



## Clinical value of serum pepsinogen in the diagnosis and treatment of gastric diseases

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### Abstract

Pepsinogen, secreted from the gastric mucosa, is the precursor of pepsin. It is categorized as pepsinogen 1 and pepsinogen 2 based on its immunogenicity. The pepsinogen content that can enter the blood circulation through the capillaries of the gastric mucosa is approximately 1% and remains stable all the time. The pepsinogen content in serum will change with the pathological changes of gastric mucosa. Therefore, the level of pepsinogen in serum can play a role in serologic biopsy to reflect the function and morphology of different regions of gastric mucosa and serve as an indicator of gastric disease. This study conducts relevant research on serum pepsinogen 1, pepsinogen 2, and the ratio of pepsinogen 1 to pepsinogen 2, and reviews their important value in clinical diagnosis of *Helicobacter pylori* infection, gastric ulcer, and even gastric carcinoma, providing ideas for other researchers.

**Key Words:** Pepsinogen 1; Pepsinogen 2; Gastric diseases; Serological marker; Serological biopsy

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**Core Tip:** Pepsinogen is the precursor of pepsin, including pepsinogen 1 and pepsinogen 2. Serum pepsinogen has certain clinical value in determining *Helicobacter pylori* (*H. pylori*) infection and its treatment monitoring, in identifying the location and extent of gastric mucosal lesions, and in diagnosing and screening ongoing gastric cancer and precancerous lesions. This work summarizes the clinical value of serum pepsinogen 1, pepsinogen 2, and the ratio of pepsinogen 1 to pepsinogen 2 in the diagnosis of *H. pylori* infection, atrophic gastritis, and gastric cancer to provide readers with research ideas.

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## INTRODUCTION

Pepsinogen is an inactive precursor of pepsin, a specific functional enzyme in gastric mucosa, which was initially reported in duodenal ulcer[1,2]. It is secreted by gastric mucosal cells. According to immunogenicity, it can be classified into two types: Pepsinogen 1 and pepsinogen 2. Pepsinogen 1 mainly comes from the secretion of the chief cells of the gastric fundus gland, which is the cervical mucus cells. Pepsinogen 2 can originate from the mucous cells of the cardiac and pyloric glands in the gastric antrum, as well as from the duodenal gland in the upper part of the duodenum. Please refer to Figure 1[3,4] for details. Pepsin is mainly stored in glandular cells as a proenzyme particle synthesized by the main cell and has no activity[5,6]. Under external or physiological chemical stimuli, these particles are secreted into the stomach[7]. Under acidic conditions in the stomach, pepsinogen can be hydrolyzed into active pepsin[8]. pepsinogen also can interact with existing active gastric proteases[8]. Pepsin can decompose most proteins in the human body, thereby completing food digestion[8]. Most of pepsinogen is secreted into the stomach, and a small portion is also secreted into the bloodstream[9]. When cells are stimulated, most pepsinogen is released into the glandular cavity under exocytosis. The pepsinogen that can enter the blood circulation is approximately 1%, and the content is always stable[10]. They participate in the circulation through the capillaries of gastric mucosa[10]. After blood circulation, about two-thirds of pepsinogen 1 is metabolized by the kidneys, whereas pepsinogen 2 is reabsorbed and completely metabolized by the kidneys[6]. The number of cells in gastric mucosa and the glands in it could be reflected by the level of pepsinogen 1/2 in the serum, not only that, but also the morphology of different regions of gastric mucosa and whether its secretion function is normal can be indirectly reflected by the level of pepsinogen 1/2[11,12]. If the patient's gastric mucosa is diseased, the pepsinogen content in the serum will also be affected. One indicator of the function of gastric acid secreting gland cells is pepsinogen 1[13]. When gastric acid secretion increases, pepsinogen I increases and vice versa[1]. The secretory sites of pepsinogen II and its influencing factors are relatively numerous, and its rise is related to the atrophy of fundus gland, epithelial metaplasia, dysplasia, and various conditions[3]. Therefore, in order to detect the status of gastric mucosa, joint monitoring of pepsinogen 1 and pepsinogen 2 can be carried out. The relevant monitoring data of pepsinogen 1/pepsinogen 2 is also of significance for serological biopsy of gastric fundus gland mucosa. This study aims to investigate the clinical value of serum pepsinogen in the diagnosis and treatment of gastric diseases, with the hope of providing valuable insights for researchers.

## PEPSINOGEN AND *HELICOBACTER PYLORI* INFECTION

*Helicobacter pylori* (*H. Pylori*) infection is a contributing factor to the development of gastric cancer[14,15]. In addition, it can induce atrophic gastritis in the antrum of the stomach[16,17]. Atrophic gastritis is widely acknowledged as a premalignant lesion of gastric cancer[18]. Lipopolysaccharides produced after *H. pylori* infection stimulate the chief cells of gastric mucosa, leading to increased pepsinogen 1 content in the serum[15]. It can also cause the release of INF- $\alpha$ , INF- $\gamma$ , and other factors that promote cell apoptosis, thereby resulting in gastric gland atrophy and decreased gastric acid secretion[19,20]. *H. pylori* can promote the release of NF- $\kappa$ B and other cytokines, as well as gene transcription. Therefore, it will affect the chief cells and pepsinogen secretion. Some scholars believe that the increase of pepsinogen 2 content in serum is directly related to the changes of gastric mucosa caused by *H. pylori* infection, which is important in distinguishing normal gastric mucosa from abnormal gastric mucosa[3]. The pepsinogen contents of *H. pylori*-infected patients before and after sterilization treatment have been compared in some studies. The pepsinogen 1 content in the successful sterilization group is significantly lower than that prior to treatment, and the pepsinogen 2 content decreases more significantly. Accordingly, pepsinogen 1/pepsinogen 2 increases significantly. In the nonsterilization group, the pepsinogen content in serum does not significantly differ from that prior to treatment. Detecting the pepsinogen content has certain clinical value in evaluating whether *H. pylori* is eradicated. The development process from *H. pylori* infection to atrophic gastritis to gastric cancer is accompanied by changes in pepsinogen[21]. Extensive clinical research data have shown that *H. pylori* infection is very important in inducing gastric cancer. The World Health Organization classifies *H. pylori* infection as Class I carcinogen. Some studies have shown that *H. pylori* can promote AE1/p16 interaction by upregulating p16, thereby inducing gastric cancer. As shown in Figure 2, if *H. pylori* eradication treatment can be completed prior to "the point of no return" of gastric cancer, it can more effectively reduce the incidence rate of cancer. It can even prevent the occurrence of intestinal cancer. Until now, there have been main methods for eradicating *H. pylori*: Proton pump inhibitor (PPI) based triple therapy and PPI dual therapy administered through high-dose amoxicillin[22, 23]. PPI has been approved by FDA and can be used for the treatment of *H. pylori* infection or other diseases, as it can effectively reduce the production of acids in the upper digestive system[7,24,25]. But new research suggests that if patients use PPI for a long time, it is likely to cause adverse reactions to the body[26,27]. Patients who receive long-term PPI treatment also have an increased risk of death[28]. Therefore, in the clinical practice of *H. pylori* eradication treatment, PPI drugs use should be used closely monitored, especially long-term medication.

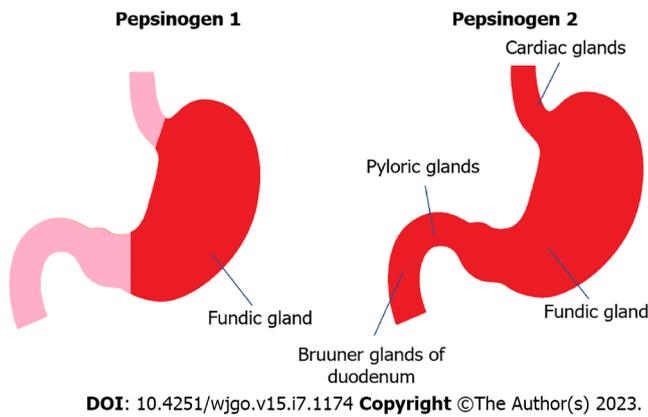


Figure 1 Expression of pepsinogen 1 and pepsinogen 2 in gastric mucosa.

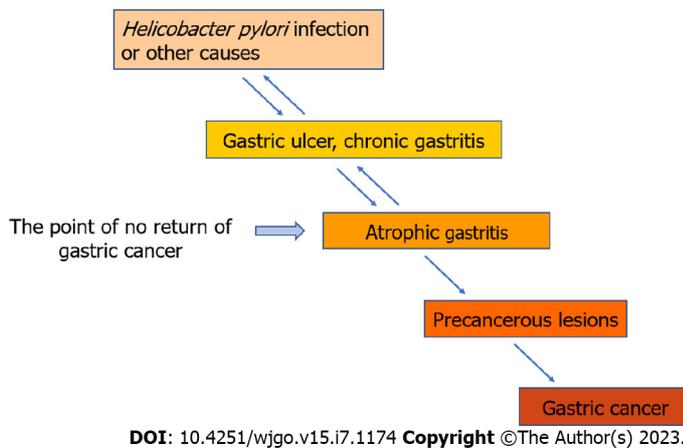


Figure 2 Development of gastric mucosal lesion.

In common cases, after *H. pylori* eradication, plasma pepsinogen 1 and pepsinogen 2 levels decrease and pepsinogen 2 decreases more significantly than pepsinogen 1[29]. Therefore, pepsinogen 1/pepsinogen 2 levels increase. Generally, pepsinogen 2 decreases after one month of *H. pylori* eradication, and the pepsinogen 1 level decreases within six months [30,31]. Currently, no unified view on whether pepsinogen can be used as a noninvasive serological indicator to evaluate the efficacy of *H. pylori* eradication. Gatta *et al*[32] suggested that the pepsinogen 2 level after eight weeks of *H. pylori* eradication is a reliable indicator of a successful procedure. The sensitivity and specificity of the optimum cutoff values (< 22.7 ng/mL) used to detect the complete eradication of *H. pylori* are 100.0% and 96.6%, respectively. No acceptable results are found with regard to other factors (pepsinogen 1 and gastrin-17) evaluated. However, according to Di Mario *et al*[3], pepsinogen 2 cannot be used as a successful marker for eradicating *H. pylori*. The biomarkers used to determine gastritis and *H. pylori* infection should be pepsinogen 2 serum level, pepsinogen 1 serum level, and pepsinogen 1/pepsinogen 2 ratio.

## PEPSINOGEN, GASTRIC ULCER AND ATROPHIC GASTRITIS

Current research results on the relationship between gastric ulcer lesions and serum pepsinogen levels, there are differences in current research results. The differences would be related to the population, and also be affected by detection methods, and interference from dietary factors. In those patients who had gastric ulcer, the increase of pepsinogen 1 and pepsinogen 2 is related to the increase in gastric acid secretion, leading to an increase in serum pepsinogen secretion, and an increase in gastric mucosal permeability, with a large amount of pepsinogen entering the blood. Therefore, in clinical diagnosis, the serum level of pepsinogen can serve as a reliable biomarker for the diagnosis of gastric ulcers in patients. Atrophic gastritis is the first step in the reaction cascade leading to gastric adenocarcinoma, and it is an important precancerous lesion[33,34]. The gold standard for diagnosing atrophic gastritis remains gastroscopy and histological examination of biopsy specimens[35]. However, because the latter is conducted randomly and atrophic gastritis is distributed patchily, histological examination reflects only the state of mucosa, and the related detection is limited. Normal mucosa and gastric glands can secrete pepsinogen and gastric acid as required[36]. Pepsinogen can be activated to produce biologically active pepsin under acidic conditions, playing its physiological role[36]. When mucosal

atrophy occurs, patients experience various degrees of atrophy of gastric glands[37]. Consequently, the gastric juice changes pH and the gastric juice decreases volume affecting the pepsinogen activity. The cells secreting pepsinogen 1 and pepsinogen 2 differ. When gastric mucosa atrophy occurs, the number of glandular cells and chief cells decreases, resulting in different changes in serum pepsinogen 1 and pepsinogen 2 contents[38,39]. Many studies have shown that the pepsinogen 1/pepsinogen 2 in serum and the pepsinogen 1 in it at low levels are indicators of atrophic gastritis[40]. Atrophic gastritis of the stomach is defined as serum pepsinogen 1/pepsinogen 2 < 3 and serum pepsinogen 1 level < 70 ng/mL[41]. Although a good correlation exists among endoscopy, histology, serology, and atrophic gastritis, the gastric atrophy presence is not always consistent with endoscopic findings[42]. The levels of pepsinogen 1 and the ratio of pepsinogen 1 to pepsinogen 2 in serum will decrease with the histological progression of atrophic gastritis. Moreover, when the stomach is severely atrophic, serum pepsinogen 1/pepsinogen 2 will also decrease accordingly[43,44]. For patients who was suffered severe atrophic gastritis, the levels of pepsinogen 1/pepsinogen 2 in their bodies would be lower than those mild atrophic gastritis patients[43,45].

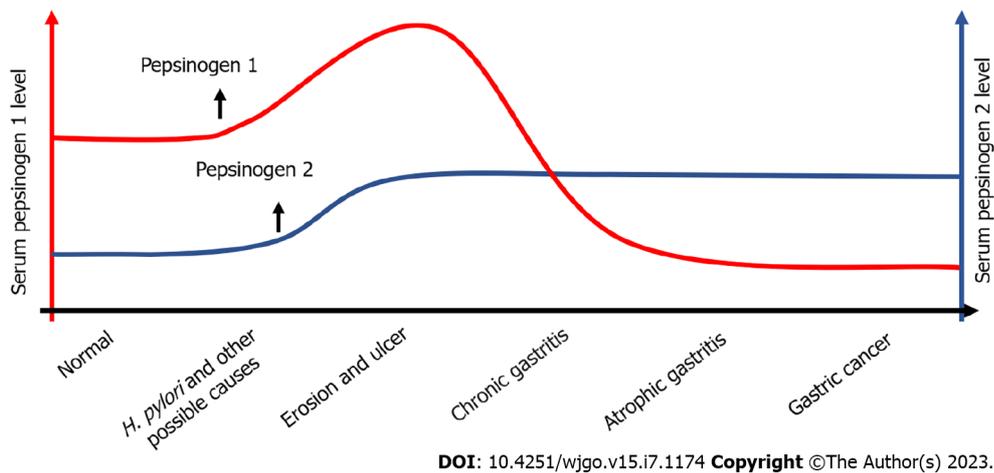
The cutoff value of atrophic gastritis diagnosis and the diagnostic efficiency also vary due to different regions, genetic backgrounds of populations, and test kits[46]. Cha *et al*[47] used pepsinogen 1/pepsinogen 2 = 4 as the cutoff value, and the sensitivity and specificity of detecting atrophic gastritis are 82.6% and 91.7%, respectively. According to Zoalfaghari A's research, the specificity and sensitivity of pepsinogen 1/pepsinogen 2 in the diagnosis of atrophic gastritis were 71%, 71%, with the receiver operating characteristic curve area 0.639 (cut-off value = 8). Nguyen *et al*[48] conducted relevant studies on the Vietnamese population and found that serum pepsinogen 1 and pepsinogen 1/pepsinogen 2 ratios have diagnostic value for patients with moderate and severe atrophic gastritis. The specificity demonstrated by the research institute is 83.9%, the detection sensitivity is 73.0%, and the optimal critical value is pepsinogen 1/pepsinogen 2 ≤ 4.6; pepsinogen 1 ≤ 69.0[48]. Therefore, it is necessary to ensure the diagnosis of atrophic gastritis through serum pepsinogen testing, based on the premise of determining reasonable diagnostic parameters according to the actual situation.

## PEPSINOGEN AND GASTRIC CANCER

The occurrence of gastric cancer is a multistep, multifactor, interactive process[49,50]. Gastric cancer develops from precancerous diseases, including atrophic gastritis, dysplasia and intestinal metaplasia[51,52]. In recent years, with the continuous deepening of clinical research, the status and function of gastric mucosa can be reflected effectively based on the serum pepsinogen level detection[16]. It can be used as a serological reference index for screening high-risk groups with precancerous lesions and early gastric cancer[53]. The significance of serum pepsinogen level change in the clinical screening of high-risk population with gastric cancer and the relationship between serum pepsinogen content and gastric cancer gradually become the research focus of scholars from various countries[6]. Persistent progression of precancerous lesions can lead to gastric cancer[54]. Therefore, the factors associated with the onset of gastric cancer are also related to the progression of precancerous lesions. The stomach is the only source of pepsinogen. Thus, the change in pepsinogen level can effectively reflect functional changes in the gastric mucosa[10]. Atrophic gastritis is an important background for mucosal gastric cancer, and pepsinogen 1/pepsinogen 2 levels continuously decrease with the continuous progression of gastric mucosal atrophy[14,55]. The atrophic degree of gastric mucosa of patients can be evaluated and judged through the detection of pepsinogen 1/pepsinogen 2 level[54].

According to existing research, there is a good correlation between changes in the morphology and function of the gastric mucosa in patients and serum levels of pepsinogen 1 and the ratio of pepsinogen 1 to pepsinogen 2. In the process of cancer screening, serum pepsinogen measurement is of great significance. According to research conducted by researchers on cancer patients and control groups, pepsinogen 1 ≤ 50 ng/mL and pepsinogen 1/pepsinogen 2 < 3 can be used for clinical diagnosis of cancer. The sensitivity, specificity, and accuracy values are 55%, 75%, and 72% respectively [11]. A 14-year cohort study based on a Japanese population shows that 97 of 2742 residents aged 40 and above develop symptomatic cancer. Among patients with early symptoms, approximately 62.8% (61 patients) showed pepsinogen 1/pepsinogen 2 levels < 3, while pepsinogen 1 levels < 70 ng/mL[56]. According to Mansour-Ghanea *et al*[57], pepsinogen 1 serum levels and pepsinogen 1/pepsinogen 2 ratios can be used as screening serum biomarkers for gastric cancer screening. If the critical value of pepsinogen 1 is 70.95 μg/L, and the critical value of pepsinogen 1/pepsinogen 2 is 2.99, indicating excellent sensitivity and specificity in patients[57]. Therefore, it can be concluded that serum pepsinogen can be used to predict gastric cancer. However, this does not mean that large-scale cancer risk screening can be conducted through serum pepsinogen level detection, as there is a high likelihood of pepsinogen negative cancers represented by diffuse cancers[58-60]. Miki *et al*[58] created a set of "ABC classification" detection methods in 2011. This detection method can detect pepsinogen negative cancers[58,59]. Assess the cancer risk of patients by measuring their *H. pylori* antibody titers and serum pepsinogen levels, and then divide them into four groups: Group 1 [*H. pylori* antibody (-) pepsinogen (-)], Group 2 [*H. pylori* antibody (+) pepsinogen (-)], group 3 [*H. pylori* antibody (+) pepsinogen (+)], and group 4 [*H. pylori* antibody (-) pepsinogen (+)]. The risk of cancer gradually increases from group 1 to group 4[61-63]. In theory, the risk of cancer in Group 1 is the lowest. However, 2% to 10% of cancer patients are classified as Group 1[64]. Some patients were inaccurately classified as Group 1 due to receiving antibiotics to eradicate *H. pylori* and showing negative *H. pylori* antibodies[65]. From this perspective, when conducting risk assessment for gastric cancer, patients with high negative *H. pylori* antibodies should be distinguished and evaluated through other tests.

In addition, the joint detection of serum pepsinogen 1 and other gastric cancer-related tumor markers have very important diagnostic value. For the early diagnosis of gastric cancer, the joint detection of serum pepsinogen and serum tumor markers (such as CA125, CA199, CA242, CA724, and CEA) can play an important role. The research team led by the author of this article conducted joint testing on pepsinogen and serum soluble Tim-3[66]. The test results obtained



**Figure 3** Relationship between serum pepsinogen level and gastric diseases. *H. pylori*: *Helicobacter pylori*.

indicate that the sensitivity for detecting cancer is 86.44%, while the specificity is 91.78%, significantly higher than those obtained by single detection[66]. For patients whose detection results indicate gradually decreased pepsinogen 1 and pepsinogen 1/ pepsinogen 2 levels, relevant endoscopic techniques can be used jointly. Some studies show that the joint detection of serum pepsinogen 1 and staining endoscopy improves the diagnostic rate of early gastric cancer, and the sensitivity of the joint detection is significantly higher than that of the individual approach[67].

## CONCLUSION

Pepsinogen is a serological marker whose subtypes are closely related to *H. pylori* and various gastrointestinal diseases [11]. Serum pepsinogen has certain clinical value in determining *H. pylori* infection and its treatment monitoring, in identifying the location and extent of gastric mucosal lesions, and in diagnosing and screening ongoing gastric cancer and precancerous lesions (Figure 3)[68]. Pepsinogen 1, pepsinogen 2, and pepsinogen 1/pepsinogen 2 are serum indicators of a certain gastric disease, and the changes in their levels in serum occur continuously throughout the process from inflammation to carcinogenesis in gastric tissue. Compared with the gastroscopy, serum pepsinogen detection is inexpensive, non-invasive, and simple. Thus, it is suitable for screening gastric diseases in large populations. The current research results on the diagnostic and therapeutic value of serum pepsinogen detection for gastric cancer are inconsistent, some shortcomings remain, and unified diagnostic standards cannot be used. However, with the establishment of screening strategies applicable to different populations and the deepening of related research, pepsinogen plays an important role in the prevention, screening, and diagnosis of cancer and atrophic gastritis. Moreover, it also performs well in predicting postoperative recurrence and metastasis of cancer. Moreover, developing novel sensitive and convenient detection methods is greatly important in further exerting the clinical value of serum pepsinogen detection.

## FOOTNOTES

**Author contributions:** Huang B and Qin Y designed this study; Qin Y and Geng JX conducted the reference analyses, drafted the initial version of the paper, and received contributions from all authors.

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