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BRIEF ARTICLE

Serum pepsinogen Ⅱ is a better diagnostic marker in gastric cancer

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Abstract

AIM: To investigate screening makers for gastric cancer, we assessed the association between gastric cancer and serum pepsinogens (PGs).

METHODS: The subjects comprised 450 patients with gastric cancer, 111 individuals with gastric atrophy, and 961 healthy controls. Serum anti-*Helicobacter pylori* (*H. pylori*) immunoglobulin G (IgG), PG Ⅰ and PG Ⅱ were detected by enzyme-linked immunosorbent assay. Gastric atrophy and gastric cancer were diagnosed by endoscopy and histopathological examinations. Odds ratios and 95%CIs were calculated using multivariate logistic regression.

RESULTS: Rates of *H. pylori* infection remained high in Northeastern China. Rates of *H. pylori* IgG positivity were greater in the gastric cancer and gastric atrophy groups compared to the control group (69.1% and 75.7% *vs* 49.7%, $P < 0.001$). Higher levels of PG Ⅱ (15.9 μg/L and 13.9 μg/L *vs* 11.5 μg/L, $P < 0.001$) and lower PG Ⅰ/PG Ⅱ ratio (5.4 and 4.6 *vs* 8.4, $P < 0.001$) were found in patients with gastric cancer or gastric atrophy compared to healthy controls, whereas no correlation was found between the plasma PG Ⅰ concentration and risk of gastric cancer ($P = 0.537$). In addition, multivariate logistic analysis indicated that *H. pylori* infection and atrophic gastritis were independent risk factors for gastric cancer. Lower plasma PG Ⅰ/PG Ⅱ ratio was associated with higher risks of atrophy and gastric cancer. Furthermore, plasma PG Ⅱ level significantly correlated with *H. pylori*-infected gastric cancer.

CONCLUSION: Serum PG Ⅱ concentration and PG Ⅰ/PG Ⅱ ratio are potential biomarkers for *H. pylori*-infected gastric disease. PG Ⅱ is independently associated with risk of gastric cancer.

Key words: Gastric cancer; Pepsinogens; *Helicobacter pylori*; Gastric atrophy; Screening

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INTRODUCTION

Gastric cancer remains the third leading cause of cancer death in China[1]. *Helicobacter pylori* (*H. pylori*) and gastric atrophy have both been identified as etiological factors for gastric cancer. However, screening and eradication of *H. pylori* in the general population is not advised because the cost of programs outweighs the modest effect on reduced incidences of gastric cancer. Therefore, identification of patients with the early stage gastric cancer could improve treatment and survival. Gastric atrophy, the precancerous lesion of gastric cancer, can be diagnosed by histological examination, and measurement of serum concentration of pepsinogens (PGs). Levels of two biochemically and immunologically distinct types, PG Ⅰ and PG Ⅱ, indicate different status of gastric mucosa. Serum PG level screening can be carried out at low cost in countries with high and moderate incidences of gastric cancer, such as Japan and China[2].

Most studies have demonstrated that low concentrations of PG Ⅰ and low PG Ⅰ/PG Ⅱ ratios in the serum or plasma are indicators of atrophic gastritis, which are linked with elevated gastric cancer risk[3-5]. However, few studies have assessed correlations between PG Ⅱ and gastric cancer risk[6,7]. It is well known that *H. pylori* infection leads to development of both atrophic gastritis and gastric cancer. Detection of serum anti-*H. pylori* immunoglobulin G (IgG) antibodies and screening for gastric atrophy and gastric cancer at an early stage are important for clinical assessments and interventions[8,9]. Absence of data on *H. pylori* infection and serum PG levels are available in large epidemiological surveys. To identify relationships between gastric mucosal lesions and serum PG levels, we carried out an assessment of PG Ⅰ and PG Ⅱ levels, PG Ⅰ/PG Ⅱ ratio and risk of gastric cancer in a cross-sectional study.

MATERIALS AND METHODS

Study participants

Four hundred and fifty patients with gastric cancer were selected from the Department of Gastric and Colorectal Surgery, and Department of Gastroenterology, First Hospital of Jilin University, from 2008 to 2010. All gastric cancer patients underwent tumor resection with histologically confirmed diagnosis of gastric adenocarcinoma. From 2009 to 2010, gastric atrophy cases and healthy controls were recruited from the check-up center of the same hospital. The subjects were of Han descent from the Changchun region. A total 1109 subjects (644 male and 465 female, aged 35-80 years) participated in the study. Gastric atrophy was diagnosed by endoscopy and histopathological examinations. Written informed consent was obtained from all subjects and the study protocol was approved by the Ethics Committee of the First Hospital, Jilin University.

Sampling and determination of serum

Fasting blood was taken for all participants and serum was collected and stored at -80 ℃. In the gastric cancer group, the samples were collected before surgery. Serum PG Ⅰ and PG Ⅱ levels were measured by enzyme-linked immunosorbent assay (ELISA) (Biohit ELISA kit, Biohit, Helsinki, Finland). Serum IgG antibodies to *H. pylori* were detected by ELISA using an *H. pylori*-IgG ELISA kit (Biohit). The antibody titers were defined by optical density values according to the manufacturer's protocol and titers higher than the cutoff value of 30 EIU were considered as positive for *H. pylori* infection. The quality control sample showed a coefficient of variation (CV) of 6.4%. For the pooled plasma samples the CV was 4.5%. According to the Chinese guidelines for diagnosis, patients are considered to have atrophic gastritis if PG Ⅰ is ≤ 82.3 μg/L and PG Ⅰ/PG Ⅱ ratio is ≤ 6.05[10]. The quality control samples showed CVs of 4.5%, 4.3% and 4.7% for *H. pylori*, PG Ⅰ and PG Ⅱ, respectively. All suspected cases with gastric atrophy by serum screening were re-determined by endoscopic biopsy and histological examinations.

Statistical analysis

The data did not fit a normal distribution, therefore, we used the Wilcoxon rank sum test to compare medians (quartiles) between the two groups. The χ^2 test was used to compare multiple sample rates. Non-conditional logistic regression analysis was used to calculate the odds ratio of risk-related factors for gastric cancer and its 95%CI. Two tailed P values < 0.05 were considered as statistically significant. All statistical analysis were carried out by SPSS version 18 software.

RESULTS

There were 450 patients with gastric cancer (324 male and 126 female, aged 35-80 years). Sixty-four cases were categorized as tumor-node-metastasis stage Ⅰ (14.2%), 182 as stage Ⅱ (40.4%), 145 as stage Ⅲ (32.2%), and 59 as stage Ⅳ (13.1%). Among the 1109 participants, 148 individuals were screened for gastric atrophy using serum PG examination and 111 patients were confirmed with gastric atrophy by biopsy and histopathological examinations. Seventeen subjects were diagnosed with pseudopositive gastric atrophy and excluded from the study; 20 participants who rejected endoscopic examinations were also excluded. The remaining 961 individuals were included in the control group. The mean age was older in the gastric cancer group than in the gastric atrophy and control groups. The subject characteristics are summarized in Table 1.

H. pylori infection

H. pylori-positive rates in the gastric cancer and gastric atrophy groups were significantly higher compared to those in the control group (69.1% and 75.7% *vs* 49.7%, P < 0.001). The *H. pylori* infection rates were higher in the 45-65 years group compared to those aged < 45 years or > 65 years. Among the 450 gastric cancer patients, *H. pylori* infection rate was higher in those with stage Ⅰ and

Table 1 Comparison of *Helicobacter pylori* infection between gastric cancer and control groups

	Gastric cancer group (%)	Gastric atrophy group (%)	Control group (%)	*P* value
No.	450	111	961	
H. pylori infection				
Negative	139 (30.9)	27 (24.3)	483 (50.3)	
Positive	311 (69.1)	84 (75.7)	478 (49.7)	< 0.001
Sex				
Male	324 (72.0)	66 (59.5)	564 (58.7)	< 0.001
Female	126 (28.0)	45 (40.5)	397 (41.3)	
Age				
< 45 yr	38 (8.4)	20 (18.0)	285 (29.7)	< 0.001
45-65 yr	240 (53.3)	81 (73.0)	607 (63.2)	
> 65 yr	172 (38.2)	10 (9.0)	69 (7.2)	

H. pylori: *Helicobacter pylori*.

stage Ⅱ disease, compared to those with stage Ⅲ and Ⅳ disease (73.6% *vs* 63.7%, $P = 0.02$). There were no correlations found between *H. pylori* infection and pathological type, tumor site, and differentiation of tumors (well-differentiated 50%, mild differentiation 69.8%, and poor differentiation 72.9%, $P = 0.47$).

PG levels

The median (interquartile range; IQR) PG I and PG Ⅱ levels, and the ratio of PG I /PG Ⅱ in the controls were 92.6 μg/L (75.0-116.1), 11.5 μg/L (7.1-18.4), and 8.4 μg/L (6.1-11.1), respectively. PG Ⅱ level in the gastric cancer group was significantly higher than that in the control group ($P < 0.001$), whereas the PG I /PG Ⅱ ratio showed a marked decline ($P < 0.001$) (Table 2). However, no statistically significant difference was found in PG I level between the two groups ($P = 0.532$). In the control group, a higher PG I level was detected in patients with *H. pylor*i infection compared to *H. pylor*i-negative patients (median: 99 *vs* 78.9 μg/L, $P < 0.001$).

Median (IQR) levels of PG I and PG Ⅱ, and PG I /PG Ⅱ ratio were 94.4 μg/L (38.9-148.8), 13.3 μg/L (7.7-22.5) and 6.2 (3.5-10.0) μg/L for 139 *H. pylor*i-negative gastric cancer patients, respectively. Median (IQR) levels of PG I and PG Ⅱ, and PG I /PG Ⅱ ratio were 92.2 μg/L (53.0-145.3), 18.4 μg/L (10.4-30.0) and 5.1 μg/L (3.5-7.2), respectively, for 311 *H. pylori*-positive gastric cancer patients. The difference in PG Ⅱ level and PG I /PG Ⅱ ratio was significant ($P = 0.01$) between *H. pylori* (-) and *H. pylori* (+) subjects. However, no significant difference in PG I concentrations was found between *H. pylori* (-)and *H. pylori* (+) cases in the gastric cancer group (92.2 μg/L *vs* 94.4 μg/L, $P = 0.96$) (Table 3). In addition, serum PG I concentration was significantly lower in patients with stage Ⅲ and Ⅳ tumors compared to stage I and Ⅱ (Table 4).

DISCUSSION

Serum PG I is produced by chief cells and mucous neck cells of gastric fundic glands, while PG Ⅱ is produced by those cells and also by pyloric glands and Brunner's glands[11]. Atrophic gastritis, characterized by loss of the specialized cells and glands in the stomach, is considered as a gastric cancer precursor lesion[12]. Serum PG levels, pepsin precursors, reflect the functional and morphological status of the gastric mucosa. It is widely accepted in gastric *H. pylori* infection that the fundic gland mucosa and PG I levels gradually decrease, whereas PG Ⅱ levels remain constant[13,14]. Consequently, a stepwise reduction of the PG I /PG Ⅱ ratio is closely linked to progression of atrophic gastritis. However, PG Ⅱ is considered to be a subordinate marker in clinical diagnosis. In fact, PG Ⅱ, a mature marker of gastric epithelia, reflects the physiological or pathophysiological functions of the gastric system[15,16].

Gastritis is more prevalent and severe in Japan, with more corpus predominant atrophy and intestinal metaplasia[17-19]. PG I ⩽ 70 ng/mL and PG I /PG Ⅱ ratio ⩽ 3.0 have been used for the diagnosis of extensive atrophic gastritis with sensitivity of 80% and specificity of 70%[20]. In contrast, our study showed a low incidence of gastric mucosal atrophy in the Chinese population. Inconsistency between studies may be due to different ethnic groups with different genetic backgrounds, different ELISA kits, and different cutoff values used for assessment of gastric mucosal atrophy[21]. We used PG I ⩽ 82.3 μg/L and PG I /PG Ⅱ ratio ⩽ 6.05 according to the study for diagnosis of atrophic gastritis in the Chinese population[10]. For reference, the cut-off points of PG I and PG I /PG Ⅱ ratio were calculated using receiver operator characteristic (ROC) curves. For patients with atrophic gastritis, the area under the ROC for PG I was 0.878 (95%CI: 0.837-0.919) and the best cutoff value was 82.30 μg/L (sensitivity 85.9%, specificity 75.1%). The area under the ROC for PG I /PG Ⅱ ratio was 0.819 (95%CI: 0.767-0.871) and the best cutoff value was 6.05 (sensitivity 78.3%, specificity 71.6%)[10]. The limitation of our study was that it could not determine the area under the curve *via* numerical integration of ROC curves, because we did not administer a further validity study. In our study, we found that serum PG I levels were significantly decreased in the gastric atrophy group, but no difference was found between the gastric cancer and control groups. Thus, it is considered that serum PG I levels represent gastric atrophy but not gastric cancer. The reason was that the prevalence of gastric atrophy was relatively low in our gastric cancer group compared with that in Japan. In Japan, the incidence of gastritis was higher than in other countries, and it was characterized by heavy predominant atrophy and intestinal metaplasia in the corpus of the stomach. Compared to the findings in Japan, our study showed a lower incidence of gastric mucosal atrophy. This may be due to differences in the research populations and their genetic backgrounds, even though the same *H. pylori* infection can lead to differences in severity of gastric atrophy[22-24]. Other factors such as the use of proton pump inhibitors (PPIs) may also influence the incidence of gastric atrophy. However, a history of using PPIs and lifestyle

Table 2 Comparison of pepsinogen levels between gastric cancer, gastric atrophy and control groups

	Gastric cancer group	Gastric atrophy group	Control group	*P* value (cancer *vs* control)	*P* value (atrophy *vs* control)
PG Ⅰ (μg/L)	93.2 (49.8-147.3)	64.0 (52.3-75.3)	92.6 (75.0-116.1)	0.537	< 0.001
PG Ⅱ (μg/L)	15.9 (9.0-28.0)	13.9 (11.9-16.9)	11.5 (7.1-18.4)	< 0.001	< 0.001
PG Ⅰ /PG Ⅱ	5.4 (3.5-8.1)	4.6 (3.6-5.3)	8.4 (6.1-11.1)	< 0.001	< 0.001

Data are expressed as median (interquartile range). PG: Pepsinogen.

Table 3 *Helicobacter pylori* infection and pepsinogen levels of serum in gastric cancer patients

	H. pylori (+) (*n* = 311)	*H. pylori* (-) (*n* = 139)	*P* value
PG Ⅰ (μg/L)	92.2 (53.0-145.3)	94.4 (38.9-148.8)	0.96
PG Ⅱ (μg/L)	18.4 (10.4-30.0)	13.3 (7.7-22.5)	0.01
PG Ⅰ /PG Ⅱ	5.1 (3.5-7.2)	6.2 (3.5-10.0)	0.01

Data are expressed as median (interquartile range). PG: Pepsinogen; *H. pylori*: *Helicobacter pylori*.

Table 4 Gastric cancer stages and serum pepsinogen levels

TNM stage (*n*)	PG Ⅰ (μg/L)	PG Ⅱ (μg/L)	PG Ⅰ /PG Ⅱ
Ⅰ (64)	101.4 (76.3-147.3)	18.4 (12.1-27.2)	6.3 (4.5-8.4)
Ⅱ (182)	96.3 (44.7-167.2)	16.3 (9.3-27.1)	5.5 (4.0-8.2)
Ⅲ (145)	85.8 (43.4-133.3)	15.4 (8.8-28.7)	4.9 (2.8-7.5)
Ⅳ (59)	71.5 (35.7-137.0)	13.1 (6.7-13.1)	5.1 (3.1-8.1)
P value	0.02	0.44	0.09

PG: Pepsinogen; TNM: Tumor-node-metastasis.

were not investigated in this study. A further prospective control study is needed. PG Ⅱ levels were significantly increased in patients with gastric atrophy and gastric cancer, especially in *H. pylori* (+) gastric cancer, resulting in a reduction in PG Ⅰ /PG Ⅱ ratio, which was consistent with a previous study[6].

A few studies have investigated PG Ⅱ serum level as an independent biomarker with potential clinical applications[25]. Higher PG Ⅱ expression has been demonstrated in patients with gastric ulcers, suggesting that PG Ⅱ level reflects chronic inflammation in *H. pylori*-related chronic gastritis[26-28]. Another study has shown that insertion/deletion polymorphisms of the PG Ⅱ gene are highly associated with genetic predisposition to gastric cancer in the carriers[16]. Our study demonstrated that chronic *H. pylori* infection is at a high level in the Chinese population. The overall *H. pylori* (+) rate in patients with gastric carcinoma was 78.6% in young patients (< 45 years), which was significantly higher than that in the control group (51%). Active gastritis caused by *H. pylori* infection and chronic inflammation resulted in elevated PG Ⅱ levels in the gastric cancer group.

We also found that serum PG Ⅰ level was significantly lower in patients with stage Ⅲ and Ⅳ tumors, compared to those with stage Ⅰ and Ⅱ tumors. The mechanism is unclear but it may be associated with gastric mucosal atrophy gradually increasing with advancing gastric cancer.

We demonstrated that serum PG Ⅱ level significantly increased in Chinese patients with *H. pylori*-infected gastric cancer, indicating that PG Ⅱ can be used as an independent diagnostic marker for gastric cancer. It is cost-effective to screen PG Ⅱ in countries with a high incidence of gastric cancer, compared with the high cost of endoscopy. Further studies on normal ranges of PG Ⅱ and its changes in gastric diseases may elucidate its physiological and pathological functions.

In conclusion, PG Ⅱ can be used as an independent diagnostic marker for gastrointestinal cancer[29-31].

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COMMENTS

Background

Early detection is an important way to reduce mortality of gastric cancer. Measurement of serum pepsinogen (PG) is a popular non-invasive serological screening test for gastric cancer.

Research frontiers

Research has shown that serum-PG testing, based on the combination of the measurement of serum PG Ⅰ concentration and the PG Ⅰ /PG Ⅱ ratio, is a good predictor of atrophic gastritis and gastric cancer development.

Innovations and breakthroughs

PG Ⅱ has been as considered a subordinate marker in clinical diagnosis. In this study, we demonstrated that the serum PG Ⅱ level significantly increased in *Helicobacter pylori*-infected gastric cancer in the Chinese population, indicating that PG Ⅱ can be used as an independent diagnostic marker for gastric cancer.

Applications

Serum PG Ⅱ level measure is a good method for screening patients with gastric cancer. It is very cost-effective to screen PG Ⅱ in countries with high incidences of gastric cancer, compared with the high cost of endoscopy.

Terminology

PGs are inactive proenzymes for the specific digestive enzyme, pepsin, originating from the gastric mucosa, and can be classified into PG Ⅰ and PG Ⅱ.

Peer review

The authors performed a clinical epidemiological study and evaluated the possibility and significance of PG Ⅱ in serum and PG Ⅰ /PG Ⅱ ratio as the diagnostic markers for Chinese patients with gastric cancer and gastric atrophy. They concluded that serum level of PG Ⅱ could be a useful diagnostic marker for patients with gastric cancer.

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