Morpho-functional comparisons in *Helicobacter pylori* – associated chronic atrophic gastritis

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Abstract

Purpose: To evaluate serum pepsinogen I (PG I) and gastrin-17 (G-17) levels in patients with *Helicobacter pylori* (*H. pylori*) – associated chronic atrophic gastritis, with reference to endoscopical Kimura-Takemoto's staging, chromoendoscopical and histological features.

Material and methods: 267 dyspeptic *H. pylori*-infected patients were examined by chromoendoscopy with biopsy sampling according to the Sydney System and according to Kimura-Takemoto's scale. Simultaneous assessment of serum pepsinogen I (PG I) and gastrin-17 (G-17) levels by enzyme immunoassay was performed. The serologic and morphologic results were compared with correlation analysis.

Results: There was strong reverse correlation between the stomach mucosal atrophy (antral part or corpus) and the proper serologic markers (respectively, G-17 or PG I) in *H. pylori*-associated chronic gastritis when gastric biopsies taken according to the Sydney System were assessed. The use of Kimura-Takemoto's scale has revealed the decrease of serum PG I levels only at O-2 and O-3 grades of the corpus mucosa atrophy. Probably, these results reflects the development of functional failure of the stomach corpus mucosa at late stages of atrophy when its compensatory capacity becomes insufficient. There were not any advantages in sampling biopsies for the detecting of intestinal metaplasia (IM) by the Sydney System, or by Kimura-Takemoto's scheme. The obvious concordance between histologically proven extent of IM and the number of IM foci detected by chromoendoscopy has been revealed.

Conclusions: The biopsy sampling for the diagnosis of precancerous changes of the stomach mucosa after non-invasive screening of atrophic gastritis (e.g., by means of EIA) should be based preferably on the visual signs acquired via chromoendoscopy than through routine endoscopy, independently of the scheme of examination of stomach mucosa, either according to the Sydney System, or to the Kimura-Takemoto's scale.

Key words: *Helicobacter pylori*, pepsinogen I, gastrin-17, atrophy, intestinal metaplasia, chromoendoscopy.

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Introduction

Helicobacter pylori (*H. pylori*) is a major causative agent in the pathogenesis of chronic active gastritis, duodenal and gastric ulcer [1]. There is a strong evidence that *H. pylori* infection may be associated also with gastric carcinoma and low-grade MALT lymphoma [2]. Our knowledge of the pathogenesis of gastric neoplasms is therefore increasing, and new approaches to the prevention of gastric cancer by eradication treatment of gastric precancerous diseases, mainly *H. pylori* gastritis, can be considered. *H. pylori* infection causes the development of infiltration of gastric mucosa by mononuclear cells and neutrophils, the latter can serve as a marker for the activity of gastritis. Chronic active inflammation is ultimately accompanied by a replacement of the gastric foveolae by a regenerative type of epithelium and a decrease in the production of mucus [3]. Besides, this damage leads to a persistent state of proliferation and regeneration, and thus increases the risk of malignant alterations of the gastric stem cells at the neck region of the gastric tubes [4]. As a consequence, the multifocal features such as atrophy, intestinal metaplasia, and epithelial dysplasia may be found in association with *H. pylori* infection. In turn, atrophic gastritis and intestinal metaplasia have been considered precursor lesions of

intestinal type of gastric cancer [5]. The effect of eradication of *Helicobacter pylori* on the prevention or regression of atrophy and IM has not been fully elucidated. The point of no return at which such a regression is possible is not known [6]. This subject is very important, because it has a great influence on a strategy of gastric cancer prevention. It has been shown that the extent and topography of *H. pylori*-associated gastritis differs when compared with age- and sex-matched patients having peptic ulcer or merely gastritis. It appears that patients with gastric cancer have much more severe gastritis in the corpus of the stomach in contrast to the antrum-predominating gastritis in duodenal ulcer patients [7]. That pronounced gastritis in the corpus may be involved in the development of gastric cancer can be explained by the finding of a decrease in acid production associated with a shift in the distribution of gastritis toward the corpus [8]. This reduction in local acid production might then result in the suppression of a defense mechanism against dedifferentiated epithelium – since atypical cells are very acid sensitive – and might thus lead to persistence and progression of atypical cells [9].

The gastric mucosa can be evaluated by gastrointestinal endoscopic examination with biopsy [10], but this is an invasive and expensive technique. Easier objective methods for evaluating gastritis and *H. pylori* infection are needed. Of course, *H. pylori* infection can be diagnosed by the assay of anti-*H. pylori* antibodies, the urease test, culture or Giemsa stain of gastric mucosa, or the urea breath test. However, measurement of serum pepsinogen is easier and does not require special equipment or techniques. The concentration of serum pepsinogen, which is an ordinary zymogen of pepsin in gastric mucosa, is known to be a marker of atrophic gastritis [11], as well as being a marker of *H. pylori* infection and eradication [12]. Moreover, gastric mass screening can be performed by assays of serum pepsinogen concentrations [13]. The same is true about measurement of serum gastrin for the non-invasive detection of gastric antral atrophy [14]. Previously, we have found that non-invasive detection of atrophic gastritis requires further endoscopy with histological examination for the recognition of possible progression of atrophy into IM, dysplasia or carcinoma [15], so it is critically important to be sure that the method of endoscopy would allow the adequate biopsy sampling from the irregularly distributed foci of above mentioned preneoplastic changes of stomach mucosa.

The aim of the present study was to evaluate serum pepsinogen I (PG I) and gastrin-17 (G-17) levels in patients with *Helicobacter pylori*-associated chronic atrophic gastritis, with reference to endoscopical Kimura-Takemoto's staging, chromoendoscopical and histological features.

Material and methods

The study was carried out according to updated Declaration of Helsinki in a group of 267 dyspeptic *H. pylori*-infected patients (175 female, 92 male, aged from 15 to 89 years, in average 61.7±13.0 years), after informed consent for examinations. Any eventual medication with proton pomp inhibitors, H2 antagonists and NSAIDs were excluded for at least one month before examinations. The diagnostic test was histology in 267 cases; 158 cases were diagnosed by chromoendoscopy using the methylene blue dye scattering method and 109 – by endoscopy using the Kimura-Takemoto endoscopic classification [16]. The assessment of the type of mucosal atrophy according to Kimura-Takemoto's grading was as follows: C-0 – absence of atrophy, C-1 – pyloric mucosal atrophy, C-2 – atrophy on a lesser curvature of a lower third of the stomach, C-3 – the atrophy on a lesser curvature of a middle third of stomach, O-1 – a border of an atrophy is between lesser curvature and anterior wall; O-2 – atrophy within the limits of an anterior wall of a stomach; O-3 – the area of atrophy is distributed from anterior wall to the major curvature of the stomach. Biopsy specimens were fixed in 10% formalin, embedded in paraffin, cut in sequential 5 μm sections, and stained with hematoxylin and eosin, PAS/alcian blue (pH 2.5), and Giemsa stain. The grade of the stomach mucosal atrophy was estimated from 0 to 3 according to Houston visual analogous scale [10]. Fasting serum *H. pylori* antibodies (Hp-Ab), serum levels of PG I and G-17 were assayed by enzyme immunoassay (EIA) with Biohit GastroPanel® (Biohit Plc, Helsinki, Finland). According to the instruction of manufacturer, serum levels of PG I <25 μg/l were accepted as markers of gastric corpus atrophy; serum levels of G-17 <5 pmol/l were estimated as markers of gastric antral atrophy; serum levels of G-17 <10 pmol/l in a combination with serum levels of PG I <50 μg/l were estimated as markers of mild gastric corpus atrophy. Hp-Ab IgG titers were estimated as follows: <32 EIU (EIU – enzyme immunoassay unit) – negative result; 32-44 EIU – doubtful result; >44 EIU – positive result. The numerical meanings of assayed parameters were analyzed by the program GastroSoft® (Biohit Plc, Helsinki, Finland) enclosed to test-system Biohit GastroPanel®. On the basis of inserted data, the program composed the diagnosis in a view of the presence or absence of *H. pylori*-infection and mucosal atrophy, with estimating of gastric cancer or peptic ulcer risk and with recommendations on the treatment according to Maastricht-2 consensus.

The statistical analysis was used to estimate the mean values of investigated parameters and to calculate statistical significance of received data by Mann-Whitney criterion, and by the Spearman's correlation coefficient (r_s).

Results

According to EIA data, the absence of the corpus mucosal atrophy was detected in 155 patients, mild corpus atrophy – in 33 patients, moderate corpus atrophy – in 48 patients, and severe corpus atrophy – in 31 patients. The corresponding values of serum PG I are presented in *Tab. 1*.

The absence of antral mucosal atrophy was detected in 14 patients, mild antral atrophy – in 40 patients, moderate antral atrophy – in 94 patients, and severe antral atrophy – in 119 patients. The corresponding values of serum G-17 are presented in *Tab. 2*.

The correlation analysis has revealed strong reverse correlation between the presence and the degree of stomach corpus atrophy and the serum levels of PG I (r_s = -0.63; $P<0.05$). Simi-

***Table 1*. The mean values of serum PG I at different degrees of the stomach corpus musocal atrophy (μg/l) in chronic gastritis**

	Mean	95% confidence interval	σ	Number of patients
No atrophy	133.30	-10.63 – 277.23	71.96	155
Mild atrophy	42.61*	-21.10 – 106.31	31.85	33
Moderate atrophy	18.66*	-19.31 – 56.63	18.98	48
Severe atrophy	7.79*	-1.21 – 16.78	4.49	31
Total				267

*P<0.05 compared to non-atrophic state and to previous degree of atrophy

***Table 2*. The mean values of serum G-17 at different degrees of the stomach antral musocal atrophy (pmol/l) in chronic gastritis**

	Mean	95% confidence interval	σ	Number of patients
No atrophy	15.46	3.15 – 27.78	6.16	14
Mild atrophy	8.71*	3.49 – 13.94	2.61	40
Moderate atrophy	6.15*	2.61 – 9.70	1.77	94
Severe atrophy	1.31*	-2.34 – 4.95	1.82	119
Total				267

*P<0.05 compared to non-atrophic state and to previous degree of atrophy

***Table 3*. The mean number of foci of chromoendoscopically detected intestinal metaplasia (IM) in relation to histological detection of IM in *Helicobacter pylori* – associated atrophic gastritis**

	Mean	95% confidence interval	σ	Number of patients
No IM	1.05	0.5 – 1.6	0.27	51
Mild IM	5.04*	-17.24 – 27.32	11.14	50
Moderate IM	8.85*	1.09 – 16.60	3.88	38
Severe IM	23.89*	-11.50 – 59.29	17.70	19
Total				158

*P<0.05 compared to non-metaplastic state and to previous degree of IM

larly, we have observed the strong reverse correlation between the presence and the degree of stomach antral atrophy and the serum levels of G-17 (r_s = -0.73; P<0.05). There were no any marked correlations between serum Hp-Ab IgG titers and the presence and the degree of stomach corpus or antral atrophy (the values of r_s, respectively, 0.12 and 0.14; P>0.05 for both corpus or antral mucosa).

Among 158 patients, which were undergone chromoendoscopy, there were 107 histologically proven cases of intestinal metaplasia (IM), 50 patients of them had mild IM, 38 – moderate IM, and 19 – severe IM. Fifty one patients had no histological features of IM (*Fig. 1*).

We have compared the histologically detected extent of IM and the number of foci of IM detected by chromoendoscopy (*Tab. 3*). The results have confirmed the high accuracy of chromoendoscopy in distinguishing IM in atrophic gastritis (r_s = 0.92; P<0.05).

***Figure 1*. The prevalence of intestinal metaplasia (IM) in the patients with *Helicobacter pylori* – associated chronic atrophic gastritis**

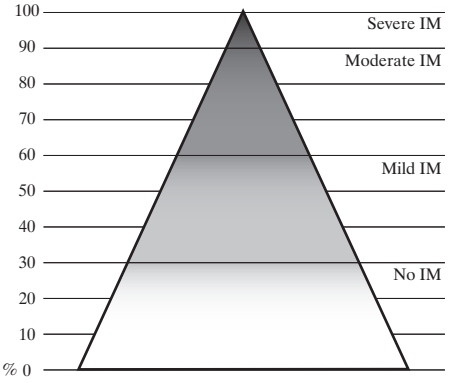
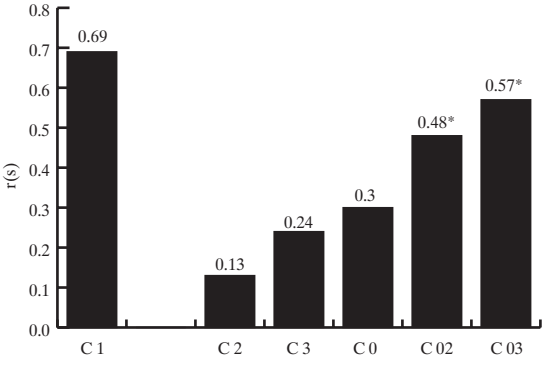


***Figure 2*. Correlations (r_s) between the results of EIA (serum G-17 levels for C 1, serum PG I levels for C 2 – O 3) with the type of stomach mucosal atrophy according to Kimura-Takemoto's grading** (*P<0.05 compared to C2 – O1 stages)



Further, we have compared the results of EIA with the type of stomach mucosal atrophy according to Kimura-Takemoto's grading (*Fig. 2*). There was strong reverse correlation between serum G-17 level and the presence of C-1 grade of stomach mucosal atrophy (antral). On the contrary, the correlations in the corpus of the stomach were not so obvious, and reached the significant values beginning from O-2 grade of corpus atrophy. So, the progression of corpus mucosal atrophy was accompanied with functional disorders only when the vast majority of gastric glands disappeared.

Discussion

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. The discovery of *H. pylori* has led to a reassessment of the importance of aging and has focused on the long-term effects of *H. pylori* infection and its role in the development of atrophic gastritis [17]. The updated Sydney

System allows precise histologic evaluation of gastritis [10], but requires gastrointestinal endoscopy and biopsy, which are invasive, expensive, and uncomfortable methods. Of course, as gastrointestinal endoscopic examination is the most accurate method of examination for gastric diseases, especially gastric malignancy, it should be used for patients exhibiting any relevant symptoms. However, in follow-up studies and screening of asymptomatic subjects, an easier and less expensive method is required.

The serum pepsinogen level reflects the secretory function of the gastric glands. Its levels decreased significantly in the patients with chronic atrophic gastritis, an important precursor of gastric carcinoma [11]. It has been suggested that the measurement of serum pepsinogens could identify people at high risk for gastric cancer. Chronic atrophic gastritis is believed to be an important premalignant condition for the development of gastric carcinoma, particularly the intestinal type [18]. The serum PG I/II ratio has been found to be reduced in gastric carcinoma, as pepsinogen I decreases proportionally more than pepsinogen II. In contrast, the serum level of gastrin was increased in atrophic corpus gastritis [19]. In Japan, where studies have shown a high prevalence of chronic gastritis, the serum pepsinogen level has been studied as a mass screening tool for the detection of gastric cancer. The Kimura-Takemoto's scale for the evaluation of gastric mucosa morphology was used in these studies [20].

Screening by using serum pepsinogen has advantages over other methods such as endoscopy and barium studies. It is simple and inexpensive, and there is no radiation hazard. In our study, there was strong reverse correlation between the presence and the degree of stomach mucosal atrophy (antral part or corpus) and the proper serologic markers (respectively, G-17 or PG I) in *H. pylori*-associated chronic gastritis when we assessed gastric biopsies taken according the Sydney System. However, the use of grading the stomach mucosal atrophy according to Kimura-Takemoto's scale has brought us some different results concerning the serum levels of PG I at various extent of corpus atrophy. We observed the decreasing of serum PG I levels only at O-2 and O-3 grades of corpus atrophy. In our opinion, these results reflects the development of functional failure of the stomach corpus mucosa at late stages of atrophy when its compensatory capacity becomes insufficient. In general, we could not find any advantages in sampling biopsies for detecting IM by the Sydney System recommendations, or by Kimura-Takemoto's scheme. Similar results are reported by Asaka et al. [21]. We can not agree with the interpretation of So et al. [22] results, showing an increase in serum PG I and II levels and a lower PG I/II ratio in gastric cancer patients. In their study, the gastric atrophy was present in a small proportion of patients with gastric cancer and the authors conclude that atrophic gastritis may not be an essential stage in gastric carcinogenesis. Hence, in their meaning, the serum pepsinogen measurement is not useful for the screening of gastric cancer in the investigated population. In contrast, many other studies have shown the correlation between the serum PG levels and the extent of atrophic gastritis.

Kreuning et al. [23] reported that serologic parameters in healthy volunteers were related to specific histologic features of the gastric body. Kawaguchi et al. [24] also confirmed that PG correlated well with the grade of atrophic gastritis regardless of the age or sex of patient. Kiyohira et al. [25] investigated the utility of serum PG concentrations for the diagnosis of *H. pylori* infection and the objective evaluation of histologic gastritis. The authors also investigated whether *H. pylori* infection could be diagnosed via serum PG concentrations alone. Kuipers et al. [26], Asaka et al. [27], and Knight et al. [28] have shown, that the serum concentrations of PG I and PG II increased and the I/II ratio decreased in *H. pylori* infection. Cave et al. [29] hypothesized that *H. pylori* leads to increased PG secretion. In patients with no or mild atrophy, both serum PG I and PG II concentrations were increased. The mass of chief cells decreases with the progression of atrophy, with chief cells gradually being replaced by pyloric gland cells. Serum PG I concentrations then decrease, but serum PG II concentrations continue to increase. Consequently, the PG I/II ratio decreases. In marked atrophy, both serum PG I and PG II concentrations decrease and the PG I/II ratio shows a marked fall.

Recently, several studies have demonstrated that successful treatment of *H. pylori* infection significantly reduces serum PG concentrations, significantly increases the PG I/II ratio, and clearly improves histological findings within approximately 1 month [12,30]. Therefore, these parameters may be useful for monitoring of anti-*H. pylori* treatment efficacy. Gastric mucosal evaluation by serum PG concentrations is an inexpensive, noninvasive, simple, and objective method.

Another important issue is revealing the intestinal metaplasia in *H. pylori*-associated atrophic gastritis. As the serum pepsinogen I/II ratio was known to be a good marker for gastric atrophy [31], Asaka et al. [21] hypothesized that the development of atrophic gastritis and intestinal metaplasia in the gastric mucosa was strongly associated with *H. pylori* infection. Recently the authors performed a case-control study of 85 asymptomatic healthy adults recruited from a health screening center in Sapporo [32]. All subjects underwent endoscopy and gastric biopsy. The prevalence of atrophic gastritis and intestinal metaplasia as assessed by pathological findings was significantly greater in those with *H. pylori* infection compared with those without *H. pylori* infection. The later study [21] was a large scale multicenter study involving different regions in Japan using three different methods to assess the prevalence of atrophic gastritis as well as evaluation of the presence of intestinal metaplasia by endoscopic biopsy. The authors have found that both atrophic gastritis and intestinal metaplasia were strongly associated with *H. pylori* infection and not with aging per se, and that the tight link is present between *H. pylori* infection, atrophic gastritis and intestinal metaplasia. The high prevalence of the precursor lesion, atrophic gastritis with intestinal metaplasia among those with *H. pylori* infection suggests that the risk of development of early gastric cancer will continue to remain high until *H. pylori* is eliminated either naturally or by therapy. Nomura et al. [33] have reported that persons with both *H. pylori* or CagA seropositivity and a low PG I level or PG I/II ratio are highly susceptible to development of noncardia gastric cancer. Hartleb et al. [34] have recently stated that the test panel composed of pepsinogen I and protein stimulated gastrin-17 may be used as the "serological gastric biopsy" detecting multifocal atrophic gastritis. The diagnostic sensitivity of this test panel is not

increased by knowledge of *H. pylori* status. Previously, we have shown similar results, with strong correlation between detection of IM by chromoendoscopy and by histology [15]. Our present study has confirmed these results in another group of patients, and there has been the obvious concordance between histologically detected extent of IM and the number of foci of IM detected by chromoendoscopy.

Conclusions

The natural history of *Helicobacter pylori*-associated atrophic gastritis is a permanent progression of the extent and severity of atrophy with ultimate imbalance between proliferation and differentiation leading to the development of intestinal metaplasia and dysplasia. The latter have patchy distribution through the stomach mucosa and, thus, the biopsy sampling for the diagnosis of precancerous changes of stomach mucosa after non-invasive screening of atrophic gastritis (e.g., by means of EIA) should be based preferably on the visual signs acquired via chromoendoscopy rather than through routine endoscopy. It holds true independently of the scheme of examination of the stomach mucosa, would it be based either on the Sydney System, or the Kimura-Takemoto's scale.

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