Commented Summary form Current Medical Literature

"Serum Pepsinogen II as a Good Marker for Mass Screening and Eradication of *H. pylori* Infection in Populations at risk for Gastric Cancer"

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Summary: Serum pepsinogen II (sPGII) is underutilized and considered an inconspicuous biomarker in clinical practice. We refocused on this neglected but novel biomarker and conducted the present study, aiming to elucidate the normal level of sPGII in healthy Chinese patients and to investigate the clinical utility of sPGII for gastric disease screening.

In 2008–2009, a total of 2022 participants from northern China were selected and enrolled in the study. sPGII and *Helicobacter pylori* (*H. pylori*)–immunoglobulin G were measured with ELISA.

sPGII showed a normal value of 6.6 microg/L in a total of 466 patients with endoscopically- and histologically-normal stomachs. A small sex difference was observed: the average value of sPGII was 7 microg/L and 6 microg/L in males and females, respectively ($P < 0.001$). In the differentiation between healthy and diseased (endoscopically-diseased stomach or gastritis/atrophic gastritis in endoscopic biopsies) stomach mucosae, the best sPGII cut-off value was 8.25 microg/L (sensitivity 70.6%, specificity 70.8%). In screening the *H. pylori* seropositivity, the optimum cut-off sPGII value was 10.25 microg/L (sensitivity 71.6%, specificity 70.1%).

We demonstrated that the mean values of sPGII in a healthy Chinese population are 7 microg/L and 6 microg/L for males and females, respectively. sPGII significantly increases in diseased and *H. pylori*-infected stomach, and the best sPGII cut-off value is 8.25 microg/L in the differentiation between patients with healthy and diseased stomach mucosae. Furthermore, Chinese patients with sPGII greater than 10.25 microg/L are at greater risk of various *H. pylori*-related gastropathies, and are therefore prior candidates for gastro-protection therapy.

Source: He CY, Sun LP, Gong YH, Xu Q, Dong NN, Yuan Y. *J Gastroenterol Hepatol*. 2011; **26:** 1039 – 1046.

Comments: It has been over three decades since the measurement of serum pepsinogens have been introduced after their purification from gastric mucosa for the diagnosis of certain advanced gastric diseases,[1–4] particularly in Japan for those at risk for gastric cancer.[5,6] Despite this widespread determination of pepsinogen I and II, attention was paid only to low serum levels of pepsinogen I and the low ratio of pepsinogen I to pepsinogen II for the diagnosis of corpus atrophy. The relationship between pepsinogen II and *H. pylori*-induced morphological changes of the gastric mucosa were ignored.

In a recent Chinese publication by He et al., according to the results of one study on a large number of patients, the authors claimed that the determination of serum pepsinogen II levels has been completely neglected in the last decades as an important, effective biomarker for the diagnosis of gastritis.[7] In this large study, serum pepsinogen II levels were measured in more than 2000 patients in relation to morphological findings of gastric mucosa. This study confirmed both our early report[8] and that of Kiyohira et al.[9] where high serum pepsinogen II levels were good biomarkers of gastritis.

Thus, we would like to comment on this thoroughly performed study, based upon our earlier and ongoing investigations:

• Unfortunately, the classification of gastritis is not performed according to the up-to-date Sydney report. Only one biopsy was taken from the corpus and two from the antrum. The authors have not considered the severity, extent, and predominance of gastritis in the antrum or corpus or the presence of multifocal pangastritis, grade of precancerous conditions and their localizations in this large study.

• As there were a large number of patients, a very small difference could be found in the levels of pepsinogen II in males and females, which seems to be of no clinical importance. However, other factors such as BMI, physical activity or exercise, and particularly the fasting state of the subjects before taking blood samples must be considered in a comparison between both sexes. Sham feeding and meal intake have an important effect on the level of total serum pepsin activity (pepsinogen I and II together) and pepsinogen I.[10] Smoking habits differ between males and females; there is higher gastric acid secretion in smokers than nonsmokers.[11]

• We found a serum pepsinogen II level of 6.6 ± 2.8 μg/mL in 51 subjects with completely normal mucosa in the antrum and corpus, which approximated the same level mentioned in the Chinese paper, with 8.25 μg/mL as the cut-off value for the differentiation between the subjects with gastritis and those with normal mucosa.

• He et al. did not find any difference in serum pepsinogen II levels in subjects with superficial gastritis and those with dysplasia and gastric cancer. Such patients usually have a very advanced atrophic gastritis with severe inflammation and intestinal metaplasia in the upper stomach. If the authors had had taken multiple biopsy specimens from the corpus, as in our study where we obtained 3 specimens, they would have verified higher levels of serum pepsinogen II in subjects with advanced disorders in the corpus.

• As serum levels of pepsinogen II decrease more than pepsinogen I, a few weeks after *H. pylori* eradication (about 50% vs. 30%),[12–18] thus it would be a suitable marker to determine successful *H. pylori* eradication. This would mean that with the measurement of serum pepsinogen II levels, not only would *H. pylori*-induced gastritis be screened in the population, but its successful eradication can be verified by its remarkable decrease in comparison with values prior to eradication.

While the measurement of pepsinogen I detects those with advanced corpus gastritis who are at risk for gastric cancer development (which, according to many studies, does not regress significantly after *H. pylori* eradication), high levels of pepsinogen II are a good parameter of *H. pylori*-induced gastritis. It is a suitable marker for the mass eradication of *H. pylori*, which would prevent the development of atrophic gastritis and precancerous conditions in areas at high risk of gastric cancer. Additionally, its decline after eradication indicates treatment success.

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