Review Article

Increased Serum Pepsinogen II Level as a Marker of Pangastritis and Corpus-Predominant Gastritis in Gastric Cancer Prevention

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Abstract

Serum pepsinogen I and II are considered as indicators of changes in gastric morphology. Important publications from the last decades are reviewed with regard to the serum level of these biomarkers for the diagnosis of normal gastric mucosa, diffuse gastritis and its change to atrophic gastritis and intestinal metaplasia as well as gastric cancer. Due to the low sensitivity of serum biomarkers for diagnosis of gastric cancer, especially at its early stage and the poor prognosis of the tumor at the time of diagnosis, its prevention by eradication of *H. pylori* remains the mandatory strategy. On the other hand, the severity of regression and non-reversibility of precancerous lesions and intestinal metaplasia in gastric mucosa through eradication of *H. pylori* make it necessary to diagnose diffuse gastritis at its early stage. Increased serum pepsinogen II compared to normal serum pepsinogen I seems to indicate the presence of diffuse gastritis without precancerous lesions suitable for eradication of *H. pylori* infection, when it is serologically positive. A diagram illustrates the strategy of this therapeutic measure depending on the age of people and the level of serum biomarkers in areas with high gastric cancer prevalence.

Keywords: Gastric cancer prevention, serum pepsinogen II

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Introduction

Gastric cancer is the leading cancer in men in some areas such as northern Iran, East Asia, Eastern Europe, and South America.[1] Due to the poor prognosis of this tumor and its late detection till metastases, its successful resection is usually impossible, making the prevention of gastric cancer an essential goal in areas with high prevalence of this tumor. The intestinal type of gastric cancer mostly develops on the basis of precancerous lesions that form long time before its occurrence. Precancerous lesions might be the sequel of *H. pylori*-induced gastritis. Gastritis in some individuals may progress from antrum to corpus (pangastritis) and become more severe (corpus-predominant gastritis) and cause atrophy and intestinal metaplasia, which are the main precancerous lesions. The *H. pylori*-induced gastritis might be reversed by eradication of *H. pylori*, when the gastritis is not advanced and not associated with intestinal metaplasia, as we have published before.[2] Therefore, the diagnosis of pangastritis and corpus-predominant gastritis without intestinal metaplasia becomes important for effective prevention of gastric cancer. As mass endoscopic screening in areas with high prevalence of gastric cancer is expensive in low income countries, serum biomarkers for diagnosis of non-advanced gastritis remains an important step toward selection of high risk individuals for *H. pylori* eradication. For this review, we selected 815 out of more than 1500 articles addressing pepsinogen and focused on 32 articles with serum pepsinogen II and gastric morphology in connection with our studies.

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Serum biomarkers for state of gastric morphology

In 1952, Mirsky *et al.* reported that the protease activities in serum are indicators of the capacity of gastric acid secretion.[3] These proteases include two enzymes: pepsinogen I and II. They were characterized by Rapp and coworkers[4–5] as well as by Samloff *et al.*[6] Pepsinogen I is localized in main cells of corpus mucosa close to parietal cells. Pepsinogen II is produced in all areas of gastric mucosa, including the duodenal bulb.[7–8] After gastrectomy, both enzymes decrease to very small, negligible amounts in serum.[9–10] While pepsinogen I is expressed very rarely in gastric neoplasms,[11–12] pepsinogen II is expressed more in differentiated rather than the undifferentiated tumor and is also released in the serum. The expression of pepsinogen II in tumor tissue is a useful marker of tumor outcome.[11]

It is the merit of Samloff *et al.* who introduced the radioimmunoassay measurement of these two proteins in serum[6] and intensively studied the relation between gastric morphology and the serum level of pepsinogen I and pepsinogen II as well as the ratio of pepsinogen I to II in patients with pernicious anemia[13] and in stomach remnant of patients with peptic ulcer after partial gastrectomy. Both enzymes increase in serum with the occurrence of superficial gastritis in antrum and corpus. While the serum level of pepsinogen I decreases with progression of superficial gastritis to atrophic gastritis and metaplastic glandular forms in corpus, the serum level of pepsinogen II inversely increases and remains high, as we have previously reported.[14] Thus, the ratio of pepsinogen I to II, as well as the absolute values of pepsinogen II, reflect the morphologic state of gastric mucosa in corpus and provide a "serologic biopsy" of gastric mucosa. The calculated sensitivity and specificity of these tests for atrophic gastritis were 80% and 73%, respectively.[15] In a Swedish study, 976 subjects underwent endoscopy along with biopsy sampling from different gastric areas and serum pepsinogen I and pepsinogen II measurement. The sensitivity and specificity of these biomarkers for the diagnosis of atrophic gastritis in corpus were 71% and 98%, respectively.[16]

In another study from Sweden, the sensitivity and specificity of measuring *H. pylori* antibody along with pepsinogen I, for the diagnosis of gastritis were 98% and 84%, respectively.[17] In 207 consecutive patients with gastric morphologic examination, negative *H. pylori* antibody in young patients and normal pepsinogen I level in serum of patients older than 45 years predicted normal gastric mucosa without inflammation.[18] In a study from European countries, a ratio of pepsinogen I to pepsinogen II smaller than 4.7 was found to have respective sensitivity and specificity values of 77.1% and 87.4% for the diagnosis of corpus-predominant gastritis.[19]

In recent years, serum ghrelin has been proposed to be a sensitive test for the diagnosis of atrophic gastritis. [20–21] It was more accurate than the ratio of pepsinogen I to II.[20] Clinical studies should verify the efficacy of this serum marker compared with pepsinogen I and II in future.

Serum biomarkers for gastric cancer screening

In a Japanese study on patients with gastric cancer and controls, pepsinogen I less than 50 ng/mL and a ratio of pepsinogen I to II smaller than 3 had sensitivity, specificity, and accuracy of 55%, 75%, and 72%, respectively for diagnosis of gastric cancer.[22] In an earlier study, among 7498 Japanese men examined from 1967 to 1970, 48 patients developed gastric cancer over 44 months. A low serum pepsinogen I was found in 15 of them and in only 6 of 98 matched controls (31.2 % versus 6.3%).[23] In a case-control study in China, the ratio of pepsinogen I to pepsinogen II or serum level of pepsinogen II alone correlated well with gastric cancer occurrence.[24] In another study in Portugal, by setting cut-off values for pepsinogen I less than 70 ng/mL and a pepsinogen I to II ratio of <3 in serum in 13,118 participants over 5 years, 446 cases had a positive test (3.4% of all). By endoscopic examination of 274 subjects with a positive test, 9 patients with gastric cancer and among 240 participants with negative test only 3 patients with gastric cancer were detected. The sensitivity, specificity, positive, and negative predictive values were 67%, 47%, 2%, and 99%, respectively.[25] In a Chinese study, among 3654 subjects, from whom 2290 underwent endoscopy, the endoscopic strategy detected more early gastric cancer and high grade intraepithelial neoplasia than the pepsinogen tests alone (29 vs. 21 cases).[26] In 108 patients younger than 40 years with gastric cancer, low pepsinogen I and high pepsinogen II level had combined sensitivity of 75% and specificity of 75% for the diagnosis of early gastric cancer.[27] In a mass screening of asymptomatic middle-aged Japanese, those with positive pepsinogen test (pepsinogen <70 ng/mL and Pepsinogen I to II ratio <3) and with negative test underwent routine endoscopy every 2–5 years. A total of 65.1% of patients with planned gastroscopy underwent the endoscopic procedure. A total of 125 cases of gastric cancer were detected. Only 0.12% of all participants and 0.91% of those with gastroscopy had early stage of gastric cancer and intra-mucosal neoplasia.[28] Forty two out of 81 symptomatic gastric cancer patients from north Iran (51.8 %) had normal serum pepsinogen I (>70 ng/mL) and high pepsinogen I to pepsinogen II ratio (>5).[29]

In a population-based cohort study over a period of 14 years, covering 2742 residents aged 40 years and above in Japan, 97 subjects developed symptomatic cancer. Out of these symptomatic patients, 61 patients (62.8%) had an initial pepsinogen I level <70 ng/mL and a pepsinogen I/II ratio of <3. The serum marker was a good predictor of intestinal type of gastric cancer.[30]

In a meta-analysis of 42 individual studies, based on a pepsinogen I level ≤70 ng/mL and pepsinogen I to II ratio of ≤3, the pooled pairs of sensitivity was 77% and the false positive rate was 27% for gastric cancer. The positive predictive value was between 0.77% and 1.25% and the negative predictive value was between 99% and 99.9%.[31]

All of these clinical studies, most of which were performed in Japan and China, showed that the measurement of serum biomarkers for detection of asymptomatic gastric cancer can be useful for identifying only a few cases of gastric cancer in an earlier stage. All patients with gastric cancer and normal serum biomarkers remained unrecognized. Therefore, the prevention of gastric cancer development regarding the unfavorable prognosis of the tumor at the time of its detection is the logic agenda for action that should be settled. The unfavorable prognosis of the tumor at the time of its detection and the fact that some of gastric cancer patients have normal serum biomarkers and are not detectable by screening, make implementing preventive measures of gastric cancer development indispensable.

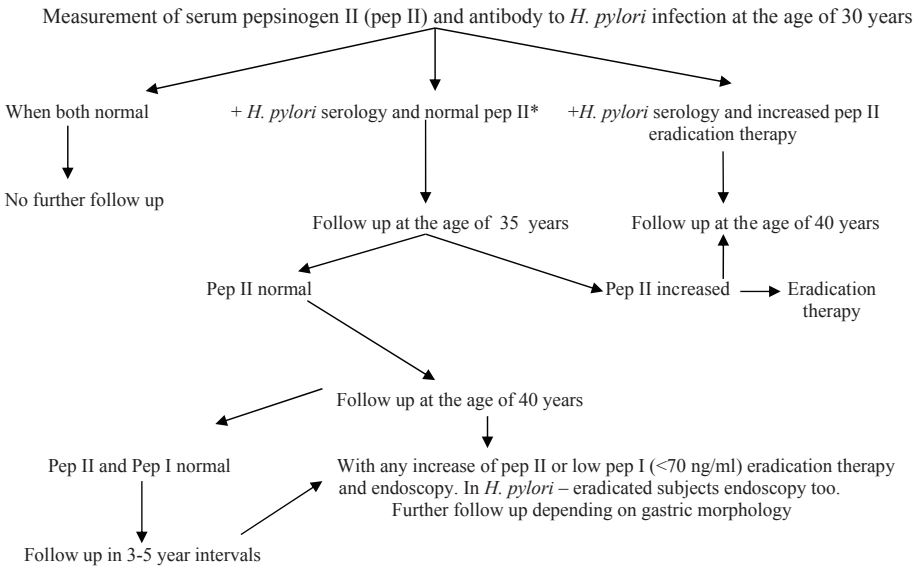
Serum biomarkers for prevention of gastric cancer

The follow up of patients in areas with high prevalence of *H. pylori* infection showed that gastric cancer occurs mostly in infected individuals.[32] Thus, the eradication of *H. pylori* was considered to be a successful and promising method for prevention of gastric cancer by reducing gastritis and elimination of environmentally induced factors for carcinogenesis. Eradication of *H. pylori* prevented the occurrence of metachronous gastric cancer after endoscopic resection of the primary tumor.[33] While many case-control studies performed in Japan had demonstrated successful effect of eradication of *H. pylori* on prevention of gastric cancer,[34] the results of interventional studies from other countries were inconclusive. The effectiveness of *H. pylori* eradication could only be proven by pooling all data in a unique meta-analysis.[35] The failure of regression of advanced atrophic gastritis together with intestinal metaplasia in spite of eradication of *H. pylori* was considered to be the cause of this ineffective prevention, as many studies confirmed this irreversibility.[2,36] The initial very low level of serum pepsinogen I in 23 patients with advanced body gastritis could not be normalized 4 years after eradication of *H. pylori*.[37] Therefore, the eradication of *H. pylori* must be undertaken long time before the atrophic gastritis develops along with metaplasia[38] and the serum level of pepsinogen I should not be decreased as it is the sign of advanced atrophic body gastritis.

The importance of serum pepsinogen II level as the main parameter for diagnosing gastritis has been neglected for a long time. Both serum pepsinogens increase in subjects with *H. pylori*-induced gastritis, and decrease soon after *H. pylori* eradication.[37] The decrease after *H. pylori* eradication is more pronounced in pepsinogen II than in pepsinogen I, as we[14] and others[37–39] have reported earlier.

We have shown that the severity of inflammation in cells of gastric mucosa in antrum and its extension to corpus is associated with the increase in serum pepsinogen II, while this is not the case for serum pepsinogen I, as many other authors have confirmed.[39–42] Thus, serum pepsinogen II is the best parameter for diagnosing any change in normal gastric mucosa leading to gastritis and its increasing severity.[14,43]

High serum pepsinogen II level along with normal serum pepsinogen I can be a suitable parameter for screening those at high



Strategy for prevention of gastric cancer in subjects at risk.

risk for gastritis or pangastritis without advanced atrophy or intestinal metaplasia in corpus. When subjects are at high risk of developing gastric cancer, namely when they have first degree relatives affected by gastric cancer or only if they are living in areas with high prevalence of gastric cancer, they have to be selected for *H. pylori* eradication. According to our study, a serum level of pepsinogen II more than 7.5 µg/mL has a sensitivity and specificity of 80% for diagnosing gastritis.[43] The upper limit of serum pepsinogen II must be determined in different countries on the basis of the characteristics of gastric morphology.

As gastritis progresses with age and many subjects older than 40–50 years have advanced atrophic gastritis, especially in areas with high prevalence of this cancer, screening must be performed in a younger age group, namely those younger than 35 years. We propose the following scheme beginning at the age of 30 years for prevention of gastric cancer in areas with high prevalence, where *H. pylori* infection and gastritis are the main cause:

Subjects at the age of 30, in areas with high risk of gastric cancer or first degree relatives of gastric cancer patients, have to be examined by a non-invasive diagnostic test of *H. pylori* infection and the measurement of serum pepsinogen II.

When no *H. pylori* infection exists and pepsinogen II level is in normal range, no gastritis can be expected and the probability of acquiring a new *H. pylori* infection will be very small after this age. Follow up of these subjects is unnecessary in future. When *H. pylori* infection is present and pepsinogen II is normal, the test should be repeated at the age of 35. In case of any increase in pepsinogen II, eradication is indicated. Otherwise, the follow up should be repeated at the age of 40 with additional measurement of pepsinogen I. After this age and later in intervals of 3 to 5 years, any increase in pepsinogen II or any decrease in pepsinogen I below 70 ng/mL, necessitates eradication of *H. pylori* together with additional endoscopic procedure. All *H. pylori*-eradicated subjects at the age of 40 have to undergo endoscopy. The eradication of *H. pylori* can prevent at least one third of gastric cancer occurrences.[44] The results of the morphological examination of biopsy specimens from antrum and corpus can determine the time interval of further follow-ups. Due to the slow progression of atrophic gastritis to intestinal metaplasia and its extension to corpus, endoscopic surveillance should be undertaken in intervals of 2–3 years.[45-46] If advanced dysplasia is detected by biopsy specimens from all areas of stomach and is confirmed by two pathologists, early gastrectomy will be indicated.

In subjects without risk for gastric cancer, clinical symptoms or increased serum pepsinogen II along with decreased pepsinogen I determine the indication for endoscopic examination.

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