Original Article

Are the Serum Biomarkers Pepsinogen I and II Good Predictors for the Detection of Subjects with Atrophic Gastritis in Areas that have Different Gastric Cancer Incidence?

Ashraf Mohamadkhani MD[1], Sodaif Darvish Moghaddam MD[2], Hassan Salmanroghani MD[3], Amin Allafsghari MD[4], Abbas Yazdanbod MD[4], Mahboobeh Mirzaei MD[1], Arghavan Haj-sheykholeslami MD[1], Jafar Bashiri MD[4], Alireza Sadjadi MD[1], Sadegh Massarrat MD•[1]

Abstract

Background: Northern Iran (Ardabil) is characterized by a high gastric cancer (GC) rate, whereas Southern Iran (Kerman and Yazd) has a low GC rate. The aim of this study is to verify the potential for pepsinogen I and II to detect atrophic gastritis (AG) in both high and low risk populations for GC.

Methods: Sera of blood donors and patients with GC from Ardebil, Kerman and Yazd were used to measure levels of pepsinogen I, II and *H. pylori* IgG antibody. GC rates in these cities were determined according to the Cancer Registry and upper gastrointestinal (GI) endoscopy results.

Results: There were 449 subjects with an average age of 45 ± 15 years. The GC rate in the endoscopy units of the hospital in Ardabil was four times higher than Kerman or Yazd. The mean serum pepsinogen I levels did not differ between Ardabil (102 ± 42.6 µg/mL), Kerman (103.3 ± 49.8 µg/mL), and Yazd (111.7 ± 39 µg/mL). Pepsinogen II levels were: 8.1 ± 4.7 µg/mL (Ardabil), 7.5 ± 5.3 µg/mL (Kerman), and 7.6 ± 4.4 µg/mL (Yazd), which were not different. The *H. pylori* infection rates were: Ardabil (61%), Kerman (55%), and Yazd (73%). A low ratio of pepsinogen I to II (≤3) was seen in Ardabil (1.3%), Kerman (1.9%), and Yazd (0.0%), which was not significant. A total of 51.9% of GC patients from Ardabil had normal pepsinogen I (≥70 µg/mL) levels and pepsinogen I/II ratios that were >5.

Conclusion: Serum biomarkers pepsinogen I and II and their ratios are probably not sensitive predictors of AG in areas that have either a high or low GC prevalence. This finding is likely related to the lack of an association between GC and advanced AG.

Keywords: Biomarker, Gastric cancer, Pepsinogen I, Pepsinogen II

Introduction

Pepsinogen I and II, as precursors of pepsin, are produced by gastric mucosa and released into the gastric lumen and peripheral circulation.[1] The advanced inflammation of gastric mucosa and its progression toward atrophic gastritis (AG) in the corpus is associated with a change in serum biomarkers pepsinogen I and II; atrophy of corpus mucosa leads to low synthesis of pepsinogen I and a low release of pepsinogen I into the serum. Advanced gastric atrophy and hypo- or achlorhydrias are associated with very low levels of pepsinogen I in contrast to pepsinogen II, which remains elevated in serum.[2,3] During the last decades following the introduction of these biomarkers there has been extensive research, particularly in Japan which has used these serum biomarkers for the early detection of gastric cancer (GC).[4–6] In a large population-based study in Japan, Miki et al., have found that 80% of all early GC detected by routine endoscopy had a level of serum pepsinogen I less than 70 µg/mL combined with a Pepsinogen I to II ratio of less than 3.[7]

We have previously reported that pepsinogen II is a good marker for the diagnosis of any type of gastritis in that it can differentiate between subjects with gastritis from those with normal mucosa. Additionally, the progression of gastritis to AG and pangastritis is associated with a continual increase in serum pepsinogen II levels, whereas the levels of pepsinogen I in the early stage of AG remain unchanged and are normal.[8]

The end stages of advanced AG causing by *H. pylori* infection is severe reversible by *H. pylori* eradication.[9,10] Thus, gastritis in patients at risk for GC is treatable, in the absence of pre-existing precancerous conditions such as mucosal atrophy and intestinal metaplasia. For the purpose of GC prevention by mass eradication, the selection of infected subjects without advanced AG in high risk areas, namely those who present with high pepsinogen II and normal pepsinogen I levels in their sera, seems to be important.

In Northern Iran, Ardabil is considered a high risk area for GC; conversely, the central areas of Yazd and its neighboring province Kerman are both areas that have low rates of GC.[11] Therefore, the purpose of this study is to evaluate the pattern of serum pepsinogens I and II and their potential to verify the proportion of patients with no advanced AG in three cities (Ardabil, Kerman, and Yazd) that have different GC rates.

Authors' affiliations: [1]Digestive Diseases Research Center, Tehran University of Medical Sciences, Tehran, Iran. [2]Physiology Research Center, Department of Internal Medicine, Kerman University of Medical Sciences, Kerman, Iran. [3]Department of Internal Medicine, Yazd University of Medical Sciences, Yazd, Iran. [4]Aras Clinic, Ardabil University of Medical Sciences, Ardabil, Iran.

•**Corresponding author and reprints:** Sadegh Massarrat MD, Digestive Disease Research Center, Shariati Hospital, Tehran University of Medical Sciences, 14117-13135 Tehran, Iran. Tel: +98-218-241-5300; Fax: +98-218-241-5400; E-mail: massarrat@ams.ac.ir

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Table 1. Serum level of biomarkers and *H. pylori* infection rates among the studied population.

**Cities	Kerman	Yazd	Ardabil
Number	152	148	149
Age (years)	45 ± 14	45 ± 14	45 ± 15
Male/female	105/47	129/17	130/19
Pep*** I (µg/mL)	103.3 ± 49.8 (95%CI: 95–111)	111.7 ± 39 (95% CI: 105–118)	102.5 ± 42.6 (95% CI: 95–109)
Pep II (µg/mL)	7.5 ± 5.3 (95% CI: 6.7–8.4)	7.6 ± 4.4 (95% CI: 6.9–8.3)	8.1 ± 4.7 (95% CI: 7.3–8.9)
Pep I/II ratio	18.1 ± 12.2 (95% CI: 16.2–20.1)	19.1 ± 14.8 (95% CI: 16.7–21.5)	15.1 ± 7.6* (95% CI: 13.9–16.4)
H. pylori infection rate (%)	55% (95% CI: 47.3–63)	73%** (95% CI: 66.1–81.3)	61% (95% CI: 53.1–68.7)
Pep I/II ratio ≤ 3	3/152 (1.9%)	0/148	2/149 (1.3%)
Pep I ≤ 25 (µg/mL)	2/152 (1.3%)	1/148 (0.6%)	3/149 (2%)
Pep I ≤ 25 (µg/mL) and ratio ≤ 3	2/152 (1.3%)	0/148	1/149 (0.6%)
Pep I ≤ 70 (µg/mL) and ratio ≤ 5	4/152 (2.6%)	0/148	5/149 (3.3%)

*Significant compared to Yazd Province; **Significant compared to Kerman (*P* < 0.001) and Ardabil (*P* < 0.05); ***Pep = pepsinogen.

Materials and Methods

Healthy blood donors over the age of 20 years in three cities (Ardabil, Yazd, and Kerman) were the target populations during 21st March, 2008 – 21st March, 2009. We also included 81 symptomatic GC patients (56 males and 25 females) whose mean age was 65 ± 10.9 years in this study. Most had advanced GC. Blood samples were obtained from each subject by voluntary blood donation. The sera were frozen and kept at -80 until analysis. We planned to collect sera from 150 subjects in each city; 30 from each decade of life, beginning from age 20 up to 60 years. However due to the lack of adequate numbers of subjects older than 60 years in the blood transfusion centers, therefore we chose 30 persons over the age of 60 years in each city from a non-gastroenterology hospital ward, mainly from the hospitals' orthopedic wards. In the main university hospitals of all three capital cities, the diagnosis of all subjects undergoing upper gastrointestinal (GI) endoscopies during a one year period (21st March, 2008 until 21st March, 2009) was verified. Blood donors' sera were analyzed for pepsinogen I and II (ELISA Kits, Biohit, Helsinki, Finland) and *H. pylori* IgG antibody titer (Trinity Company, Italy) by ELISA. The sera were considered positive for *H. pylori* when the color extinction was ≥1.1 or equivocal (0.9 and 1) and negative when the extinction was <0.9 according to the manufacturer's instructions. The number of subjects needed for the study was calculated on the assumption that the prevalence of AG in adults from Ardabil was more than 15%[12] and in the city of Kerman or Yazd, it was less than 5%. By a power of 90% and β of 0.10, we needed at least 120 cases in each city. We decided to enroll 150 subjects. In addition, to evaluate the severity of precancerous conditions associated with GC in the high risk area, blood samples were taken from patients diagnosed with GC, as verified by endoscopy and histologic examination in the city hospital of Ardabil. All GC patients were symptomatic and had advanced GC. The majority had not undergone surgery.

Statistical analysis was performed with SPSS version 16, mean ± SD, 95% confidence interval (CI) and *t*-test. *P* < 0.05 was considered significant. Information about the cancer incidence was obtained from either the literature or the Cancer Registries of the Iranian Ministry of Health and Education (MHD). The Iranian Cancer Registry was established in 1995 in collaboration with the International Agency for the Research of Cancer (IARC). The Iranian Parliament established a law that required all physicians and pathology centers to report all cancer cases to MHD. The Cancer Registry information is published annually in Farsi in a Cancer Registry book, of which the latest one is from 2007.

Results

There were 449 subjects (83 females and 366 males) whose mean age was 45 ± 15 years (19–86 years). The number of subjects and their mean ages in the three cities was identical. There were no differences in the means of pepsinogen I and II between males and females; the concentration of pepsinogen I amongst males was 107.8 ± 42 µg/mL (95% CI: 103–112) and amongst females, 96 ± 55 µg/mL (95% CI: 85–107). The levels of pepsinogen II among males was 7.4 ± 4.4 µg/mL (95% CI: 7–7.9) and among females, 8.8 ± 6.1 µg/ml (95% CI: 7.5 – 10.1).

The serum levels of pepsinogen I and II, the ratio of pepsinogen I to II and the *H. pylori* infection rate in each city as well as the percentages of those with low pepsinogen I (<25 µg/mL) and the percentages of those with a combination of low pepsinogen I and low pepsinogen I to II ratio (<3 or <5) are presented in Table 1. There was no significant difference in the serum levels of pepsinogen I and II between the three cities. The mean pepsinogen I to II ratio was significantly less in Ardabil than in Yazd and Kerman. Few subjects had a pepsinogen I to II ratio less than 5 in Ardabil and Kerman, while no subject had a pepsinogen I to II ratio less than 5 in Yazd. The *H. pylori* infection rate was higher in the city of Yazd compared to the other cities. When the study population was classified into age groups of 10 year intervals, we noted a trend of decreasing pepsinogen I and increasing pepsinogen II levels with advancing age. Pepsinogen II levels were significantly higher in the age groups over 30 years when compared to those less than 30 years (Table 2). The pepsinogen I to II ratio decreased with age and the means were significantly less among those over the age of 50 years when compared to those less than age 40 years.

Serum pepsinogen II levels in subjects with *H. pylori* infection was significantly higher (8.5 ± 4.8 vs. 6.5 ± 4.6µg/mL, *P* < 0.05) and the pepsinogen I to II ratio was lower (15 ± 7.5 vs. 21.6 ± 16.4 µg/mL, *P* < 0.01). However, the mean pepsinogen I levels did not differ between infected (106 ± 41 µg/mL) and uninfected subjects

Table 2. Serum pepsinogen levels and ratio of pepsinogen I/II in Ardabil, Kerman, and Yazd according to age groups (means, SD and 95% confidence intervals).

Age group (years)	20–29 (N = 83)	30–39 (N = 85)	40–49 (N = 97)	50–59 (N = 83)	>60 (N = 101)
Pepsinogen I (µg/ml)	130 ± 49.8* (95% CI:119–140)	105 ± 38 (95% CI: 97–113)	99 ± 32 (95%CI: 92–105)	93 ± 36 (95% CI: 85–101)	102 ± 52 (95% CI: 91–125)
Pepsinogen II (µg/ml)	5.5 ± 3.9* (95% CI: 4.7–6.3)	7.6 ± 4.4 (95% CI: 6.7–8.6)	7.9 ± 4.4 (95% CI: 7–8.8)	7.7 ± 3.7 (95% CI: 6.9–8.6)	9.4 ± 6 (95% CI: 8.1–10.6)
Pepsinogen I/II ratio	31.4 ± 18.9* (95% CI: 27.3–35.6)	16.9 ± 8.1** (95% CI: 15.2–18.7)	14.8 ± 6.3 (95% CI: 13.5–16.1)	7.7 ± 3.7 (95% CI: 6.9–8.6)	9.3 ± 6.1 (95% CI: 8.1–10.6)

*Significant compared to all other age groups ($P < 0.01$); **Significant compared to age groups 20–29 and more than 50 years ($P < 0.05$).

Table 3. Relevant findings from upper gastrointestinal (GI) endoscopies conducted in the main university hospitals in Kerman, Yazd, and Ardibil during 2008.

Cities	Kerman	Yazd	Ardabil
Upper GI endoscopies (N)	2306	2027	2217
Male/female	1095/1211	1140/887	1090/1127
Duodenal ulcer	151 (6.5%)	197 (9.7%)	115 (5.1%)
Gastric ulcer	67 (2.9%)	34 (1.6%)	159 (7.1%)
Gastric cancer (GC)	46 (1.9%)	20 (0.9%)	192 (8.7%)*
Age (years)	60 ± 16	69 ± 16	66 ± 4.5
Male/female	30/14	16/4	127/65
Esophageal cancer	15 (0.65%)	28 (1.3%)	35 (1.5%)

*$P < 0.0001$ compared to other cities.

Table 4. Serum biomarkers pepsinogen I, pepsinogen II and pepsinogen I/II ratio in 81 patients with gastric cancer (GC) from Ardabil in relation to tumor histologic type and localization.

		Pep I (µg/L) *	Pep II (µg/L) *	Pep I/II ratio	Pep I <25 µg/L N (%)	Pep I <25 µg/L & Pep ratio <5 N (%)	Pep I <70 µg/L & Pep ratio <5 N (%)
Histologic type of gastric cancer (GC)	Intestinal N = 47	92.8 ± 79.15	26.2 ± 18.2	3.8 ± 2.4	7 (14.9%)	6 (12.8%)	23 (48.9%)
	Diffuse N = 34	92.8 ± 90.3	24.2 ± 17.8	4.2 ± 3	4 (11.8%)	4 (11.8%)	16 (47.1%)
Tumor localization	Mostly proximal N = 14	86.7 ± 54.95	26.2 ± 18.3	4.3 ± 3.3	1 (7.1%)	1 (7.1%)	7 (50%)
	Mostly middle N = 33	75.7 ± 63	23.8 ± 16.5	3.6 ± 2.6	4 (12.1%)	4 (12.1%)	18 (54.5%)
	Mostly distal N = 34	111.9 ± 105.7	26.5 ± 19.6	4.25 ± 2.4	6 (17.6%)	5 (14.7%)	14 (41.2%)
Total (n = 81)		**92.8 ± 83.5**	**25.4 ± 17.9**	**4 ± 2.6**	**11 (13.6%)**	**10 (12.3%)**	**39 (48.1%)**

*(Mean ± 1SD)

(104 ± 49 µg/mL). The percentage of subjects with pepsinogen I levels < 25 µg/mL alone or in combination with pepsinogen I to II ratios less than 5 or 3, or the percentage of those with pepsinogen I levels <70 µg/mL in combination with pepsinogen ratio I to II <5, as a sign of severe stage advanced AG[13,14] were low and did not differ among the three populations. The diagnoses of all patients who underwent upper GI endoscopies in the main hospitals of the three cities and the incidences of GC for males and females during the study period are given in Table 3.

The levels of pepsinogen I, pepsinogen II and pepsinogen I to II ratio in the sera of 81 GC patients and their relation to histological type and the localization of tumor in stomach as well as the number of subjects with low pepsinogen I alone or combined with low pepsinogen I to II ratio are given in Table 4. The serum levels of pepsinogen I and II were not different between two types of GC and those with different localization in the stomach. Twelve point three percent (12.3%) of GC patients had signs of very advanced of atrophic gastritis and 48.1% of them had any type of AG. This means that more than half of the GC patients in Ardabil had no AG according to the levels of the serum biomarkers.

The city of Ardabil had the highest rate of GC and gastric ulcers compared to Kerman and Yazd. The rate of GC among all subjects who underwent endoscopies in Ardabil was 4 times higher than Kerman and 9 times higher than Yazd. According to the Cancer Registry data of the Ministry of Health, the ASR/100.000 for GC in Ardabil is 49.1 for males and 21.5 for females. In Kerman, the rate is 10.2 for males and 5.1 for females.[11,15] The ASR/100.000 for GC in Yazd is 8.35 for males and 6.75 for females during 2006 – 2007.[16]

Discussion

H. pylori infection plays a pivotal role in the development of gastritis and its advanced type AG. GC may develop in the majority of cases as a result of AG under the influences of various genetic end environmental factors.[17] A recent meta-analysis study has shown long-term reduction of GC following the eradication of *H. pylori* in comparison with a control group.[18] The prevention of GC is probably an achievable goal with the eradication of *H. pylori* infection and is indicated in those areas with high an incidence of GC, as recommended by Asian guidelines.[19] However, few individuals infected with *H. pylori* develop GC. Therefore, mass eradication of *H. pylori* infection in at risk population can benefit only a small number of susceptible patients. Mass eradication of *H. pylori* is not advantageous for a substantial part of those who do not develop GC and may cause patients to suffer from the side effects of therapy as well as the potential for development of bacterial resistance, in addition to causing an additional financial burden for the society. Among the population at risk, we must therefore select those affected by pangastritis or predominant corpus gastritis who present with either no atrophy or less advanced atrophy and/or no intestinal metaplasia. Serum biomarkers are suitable for selecting that proportion of the population characterized by a normal pepsinogen I level with no sign of advanced atrophy but with a remarkable increase of serum pepsinogen II as a sign of diffuse gastritis or pangastritis.[8]

Advanced AG is reported to be very common in countries that have a high GC prevalence. In a comparative study with age-matched consecutive patients from the endoscopy units of Leeds and Tokyo, it has been shown that the Japanese subjects had prevalent, more severe gastritis and more predominant corpus gastritis than those from the United Kingdom.[20] In Portugal, which has a high GC prevalence, the rate of endoscopically diagnosed AG is 36.3%, while it is 8.3% in Mozambique that has a low prevalence of GC, although the rate of *H. pylori* infection is high in both countries.[21,22]

In Iran, as shown in our study, GC was diagnosed four and nine times more in the endoscopy unit of Ardabil compared to Kerman and Yazd, respectively, during a one year period. The endoscopy units of the hospitals in all three cities are the largest endoscopy units in these capital provinces, where the majority of middle and lower economic status patients are referred for endoscopic procedures. According to the Cancer Registry of these provinces, [11,15] the GC incidence is four times greater in Ardabil than Kerman and Yazd. These differences in GC incidence should be associated with a different prevalence of AG in these cities.

The mean levels of pepsinogen I and II did not differ amongst populations of the same mean ages in Ardabil, Kerman and Yazd, although the prevalence of GC was remarkably high in Ardabil.[12] No corresponding studies exist from other cities concerning the prevalence of AG. In all Iranian provinces, the *H. pylori* infection rate is high and not related to areas that have a high prevalence of GC.[23–24]

Serum pepsinogen I levels were higher in the age group less than 30 years compared with those in older groups. The pepsinogen II levels have shown a trend toward a non-significant increase and the pepsinogen I to II ratio to a significant decrease in Ardabil when compared to Kerman and Yazd. It seems that each of the two serum biomarkers alone or their combination with a low pepsinogen I to II ratio is not sensitive enough to diagnosis AG.

However, the ratio can show the trend of progression of gastritis with increasing age. Our results contradict the results by Stemmermann et al. who have reported a fourfold higher rate of low pepsinogen I levels in the sera of Japanese subjects to Hawaiian subjects of the same age.[25] The Japanese population was shown to have a fourfold higher incidence of GC when compared to the Hawaiian population. However, the number of subjects studied in Hawaii (n = 43) was lower than in Japan (n = 150). Additionally, the sensitivity of the pepsinogen I measured by radioimmunoassay to detect extensive intestinal metaplasia was 36.4%, very low in this study.

A high percentage of GC patients in Ardabil have normal level of pepsinogen I and a pepsinogen I to II ratio. This can mean that ahigh number of GC patients in this area had no remarkable precancerous conditions as observed in some countries. Genta et al. have found normal gastric mucosa in a quarter of the patients with GC in Switzerland.[26] This fact may diminish the importance of the measurement of serum biomarkers in areas where the proportion of GC with no advanced AG is quite high.

In the group with subjects older than 60 years that were selected from orthopedic wards, the possibility of increased pepsinogens in their sera due to NSAIDS intake could not be excluded. However, as all subjects in this age group were mostly from the orthopedic wards of hospitals in the three cities, the pepsinogen levels were compared and evaluated together.

In conclusion, identifying the proportion of AG in at-risk populations is not possible by the pepsinogen I level and ratio of pepsinogen I to II in this area, as claimed by Kekki et al.[27] The low sensitivity of serum biomarkers for the diagnosis of AG has been confirmed by other authors, as well.[28–31] Furthermore, GC could occur in some areas with no necessary development of precancerous conditions.

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