone secretagogue receptor (3,4). Ghrelin influences appetite, growth hormone secretion, energy balance, gastric motility, and acid secretion. It is produced by X/A-like cells in oxyntic glands in the stomach.

There are contradictory reports on the relation between *H. pylori* and ghrelin; a Turkish study reported that *H. pylori* infection had no effect on plasma ghrelin levels (5), whereas a British study demonstrated an increase in circulating ghrelin levels following cure of *H. pylori* (6). We speculated that the production and release of ghrelin are affected by inflammatory and atrophic events associated with *H. pylori*, and assessed the correlation of ghrelin levels with histologic severity and topographic extent of *H. pylori*-associated chronic gastritis.

**METHODS**

We enrolled consecutive outpatients between the ages of 18 and 80 years who had been referred for upper gastrointestinal endoscopy between April 2002 and March 2003. All patients provided written informed consent. We excluded those with any of the following: pregnancy, body mass index >30 kg/m², diabetes mellitus, cachexia (cancer, systemic infection, thyroid and liver diseases), renal impairment, peptic ulcer, use of medications effective against *H. pylori* during the preceding 3 months, alcohol abuse, drug addiction, and chronic corticosteroid or nonsteroidal anti-inflammatory drug use. None of the subjects had undergone gastrointestinal surgery.

Blood was taken between 8:00 AM and 10:00 AM after an overnight fast, transferred into chilled tubes containing ethylenediaminetetraacetic acid-2Na and aprotinin, and stored on ice during collection and centrifuged. Plasma was separated and stored at −80°C until assay. Ghrelin levels were measured in house in duplicate by radioimmunoassay (4). This assay system employs a rabbit polyclonal antibody raised against the C-terminal fragment [13–28] of human ghrelin, and can measure both the acylated and des-acyl forms. The intra-assay coefficient of variation was 2.8%; the inter-assay coefficient of variation was 3.1%. The minimum detection level was 10 fmol per tube. Plasma gastrin, leptin, and pepsinogen levels were determined by commercial radioimmunoassay kits. Serum samples were examined for anti–*H. pylori* immunoglobulin G antibodies by an enzyme-linked immunosorbent assay.

During endoscopy, two pairs of biopsy specimens were obtained from the antrum and corpus for histopathologic assessment of gastritis and presence of *H. pylori*. Biopsy specimens were fixed in 10% formalin and embedded in paraffin. The sections (4-μm thick) were deparaffinized, rehydrated, and stained with hematoxylin and eosin. Giemsa staining was used to detect *H. pylori*. According to the Sydney system, each histologic parameter of activity (neutrophils), chronic inflammation (mononuclear cells), glandular atrophy, and intestinal metaplasia was graded as none, mild, moderate, or severe (1). Topographic distribution of gastritis was designated as antrum predominant, pangastritis, or corpus predominant (2). Biopsy specimens were examined blindly without knowledge of ghrelin levels.

We treated 12 *H. pylori*-positive patients with a 7-day course of triple therapy consisting of lansoprazole, amoxicillin, and clarithromycin (7). Four weeks after cessation of treatment, fasting plasma ghrelin levels were measured. Eradication of *H. pylori* was considered successful when the 13C-urea breath test was negative (7).

**Statistical Analysis**

Statistical analyses were performed using the Fisher exact test, the chi-squared test, the Student t test, the Mann-Whitney U test, the Kruskal-Wallis test, or analysis of variance, as appropriate. A P value of less than 0.05 was accepted as statistically significant. The study was approved by the Nagasaki University Ethics Committee.

**RESULTS**

We studied 68 patients (mean ± SD age, 56 ± 14 years; range, 20 to 80 years), including 35 women. Eighteen were current smokers and 16 drank alcohol. Based on histopathology and serology, 43 patients were designated as positive for *H. pylori* infection. The mean plasma
The ghrelin level was 127 ± 88 fmol/mL (range, 42 to 584 fmol/mL). Baseline characteristics, including age, sex, alcohol intake, smoking habits, body mass index, and biochemical markers, were not associated with ghrelin levels. However, the mean ghrelin level in *H. pylori*–positive patients (99 ± 44 fmol/mL) was significantly lower than in *H. pylori*–negative patients (175 ± 119 fmol/mL, *P* < 0.001).

There were also significant differences in ghrelin levels based on the grades of each histopathologic parameter: activity in the antrum and corpus, chronic inflammation in the corpus, glandular atrophy in the antrum and corpus, and intestinal metaplasia in the corpus (Table). There was a stepwise decrease in ghrelin levels from normal to the antrum-predominant pattern to pangastritis to corpus-predominant gastritis (Figure 1).

Plasma ghrelin levels correlated significantly with pepsinogen I levels and pepsinogen I/II ratios (Figure 2), but not with pepsinogen II (*r* = 0.15, *P* = 0.22) or gastrin (*r* = 0.09, *P* = 0.47) levels.

Within the *H. pylori*–positive group, there was a negative correlation between age and ghrelin levels (*r* = −0.31, *P* < 0.05). In comparison, ghrelin levels did not correlate with age in *H. pylori*–negative patients (*r* = 0.07, *P* = 0.74). There was a negative correlation between age and pepsinogen I/II ratios (*r* = −0.30, *P* < 0.05) in *H. pylori*–positive patients.

*H. pylori* infection was cured in 9 of the 12 patients who received eradication therapy. There was no significant difference in plasma ghrelin levels measured before and after treatment (Figure 3).

**DISCUSSION**

We found that plasma ghrelin levels were significantly lower in *H. pylori*–positive than in *H. pylori*–negative patients. The results contrast with those from a previous study that reported no effect of *H. pylori* infection on ghrelin levels (5). There are several possible explanations for this disparity, including differences in the radioimmunoassay protocols for ghrelin; differences in the assessment of *H. pylori* status (the prior study used histology vs. serology); and differences in the extent of gastritis.

**Table.** Plasma Ghrelin Levels and Histologic Severity of Each Parameter of Gastritis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>179 ± 87 (33)</td>
<td>75 ± 8 (18)</td>
<td>117 ± 48 (12)</td>
<td>102 ± 52 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Corpus</td>
<td>177 ± 86 (23)</td>
<td>123 ± 48 (16)</td>
<td>85 ± 30 (24)</td>
<td>98 ± 34 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Chronic inflammation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>146 ± 84 (33)</td>
<td>105 ± 46 (24)</td>
<td>106 ± 43 (8)</td>
<td>121 ± 105 (3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Corpus</td>
<td>152 ± 81 (33)</td>
<td>95 ± 41 (18)</td>
<td>95 ± 35 (12)</td>
<td>86 ± 20 (5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>Glandular atrophy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>166 ± 85 (27)</td>
<td>115 ± 48 (21)</td>
<td>79 ± 28 (13)</td>
<td>85 ± 53 (7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Corpus</td>
<td>168 ± 74 (34)</td>
<td>93 ± 21 (12)</td>
<td>78 ± 16 (17)</td>
<td>59 ± 12 (5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Intestinal metaplasia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antrum</td>
<td>143 ± 77 (44)</td>
<td>107 ± 57 (11)</td>
<td>78 ± 41 (7)</td>
<td>93 ± 42 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Corpus</td>
<td>134 ± 73 (56)</td>
<td>No data</td>
<td>78 ± 16 (8)</td>
<td>63 ± 15 (4)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

**Fig. 1.** Relation between topographic distribution of chronic gastritis, *Helicobacter pylori* infection, and plasma ghrelin levels. Mean (± SD) ghrelin levels were 190 ± 90 fmol/mL in those with normal mucosa without *H. pylori* infection, 139 ± 98 fmol/mL in those with antrum-predominant gastritis, 80 ± 24 fmol/mL in those with pangastritis, and 56 ± 15 fmol/mL in those with corpus-predominant gastritis (*P*<0.0001).
ogy only, thereby underestimating infection); differences in the samples with respect to race, nutrient status, and dietary habits; and small sample size (8).

Although gastrin may modify the production or release of ghrelin (9), we found no significant correlation between plasma ghrelin and gastrin levels, irrespective of H. pylori status. Consistent with our findings, recent observations demonstrated that ghrelin administration does not affect circulating gastrin levels in humans (10). In addition, increased levels of gastrin caused by omeprazole treatment failed to raise either the level of ghrelin messenger RNA in oxyntic mucosa or circulating ghrelin levels in a rat model (11). Based on these findings, ghrelin production or release does not seem to be controlled by gastrin.

The major finding of our study was that the severity of histopathologic changes and topography of gastritis affected circulating ghrelin levels, which were decreased markedly in patients with extensive atrophic gastritis involving the corpus. The reduced plasma ghrelin levels were accompanied by decreased pepsinogen I levels and low pepsinogen I/II ratios, which are thought to be markers of gastric mucosal atrophy (2). Indeed, a low plasma ghrelin level has been observed in a young woman with an evolving autoimmune gastric process, including serum anti–parietal cell antibodies and a low B12 level (12). Given the close juxtaposition of the endocrine and parietal cell compartments, ghrelin biosynthesis in fundic mucosa may be affected by inflammatory and atrophic events associated with either H. pylori infection or an autoimmune reaction. This may explain the progressive fall in circulating ghrelin levels with increased severity and extent of gastritis that we observed, probably reflecting the loss of ghrelin-producing cells.

However, Nwokolo et al (6) reported that 6-hour integrated plasma ghrelin levels increased substantially following cure of H. pylori infection, suggesting that depressed ghrelin levels in H. pylori infection were caused in part by a functional impairment due to inflammation, rather than loss of ghrelin-producing cells. We did not observe a rise in plasma ghrelin levels after cure of H. pylori infection, although we measured levels at only one point after an overnight fast. Study of a large number of patients with placebo controls is warranted to elucidate the reversibility of ghrelin production after cure of H. pylori infection.

We observed a significant negative correlation between age and circulating ghrelin levels in H. pylori–infected patients, perhaps reflecting progressive atrophic gastritis with greater years of infection. One other study reported lower plasma ghrelin levels in elderly persons (13). Since ghrelin levels did not correlate with age in H. pylori–negative patients, we believe that this age effect may be restricted to those infected with H. pylori.

Further characterization of the implications of low production or release of ghrelin on physiological functions is warranted. In particular, ghrelin deficiency could be viewed as an H. pylori–associated endocrine disorder (e.g., somatotroph dysregulation and anorexia of aging). The high plasma ghrelin levels in H. pylori–negative pa-
Patients may affect appetite and food intake, and even contribute to increased obesity seen in developed countries where the prevalence of _H. pylori_ infection is on the decline.

REFERENCES


From the Second Department of Internal Medicine (HI, YM, HM, YY, SK), and Department of Molecular Medicine, Atomic Bomb Disease Institute (AO, SY), Nagasaki University School of Medicine, Nagasaki, Japan; and Third Department of Internal Medicine (MN, HU, YD), Miyazaki Medical College, Miyazaki, Japan.

Requests for reprints should be addressed to Hajime Isomoto, MD, Gastrointestinal Unit, Massachusetts General Hospital, Jackson 706, 55 Fruit Street, Boston, Massachusetts 02114-2696, or hajime2002@yahoo.co.jp.