Influences of *Helicobacter pylori* on serum pepsinogen concentrations in dialysis patients

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Abstract

**Background.** Patients with impaired renal function have been known to have elevated concentrations of serum pepsinogens, which are raised by *Helicobacter pylori* infection of the stomach. The present study was performed to examine the effect of *H. pylori* infection on serum pepsinogen concentrations in dialysis patients.

**Methods.** Forty nine patients on dialysis and 48 subjects with no known kidney disease were examined for upper gastroduodenal endoscopy, *H. pylori* infection and serum concentrations of pepsinogen I and II. The status of *H. pylori* infection was evaluated from results of a urease test, histology and culture of biopsy specimens of the gastric mucosa. Serum pepsinogen levels were measured by radioimmunoassay.

**Results.** Serum concentrations of pepsinogen I and II were elevated in the dialysis patients in comparison with those in the controls (277.4 ± 24.2 vs 52.6 ± 4.0 pg/ml, *P* < 0.01 for pepsinogen I, and 30.2 ± 2.9 vs 14.9 ± 1.3 pg/ml, *P* < 0.01 for pepsinogen II). In both the dialysis patients and controls, those with *H. pylori* infection had significantly higher concentrations of serum pepsinogen I and II and a lower ratio of pepsinogen I to pepsinogen II than those without infection. Among the controls, 15 of 25 subjects with atrophic gastritis had a pepsinogen I/pepsinogen II ratio ≤ 3.0, while only two out of 17 patients on dialysis fell into this range.

**Conclusions.** We conclude that *H. pylori* status should be taken into account when serum pepsinogen concentrations are evaluated in dialysis patients.

**Key words:** dialysis; end-stage renal disease; gastritis; *Helicobacter pylori*; pepsinogen

Introduction

There are two immunochemically distinguishable pepsinogens in humans: pepsinogen I (PG I) and pepsinogen II (PG II). Both are secreted by the chief and mucous neck cells of the gastric fundus and corpus; PG II is also secreted by the pyloric glands in the antrum and Brunner’s glands in the proximal duodenum [1]. This topographical difference results in dissimilar behaviour of PG I and PG II in various gastric mucosal lesions [2,3]. It has been suggested that serum pepsinogen concentrations and the PG I/PG II ratio can be used for detecting patients at high risk of developing peptic ulcer diseases or gastric cancer [2–5]. The kidney is considered a key organ for eliminating serum pepsinogens [6], and serum pepsinogen concentrations are elevated in patients with impaired renal function [7,8]. Besides this, it is now evident that *Helicobacter pylori* infection of the stomach affects the serum pepsinogen concentrations in asymptomatic healthy persons [9].

Gastroduodenal lesions are common in patients with end-stage renal disease who are undergoing dialysis [10]. A recent survey showed that the prevalence of *H. pylori* in such patients is comparable with that in persons with normal renal function [11]. Nonetheless, there has been no report investigating the relationship between *H. pylori* infection of the stomach and the serum concentrations of pepsinogens in patients on dialysis. We therefore examined the effect of *H. pylori* infection on serum concentrations of PG I and PG II as well as the relationship between these parameters and gastric atrophy in dialysis patients.

Subjects and methods

**Subjects**

Subjects consisted of 49 patients on dialysis: 29 males and 20 females, mean age 52.2 ± 1.8 years. The etiologies of their renal disease were chronic glomerulonephritis in 30 patients;
diabetes mellitus in 13; nephrosclerosis in four, and autosomal dominant polycystic kidney disease in two. Forty one of the patients were on haemodialysis (HD), and eight were on continuous ambulatory peritoneal dialysis (CAPD). The mean duration of dialysis was 29.3 ± 5.4 months. Forty eight other patients who had no kidney disease were used as controls: 25 males and 23 females, mean age 48.6 ± 1.6 years. The mean age of the controls did not differ statistically from that of the patients on dialysis.

All subjects including the controls were referred for upper gastroduodenal endoscopy to investigate their gastrointestinal symptoms and signs. These included nausea, abdominal pain, heartburn, anorexia, anaemia, occult blood in the stools, etc. Patients who were treated with H₂-blockers or proton-pump inhibitors 2 weeks prior to the endoscopic examination or who took antibiotics 4 weeks prior to the endoscopy were excluded. Informed consent was obtained from all of the subjects.

Methods

Endoscopic examinations were performed after an overnight fast. The status of *H. pylori* infection was evaluated by methods described previously [12]. Briefly, at each endoscopy, three pairs of biopsy specimens were obtained from either the lesser or greater curvature of the antrum and the greater curvature of the corpus. *Helicobacter pylori* was determined by culture, histological examination and a urease test. Subjects in whom *H. pylori* was identified by at least two of the test methods were included in a group positive for *H. pylori* infection, while those in whom no *H. pylori* was found by any of the three methods were designated negative. Subjects in whom *H. pylori* was found by only one test were excluded from the study.

Prior to endoscopic examination, venous blood was drawn, and the serum concentrations of PG I and PG II were measured by radioimmunoassay (Dainabot, Tokyo, Japan) [13]. The normal ranges with this test kit are 15–100 pg/ml for PG I, and 3–40 pg/ml for PG II.

Statistical analyses

Results are expressed as mean ± SEM. Analysis of variance was used to compare the serum concentrations of PG I and PG II as well as the ratio of PG I and PG II. The unpaired t-test was used to compare the mean ages of patients on dialysis with those of the controls. Comparisons of proportions between the two groups were tested by Fisher’s exact test. A probability of <0.05 was considered significant.

Results

*Helicobacter pylori* was identified in 25 of 49 patients on dialysis (51.0%), and in 26 of the 48 control subjects (54.2%). Gastroduodenal lesions in dialysis patients were determined to be erosive gastritis in 21 patients, atrophic gastritis in 17, gastric ulcer in four, superficial gastritis in three, duodenitis in two, and duodenal ulcer in one; a normal gastric mucosa was seen in one patient. Among the control subjects, 25 lesions were identified as atrophic gastritis, six as erosive gastritis, five as superficial gastritis, three as gastric ulcer, two as duodenal ulcer, and two as gastric cancer; five subjects had normal gastric mucosa.

Respective mean values of the serum concentrations of PG I and PG II, and the PG I/PG II ratio were 277.4 ± 24.2 pg/ml, 30.2 ± 2.9 pg/ml and 9.2 ± 0.7 in the dialysis patients, and 52.6 ± 4.0 pg/ml, 14.9 ± 1.3 pg/ml and 3.5 ± 0.3 in the controls. All of these parameters were elevated significantly in the dialysis patients compared with the controls (P < 0.01).

Serum concentrations of PG I and PG II and mean PG I/PG II ratios in terms of *H. pylori* status are presented in Table 1. The *H. pylori*-positive dialysis patients had a higher PG I level than their *H. pylori*-negative counterparts. Among the subjects with *H. pylori* infection, those on dialysis had significantly higher concentrations of PG I than the controls. This was also the case among the subjects without *H. pylori* infection. The serum PG II concentrations in subjects with *H. pylori* infection were significantly higher than in those without infection in both dialysis patients and controls. A comparison of the *H. pylori*-positive patients on dialysis and the *H. pylori*-positive controls showed significantly higher values in the former. On the contrary, PG II levels did not differ significantly between the *H. pylori*-negative groups. Subjects who were infected with *H. pylori* showed significantly lower PG I/PG II ratios than those who were not infected in both the dialysis and control groups. The PG I/PG II ratio in the *H. pylori*-positive patients on dialysis was significantly elevated in comparison with that of the *H. pylori*-positive controls. The same difference was observed in the *H. pylori*-negative groups.

Serum concentrations of PG I and PG II and the PG I/PG II ratios in dialysis patients treated by different dialysis methods are shown in Table 2. The values in patients on a HD and those on CAPD were comparable between the *H. pylori*-positive and -negative groups.

The PG I/PG II ratios of the patients who showed endoscopic atrophic gastritis are presented in Figure 1. Dialysis patients in this group showed significantly higher ratios than the controls: 9.2 ± 2.2 and 3.5 ± 0.7, respectively, P < 0.01. Among the controls, 15 of 25 subjects (60.0%) with atrophic gastritis showed PG I/PG II ratios ≤3.0, but only two of 17 patients on dialysis fell into this range (11.8%, P < 0.01 compared with the controls).

Discussion

The present study showed serum concentrations of PG I and PG II to be significantly elevated in dialysis patients when compared with controls. Our findings agree with the previous reports in patients with chronic renal failure [2,6–8]. Among dialysis patients, those infected with *H. pylori* had higher serum PG II concentrations and lower PG I/PG II ratios than those who were not infected with this bacterium. The same pattern has been shown in asymptomatic healthy subjects [9]. To our knowledge, however, the present study is the first examining the effects of *H. pylori* infection on the serum pepsinogens in dialysis patients.
Table 1. Serum pepsinogen concentrations

<table>
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<tr>
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<th>Dialysis patients</th>
<th>Controls</th>
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<tbody>
<tr>
<td></td>
<td>( H. pylori )-positive ( (n=25) )</td>
<td>( H. pylori )-negative ( (n=24) )</td>
</tr>
<tr>
<td>PG I (pg/ml)</td>
<td>346 ± 39.1*****</td>
<td>206 ± 20.0***</td>
</tr>
<tr>
<td>PG II (pg/ml)</td>
<td>43.1 ± 4.3***</td>
<td>16.8 ± 1.3</td>
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<tr>
<td>PG I/PG II</td>
<td>8.0 ± 0.8***</td>
<td>12.2 ± 0.9***</td>
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**Significant at \( P < 0.01 \); ***significant at \( P < 0.001 \) compared with the \( H. pylori \)-negative counterparts.

Table 2. Serum pepsinogen concentrations in patients treated with different dialysis methods

<table>
<thead>
<tr>
<th></th>
<th>Haemodialysis</th>
<th>CAPD</th>
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<tr>
<td></td>
<td>( H. pylori )-positive ( (n=20) )</td>
<td>( H. pylori )-negative ( (n=21) )</td>
</tr>
<tr>
<td>PG I (pg/ml)</td>
<td>319 ± 44.5</td>
<td>208 ± 20.7</td>
</tr>
<tr>
<td>PG II (pg/ml)</td>
<td>43.2 ± 5.3**</td>
<td>16.7 ± 1.4</td>
</tr>
<tr>
<td>PG I/PG II</td>
<td>7.4 ± 1.0**</td>
<td>12.4 ± 0.9</td>
</tr>
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**Significant at \( P < 0.01 \) compared with the \( H. pylori \)-negative counterparts.

In the general population, participation of serum pepsinogens in gastroduodenal disorders has been suggested by the following observations [1]: serum pepsinogen levels reflect secretory cell mass of the gastric mucosa; pepsinogens secreted into the gastric lumen are converted to pepsins which possess a potent proteolytic activity; and hyperpepsinogenaemia is a risk factor for peptic ulcer diseases. Until now, however, correlation between serum pepsinogen levels and gastroduodenal lesions, or the influence of hyperpepsinogenaemia on gastric acid secretory function has not been studied for dialysis patients. Moreover, multiple factors appear to contribute to gastritis as well as peptic ulcer diseases in patients with chronic renal failure [14]. Therefore, the pathogenetic implication of hyperpepsinogenaemia in gastroduodenal lesions, if any, remains to be defined in dialysis patients.

Although the mechanism by which \( H. pylori \) infection produces hyperpepsinogenaemia remains unknown, it has been suggested that inflammation of the gastric mucosa induced by \( H. pylori \) may increase leakage of pepsinogens into the systemic circulation [15]. Dialysis patients with \( H. pylori \) infection, on the other hand, have elevated concentrations of serum gastrin [11,12]. We have shown recently that dialysis patients infected with \( H. pylori \) had significantly higher concentrations of serum gastrin than those who were not infected, in spite of comparable atrophic changes of the gastric mucosa (unpublished data). We have also demonstrated the resolution of hypergastrinaemia after successful eradication of \( H. pylori \) in such patients [16]. Therefore, it seems possible that the hypergastrinaemia seen in dialysis patients is attributable to \( H. pylori \) infection of the stomach, rather than a loss of renal function or gastric atrophy. Gastrin possesses a trophic action on gastric mucosal cells [17], leading to an increase in chief cell mass. Gastrin also stimulates pepsinogen secretion from gastric chief cells by increasing the free cytoplasmic calcium concentration [18]. Accordingly, we speculate that serum pepsinogens can...
be elevated in dialysis patients with *H. pylori* infection by the increase in serum gastrin levels. Whatever the mechanism is, our findings indicate that *H. pylori* infection affects serum pepsinogens in dialysis patients similarly to subjects without any kidney disease. This implies that *H. pylori* status should be taken into account when serum pepsinogen concentrations are evaluated in dialysis patients.

The serum PG II concentrations were comparable between the *H. pylori*-negative dialysis patients and the *H. pylori*-negative controls, whereas serum PG I levels were significantly higher in the former than in the latter. Thus, PG I appears to accumulate more than PG II in dialysis patients. This suggests that the elimination of PG I and PG II from the systemic circulation by dialysis may not be the same. In subjects with normal renal function, it has been shown that the metabolism of PG I and PG II in the kidney is not the same in spite of the similar molecular weights and radii of both pepsinogens [19,20]. The reasons for the different metabolic properties of PG I and PG II remain obscure.

The present study showed no significant differences in PG I, PG II or the PG I/PG II ratio between patients on HD and those on CAPD. However, it should be noted that the numbers of subjects in each dialysis group were small. Thus, further study with an increased number of subjects is needed to see whether different dialysis methods affect serum pepsinogen concentrations.

Among the control subjects of the present study, 25 cases out of 48 had atrophic gastritis. A high incidence of atrophic gastritis agrees with a recent study for Japanese adults [21]. This phenomenon seems to be attributable to the high prevalence of *H. pylori* infection in persons over 40 years old in Japan [9,21].

Since patients with severe atrophic gastritis are at an increased risk of developing gastric cancer [22], there has been an attempt to use serum pepsinogen concentrations and the PG I/PG II ratio for non-invasive screening of individuals at risk [4,5]. A PG I/PG II ratio of 3.0 has been proposed as a cut-off point for the screening test [4]. However, we found that a substantial number of dialysis patients with atrophic gastritis exhibited PG I/PG II ratios >3.0. The reason for this is that PG I tends to be elevated more than PG II, leading to further elevation of the PG I/PG II ratio in dialysis patients. The question of whether dialysis patients have a greater incidence of gastric cancer than the normal population is still unanswered [23], but it is clear from our study that the absolute value of these parameters cannot be applied in screening patients on dialysis. To confirm our observations further, correlation between serum pepsinogen levels and histologic changes of the gastric mucosa must be examined.

In conclusion, we found that *H. pylori*-positive patients on dialysis had higher concentrations of serum PG I and PG II, and a lower PG I/PG II ratio than did *H. pylori*-negative patients. This suggests that *H. pylori* infection in the stomach has a role in the hyperpepsinogenaemia experienced by patients on dialysis.

References


Received for publication: 16.6.98
Accepted in revised form: 6.10.98