Serum pepsinogen I concentrations in peptic ulcer patients in relation to ulcer location and stage

Y Tanaka, K Mine, Y Nakai, N Mishima, T Nakagawa

Abstract

To investigate the relation of the serum group I pepsinogen (PG I) concentration to the location of gastric ulcers and chronicity of peptic ulcers, ulcer patients (n=322) were compared with endoscopically normal subjects (n=174). The mean PG I concentration was significantly higher in male control subjects (n=90) than in female control subjects (n=84). In male patients with ulcers in the duodenum (n=69), antrum (n=34), or angulus portion (the lower third of the body; n=83), the mean serum PG I concentration was significantly higher than in the control subjects but in patients with an ulcer in the upper body (n=49) it was similar to control values. Men with active or healing ulcers (n=149) showed a significantly higher serum PG I concentration than those with scarred lesions (n=86) when the abnormality was located in either the upper body or in the angulus portion. For female patients (n=87), the results were similar. These results suggest that serum PG I concentrations reflect the stages of activity of peptic ulcer.

It has been reported that hyperpepsinogenemia may be considered as a subclinical marker of the genetic predisposition to duodenal ulcers. It has been fairly well established that duodenal ulcer patients often show increased serum concentrations of group I pepsinogen (PG I) It has been fairly well established that duodenal ulcer patients often show increased serum concentrations of group I pepsinogen (PG I)7-11 Several studies have found a significant relation between the serum PG I concentration and gastric acid and pepsin output in response to maximal stimulation with histamine or pentagastrin, suggesting that the serum PG I concentration may reflect the acid and pepsin secretory capacity of the gastric mucosa.11-12

With regard to gastric ulcers, however, the importance of the serum PG I concentration has not yet been established and there is still no unified view on the subject.3-11 There have been few reports of serum PG I concentrations in relation to the location of gastric ulcers.8-10,15 No has the relation of serum pepsinogen or PG I to the stage of activity of peptic ulcers been investigated often.2,10,15

This study was undertaken to further a better understanding of the relation between serum PG I and peptic ulcers. Peptic ulcer patients were compared with endoscopically normal control subjects with regard to serum PG I concentrations. In particular, we investigated whether there was any relation between the location of the ulcer and the serum PG I concentration. All subjects were socioculturally relatively homogeneous inhabitants of an isolated island.

Subjects and methods

SUBJECTS

All subjects were from Iki island, Japan. Iki is an isolated island with a population of about 40,000 and is 139 km² in area. Almost all residents are engaged in either fishing or agriculture and have similar customs and environment. Migration from or to the island is rare.

We examined all subjects by endoscopy in Iki Public Hospital over a seven year period from 1980 to 1986. Almost all endoscopic examinations of the patients from Iki island were performed at this hospital. We used an Olympus GIF Q endoscope. In all patients with gastric ulcer biopsy specimens were taken, none of which showed malignancy.

The control group consisted of healthy volunteers and outpatients who were suspected of having gastric or duodenal disease after mass cancer X ray screening, as well as those who had a negative history of peptic ulcers and in whom no gastric or duodenal abnormalities could be observed by endoscopy. All healthy volunteers were informed of the study by letter and gave their written consent.

Patients with gastrointestinal symptoms not attributable to peptic ulcers were also included, but none of the control subjects had any severe underlying diseases.

The peptic ulcer group consisted of patients with a single gastric or duodenal ulcer that was shown to be active, healing, or in the scarred stage at endoscopy. Patients with multiple ulcers and those in whom the ulceration was considered to be induced or affected by taking anti-inflammatory agents such as aspirin or indomethacin were excluded. All ulcer patients were treated with antacid and sucralfate, combined with firm persuasion to better their eating habits and life style. No patient receiving either anticholinergic agents or H2 blockers was included in the patient group.

There were 174 subjects in the control group – 90 men and 84 women with a mean (SD) age of 48 (14) years. The peptic ulcer group consisted of 322 patients. Some 217 had a gastric ulcer – 166 men and 51 women, with a mean (SD) age of 54

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Mean (SD) serum pepsinogen I (PG I) concentration in subjects according to age and sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>No</td>
</tr>
<tr>
<td>---------</td>
<td>----</td>
</tr>
<tr>
<td>20-29</td>
<td>5</td>
</tr>
<tr>
<td>30-39</td>
<td>23</td>
</tr>
<tr>
<td>40-49</td>
<td>19</td>
</tr>
<tr>
<td>50-59</td>
<td>19</td>
</tr>
<tr>
<td>60-69</td>
<td>18</td>
</tr>
<tr>
<td>70-78</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
</tr>
</tbody>
</table>

Comparison men to women
(13) years – and 105 had a duodenal ulcer – 69 men and 36 women with a mean (SD) age of 48 (12) years.

MEASUREMENT OF SERUM PG I CONCENTRATIONS
On the day of endoscopy, blood samples from all subjects were collected in glass tubes early in the morning after an overnight fast. After centrifugation the serum was stored at −20°C until assays were performed. The concentration of PG I was determined by radioimmunoassay according to Samloff’s method, using a PG I RIA kit (Midori Jui). For all the samples, duplicate measurements were performed.

With regard to the control group, we examined the distribution of serum PG I concentrations according to age and sex.

The 322 peptic ulcer patients were classified into four groups according to the location of the ulcer. These locations were: the duodenal bulb; the antrum distal to the angulus; the distal third of the corpus including the angulus, referred to in this text as the ‘angulus portion’; and the proximal two thirds of the corpus, referred to as ‘upper corpus’.

In addition, for each location we compared the patients with an ulcer in the active or healing stage, referred to as an ‘open ulcer’ with patients with an ulcer in the scarred stage according to Sakita’s classification.15 16

RESULTS

CONTROL GROUP
Comparing the different age groups among control subjects showed no significant differences in the mean serum PG I concentration. This result can be attributed to the small number of subjects in each age group. The PG I concentration was significantly higher, however, in men than in women (Table I). The control group subjects have a mean (SD) serum PG I concentration of 71.2 (24.4) ng/ml.

PEPTIC ULCER GROUP
Because there were statistically significant differences between the men and women in the control group, we investigated the male and female ulcer patients separately. The ulcer patients were divided into those with open (active or healing) ulcer lesions and those with an ulcer scar.

COMPARISON BETWEEN PATIENTS AND CONTROL SUBJECTS
Male patients with ulcers in the angulus portion, the antrum, or the duodenum, either active or healing as well as in the scarred stage, had appreciably higher serum PG I concentrations than the control group (Table II).

The patients with an open ulcer or a scar in the upper corpus, however, showed no significant difference in serum PG I concentrations compared with the control subjects. With regard to ulcer location, the serum PG I concentration was significantly lower in patients with ulcers in the upper corpus than in those with ulcers in other locations, both for men with an open ulcer and for those with an ulcer scar.

The results in female ulcer patients were similar to those in male patients, except that there were too few women with a scar in the antrum to determine any statistical significance when comparing the difference in serum PG I concentrations (Table III). Although PG I concentrations tended to be higher among female patients with a scar in the angulus portion compared with those with a scar in the upper corpus, there was no statistically significant difference between these locations.

COMPARISON BETWEEN PATIENTS WITH AN OPEN ULCER AND A SCAR
Men with a gastric ulcer that was active or healing had noticeably higher serum PG I concentrations than those with scarring. In patients with an ulcer in the upper corpus or angulus portion, the serum PG I concentration was significantly higher in those with an open ulcer than in those with a scar. In patients with an ulcer in the antrum or duodenum, the PG I concentration also seemed to be higher in active or healing lesions than in scarred ulcers. This difference was not, however, statistically significant (Table II).

Female patients with an active or healing gastric ulcer also showed a significantly increased concentration of serum PG I compared with those with an ulcer scar. In ulcers located in the angulus portion in particular, the serum PG I concentrations of patients with an open ulcer seemed to be significantly higher than in those with scarring (Table III).

DISCUSSION
In this study, all those investigated lived in a similar environment, had similar eating habits and lifestyle, and were of the same race. For a study on peptic ulcers, which is considered to have a multifactorial aetiology, this group of subjects can be regarded as very suitable.

The mean serum PG I concentration of the control group in this study corresponds well with

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**Table I** Mean (SD) serum pepsinogen I (PG I) concentration in male ulcer patients according to location and stage of ulcer

<table>
<thead>
<tr>
<th>Location</th>
<th>Open ulcer</th>
<th>Ulcer scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric ulcer:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No  PG I (ng/ml)</td>
<td>No  PG I (ng/ml)</td>
</tr>
<tr>
<td>U.S.</td>
<td>106</td>
<td>130.7 (58.3)^*</td>
</tr>
<tr>
<td>Upper corpus</td>
<td>35</td>
<td>86.5 (35.3)</td>
</tr>
<tr>
<td>Antrum</td>
<td>43</td>
<td>157.7 (56.2)^**</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>28</td>
<td>144.3 (53.4)^**</td>
</tr>
<tr>
<td>Control</td>
<td>43</td>
<td>145.2 (51.8)^*</td>
</tr>
</tbody>
</table>

* p<0.01 compared with the control group. ^p<0.01 compared with the patients with an ulcer in the upper corpus. **p<0.05 compared with the patients with an ulcer in the upper corpus. ^p<0.01 compared with the patients with duodenal ulcer.
Serum pepsinogen I concentrations in peptic ulcer patients in relation to ulcer location and stage

<table>
<thead>
<tr>
<th>Location</th>
<th>Open ulcer No</th>
<th>PG I (ng/ml)</th>
<th>Ulcer scar No</th>
<th>PG I (ng/ml)</th>
<th>Comparison open to scar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric ulcer</td>
<td>26</td>
<td>120±8 (53-6)*</td>
<td>25</td>
<td>85±8 (33-1)**</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Upper corpus</td>
<td>8</td>
<td>68±5 (31-6)</td>
<td>13</td>
<td>73±3 (50-6)</td>
<td>NS</td>
</tr>
<tr>
<td>Angular portion</td>
<td>9</td>
<td>127±9 (62-7)**</td>
<td>9</td>
<td>97±3 (35-6)*</td>
<td>NS</td>
</tr>
<tr>
<td>Antrum</td>
<td>9</td>
<td>160±9 (59-3)**</td>
<td>3</td>
<td>105±9 (29-3)</td>
<td>NS</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>29</td>
<td>123±13 (36-4)**</td>
<td>7</td>
<td>134±6 (30-7)*</td>
<td>NS</td>
</tr>
</tbody>
</table>

*p<0.01 compared with the control group. 1p<0.01 compared with the patients with an ulcer in the upper corpus. 2p<0.05 compared with the patients with duodenal ulcer.

From information obtained from multiple biopsy specimens in 570 Japanese patients, the fundic-pyloric border was found to transit proximally with advancing age and a proximal transition occurs extending more rapidly along the lesser curvature of the stomach. In addition, atrophic gastritis was also found to extend proximally, extending more rapidly in the lesser than in the greater curvature. 21

The study also suggested that the fundic gland along the fundal side of the fundic-pyloric border undergoes metaplastic changes into the pyloric gland, resulting in expansion of the area of secretion by the pyloric glands in accordance with expanding atrophic gastritis. From the results of these studies, it may be presumed that the more proximally ulcers are located in the stomach, the smaller the area that covers the fundic mucosa. These investigations may explain the differences in serum PG I concentrations in relation to the location of ulcers by virtue of the fact that PG I is synthesised only in the fundic gland mucosa. 22

It has been suggested that the serum PG I concentration may reflect the acid secreting potential. 23,24 It has been shown that, in general, patients with an ulcer in the corpus tend to have either a normal or lower than normal rate of acid secretion, whereas in patients with an antral ulcer the acid secretion is either normal or greater than normal. 25-27 The different serum PG I concentrations that we observed at three different locations of gastric ulcers, correlate roughly with these different rates of acid secretion. If we assume, however, that the PG I concentration is an index of acid secretory capacity, many patients with an ulcer in the lower third of the corpus (angular portion) could be presumed to have a relatively high acid secretion.

Our finding of a statistically significant difference in serum PG I concentrations according to the localization of the ulcer 28 was recently confirmed by the results of a study by Samloff et al in which serum PG I I concentration was significantly higher in patients with an ulcer located in the fundus than in those with an ulcer located at the antrum or pylorus. 29

Previous reports, therefore, show variable results concerning gastric ulcers, especially with regard to those either at or proximal to the antrum. This lack of consistency may partly be explained by the fact that in previous studies the gastric ulcer patients were divided into only two groups according to ulcer location. In some studies ulcers in the antrum were grouped with antral ulcers while in others they were grouped with ulcers in the corpus.

In this study, we were more precise about gastric ulcer locations, investigating the angular portion separately from the upper two thirds of the corpus. We found significantly higher PG I concentrations not only in patients with antral ulcers but also in those with ulcers localised in the angular portion, whereas PG I concentrations in patients with an ulcer in the upper corpus were similar to those in control subjects. On the other hand, patients with an ulcer located in the fundus had significantly higher serum PG I concentrations than in controls. 30,31

Plebani et al found that the serum PG I concentration was significantly higher in patients with ulcers located in the fundus than in those with ulcers proximal to the antrum. They suggested that this difference could be explained by the fact that in patients with fundic ulcers, the serum PG I concentration was significantly higher than in patients with ulcers located in the corpus. These results are in accordance with the findings of previous studies. 32,33

From both these studies, it has been suggested that the fundic-pyloric border region is associated with a higher acid secretion rate, whereas in patients with antral ulcers, the acid secretion rate is either normal or greater than normal. 34-36

Another possible mechanism for the difference in serum PG I concentration in open versus scarred ulcers is the difference in the size of the ulcer. 37,38 In our study, serum PG I concentration was significantly higher in patients with an ulcer located in the fundus than in those with antral ulcers. This suggests that the size of the ulcer may be an important factor in determining the concentration of serum PG I.

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Samloff et al suggested that serum pepsinogen II (PG II) is produced by the chief cells in fundic glands and in the pyloric glands in the gastric antrum, and that raised serum PG II value and a low PG I:PG II ratio are major risk factors for gastric ulcers. 39 To elucidate the cause of the difference in serum PG I concentrations during the clinical course of gastric ulcer, especially in the antrum, we should investigate serum PG II concentration in further studies.

Another possible mechanism for the difference in serum PG I concentration in open versus scarred ulcers is the difference in the size of the ulcer. 37,38 In our study, serum PG I concentration was significantly higher in patients with an ulcer located in the fundus than in those with antral ulcers. This suggests that the size of the ulcer may be an important factor in determining the concentration of serum PG I.
ference in serum PG I in open versus scarred gastric ulcers is a change in the parasympathetic activity. The serum PG I concentration in duodenal ulcer patients decreases significantly when atropine is administered. It has been shown in organ culture that the gastric secretion of pepsinogen is stimulated considerably by acetylcholine. Furthermore, there have been many reports on the significant reduction in serum PG I concentrations after a proximal gastric vagotomy has been performed in duodenal ulcer patients. Based on these findings it might be postulated that the serum PG I concentration is an expression of the function of the parasympathetic nervous system, and that in the active stage of peptic ulcers the function of the parasympathetic nervous system is at a higher level, resulting in an increased concentration of PG I in serum through the increased neural stimulation of the chief cells.

In duodenal ulcer patients, it has already been shown that increased serum concentrations of PG I at the time of diagnosis are associated with a significant tendency to ulcer relapse. In gastric ulcer patients, the clinical significance of measuring serum PG I concentration is not yet clear. We found a difference in serum PG I concentrations in patients with an open ulcer compared with those with a scar, not only for the antrum and the angular portion but also for the upper corpus. If the serum PG I concentration reflects the acid secretory potential, it could be presumed that the increase in acid and pepsin secretion might play an important role in the onset and recurrence of gastric ulcers, regardless of their location.

It is, however, difficult to elucidate clearly the relation between gastric secretion and ulcer activity from our results. Contrary to the reports showing that serum PG I concentration and the acid and pepsin secretory capacity of the gastric mucosa correlate closely with each other, Feldman et al. and other authors reported that maximal acid secretion correlated significantly with serum PG I, the correlations were not strong.

Serum PG I concentrations might be considered useful as parameters of ulcer activity in following the clinical course of gastric ulcer patients. Because our findings are based on a cross-sectional study, it is difficult to determine whether serum PG I concentrations increase in the active stage in patients with gastric ulcer or not. In future investigations, longitudinal study of the same patients during the clinical course is required to confirm the clinical importance of serum PG I concentrations.

Since we found statistically significant differences according to sex, the three gastric ulcer sites, and the stages of the ulcer, we recommend that future studies of serum PG I should consider all these aspects.

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