EDITORIAL

Korean J Intern Med 2020;35:544-546
https://doi.org/10.3904/kjim.2020.139

Is serum pepsinogen testing necessary in population-based screening for gastric cancer?

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Population-based screening is needed for diseases with important public health implications; there should also be established treatment modalities for such diseases in the early stages. Furthermore, tests and examinations for these diseases, and precursor conditions, are required. Finally, screening and treatment programs should confer a demonstrable survival benefit. Endoscopic screening of large populations is effective in countries with a high prevalence of gastric cancer, such as South Korea and Japan [1,2]; in the former country, endoscopic screening reduced the gastric cancer-related mortality rate by 47% in a nested case-control study [3]. Periodic endoscopic examinations improve the survival of patients with gastric cancer. However, in regions with a low incidence of gastric cancer, endoscopic mass screening is unlikely to be efficient or cost-effective. Identification of individuals at high risk for gastric cancer and implementation of individualized screening programs are important.

The carcinogenic cascade of intestinal-type gastric adenocarcinoma is a multistep process that proceeds from normal gastric epithelium to chronic gastritis, chronic atrophic gastritis (CAG), intestinal metaplasia (IM), and dysplasia/gastric cancer [4]. Patients with CAG or IM are at considerable risk of developing gastric cancer, so early detection of lesions is important. Conventional gastroduodenoscopy is an effective diagnostic modality for gastric diseases. However, because gastroduodenoscopy is invasive and uncomfortable, it is associated with poor patient compliance. Also, the sensitivity and specificity of endoscopy for diagnosing gastric atrophy based on histological findings are only 61.5% and 57.7% in the gastric antrum and 46.8% and 76.4% in the corpus, respectively. Endoscopy also has low sensitivity and specificity for the diagnosis of IM [5]. If the atrophic mucosal change is mild, there can be a marked diagnostic discrepancy with endoscopy. Therefore, a reliable biomarker is needed.

The utility of serum pepsinogen (PG) as a marker of the functional status of the gastric mucosa has been investigated. Human PGs, which are protein-digestive enzymes secreted as proenzymes by the chief cells, are classified as PG I or II. The serum PG (sPG) I level and sPG I/II ratio reflect the functional status of the gastric mucosa. A low level of sPG I and low sPG I/II ratio are used as markers of advanced-stage atrophic gastritis, and have also been investigated as biomarkers for screening individuals at

Received: April 7, 2020
Accepted: April 23, 2020

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pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

high risk of gastric cancer. Although a variety of cut-off values have been suggested, an sPG I level of < 70 ng/mL and sPG I/II ratio of < 3 are widely accepted as predictive of CAG or gastric cancer [6]. A systematic review and meta-analysis of the diagnostic performance of sPG testing showed that it was predictive of CAG. A low PG I level and low sPG I/II ratio are related to the severity of atrophy [7]. However, whether the sPG test could replace periodic endoscopic examination for mass screening of gastric cancer is questionable. In a meta-analysis of the accuracy of sPG testing for predicting gastric cancer and precancerous lesions, the area under the curve (AUC) and diagnostic odds ratio (DOR) for diagnosis of gastric cancer were 0.76 (95% confidence interval [CI], 0.72 to 0.80) and 6.01 (95% CI, 3.69 to 9.79), respectively. For gastric atrophy, the AUC and DOR were 0.85 (95% CI, 0.82 to 0.88) and 16.50 (95% CI, 8.18 to 33.28), respectively [8]. Although this test is predictive of gastric atrophy, it has limited value for detecting gastric cancer. Therefore, it should be considered as supplementary rather than as an alternative to periodic endoscopic examination for population-based screening of gastric cancer.

Rapidity, excellent performance, high diagnostic accuracy (sensitivity and specificity), and reproducibility are required for a diagnostic test to be considered effective. Many factors influence the reliability of the serum PG test, including *Helicobacter pylori* infection. The serum PG I/II ratio is markedly altered by *H. pylori* eradication [9]. The sPG I/II ratio increases significantly after *H. pylori* eradication, and is used as an indicator of treatment success. Other factors, such as age, gender, height, body weight, body surface area, smoking, and alcohol consumption, might also be related to the levels of sPG I and II. Male sex is associated with a higher PG I level than is female sex, so we speculate that the PG I level is affected by hormones [9]. Also, the sPG test showed poor performance for detecting moderate-to-severe histological corpus atrophy [10]. In this study, a low sPG I level, low PG I/II ratio, and more severe endoscopic atrophy were significantly correlated, whereas there was no significant correlation between gastric fluid acidity and the sPG I level or sPG I/II ratio. Although the authors suggest that gastric acid secretion results from the activity of gastric hormones and vagus nerve stimulation, the diagnostic accuracy of the sPG test is questionable. Furthermore, the sPG I/II ratio of low-grade dysplasia was lower than that of high-grade dysplasia and early gastric cancer, although we did not take into account the *H. pylori* infection status or history of eradication [11]. Therefore, more factors should be considered, and a study with a larger number of samples is needed.

Because sPG testing could play a role in gastric cancer risk assessments, use of other markers together with sPG testing might be considered to assure test reliability and improve the efficiency of gastric cancer screening. The plasma level of ghrelin is closely related to the sPG level and sPG I/II ratio of CAG patients. A low serum level of PG I, low PG I/II ratio, and low plasma level of ghrelin are significantly correlated [12]. Indeed, an inverse correlation between ghrelin and gastric cancer was observed in a human study. The ghrelin level in tumor tissue was significantly lower than that in normal tissue, and the degree of cellular differentiation was correlated with the production of ghrelin [13]. Therefore, serum ghrelin has potential as a biomarker for gastric cancer. We hope that this work will stimulate prospective trials on the role of sPG testing, and provide information on promising biomarkers for gastric cancer screening. Finally, periodic endoscopy combined with biomarker testing would enhance mass screening for gastric cancer.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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https://doi.org/10.3904/kjim.2020.139