Serum Pepsinogens in Relation to Precancerous Gastric Lesions in a Population at High Risk for Gastric Cancer[1]

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Abstract

Concentrations of serum pepsinogens (PG) I and II were determined for 3252 randomly selected adults who participated in a population-based gastroscopic screening in an area of China with one of the world's highest rates of gastric cancer. PG I and II concentrations in both sexes tended to be higher than reported in other countries, with levels generally higher among males than females. PG I tended to decrease and PG II to increase with age, but the most pronounced associations were between PG I:II ratios and gastric histology. Median PG I:II ratios monotonically declined from 9.1 to 7.2 to 5.7 to 5.4 to 3.8 among those with superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, dysplasia, and stomach cancer, respectively. The prevalence of dysplasia was nearly 3 times greater among those with PG I:II ratios less than 3 compared with those whose PG I:II ratios were greater than 10. While average levels differed significantly among the histologic groups, the PG I:II ratios were neither sensitive nor specific markers of an individual's likelihood of advanced gastric lesions in this population.

Introduction

A screening survey for SC[4] and precancer was recently conducted in Linqu county, Shandong province, China, an area with one of the world's highest rates of SC (1-2). Endoscopic examinations involving multiple biopsies from standard locations enabled the detection of SG, CAG, IM, and DYS in addition to SC among adults randomly selected from the Linqu population. From blood samples, levels of serum PG I and II were also determined. Herein we report the extent of the correlation between serum PG concentrations and histologically determined gastric mucosal status and comment on the utility of the markers as surrogates for endoscopic diagnoses at the individual and group levels in this population.

Materials and Methods

Enrolled in this study were 3433 participants, representing 83% of eligible residents aged 35–64 in 14 villages selected at random within four townships of Linqu county. After the names of all residents were transcribed from the village population rosters, health workers visited each person and delivered a consent form to explain the study and invite him/her to participate in a SC screening program. If an individual was willing to participate, an appointment was made for a physical and endoscopic examination. The gastric mucosa was observed visually by a gastroenterologist, and 7 biopsies were taken from the following standard locations: midway between the cardia and angulus on the lesser curvature, the middle portion of the greater curvature of the body, the center of the angulus along the middle portion of the lesser curvature, the posterior and anterior wall of the antrum, and the lesser and greater curvatures of the antrum. In two of the villages, an eighth biopsy was taken within 2 cm of the cardia along the lesser curvature.

Histological diagnoses were made according to criteria proposed by the Chinese Association of Gastric Cancer. Each slide was reviewed by three senior pathologists at the Beijing Institute for Cancer Research; a sample was reviewed by experts on stomach pathology both in China and the United States, and a consensus diagnosis was made. The presence or absence of SG, CAG, IM, or DYS was recorded for each biopsy, and each was given on overall diagnosis based on the most severe histology. Each subject was assigned a global diagnosis based upon the most severe diagnosis among any of the biopsies. Further details of the pathologic procedures and classification criteria, along with photographs of SG, CAG, IM, and DYS, are provided elsewhere (1).

During the physical examination, approximately 15 ml of blood were collected from each fasting subject. The blood specimen, covered with aluminum foil, clotted for 30 to 40 min at room temperature. The blood was centrifuged at 2400 rpm for 15 min, and the serum was aliquoted, stored immediately at −20°C, and then moved into a −70°C freezer. Serum aliquots were air shipped on dry ice to the Veterans Administration Medical Center

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[4] The abbreviations used are: SC, stomach cancer; SG, superficial gastritis; CAG, chronic atrophic gastritis; IM, intestinal metaplasia; DYS, dysplasia; PG, pepsinogen.

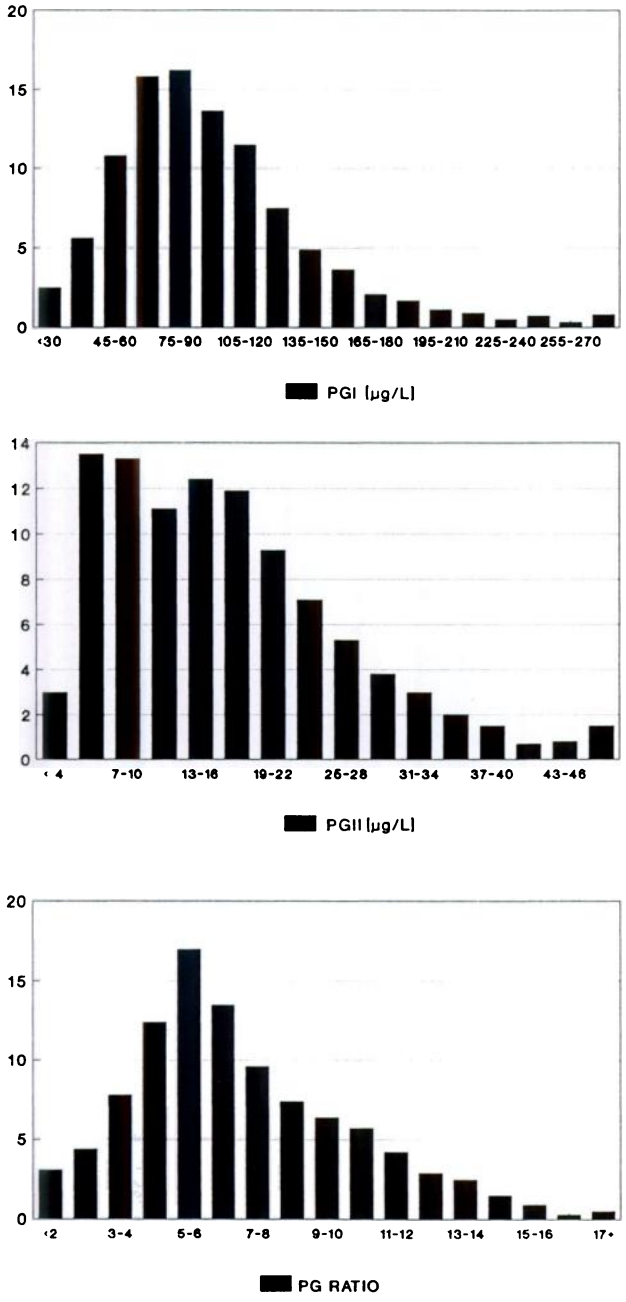

Fig. 1. Distributions of PG I, PG II, and PG I/II.

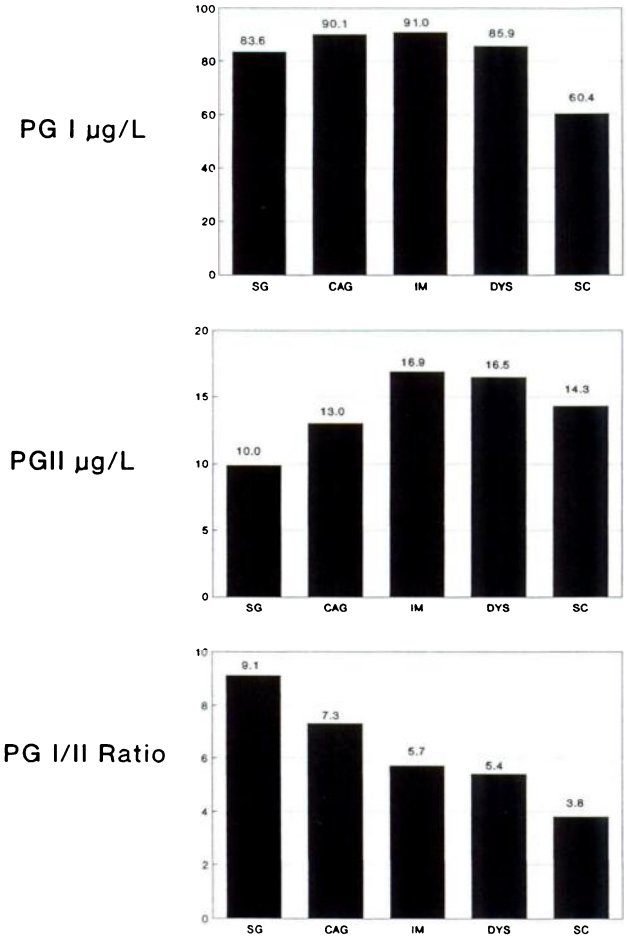

Fig. 2. Median PG levels according to gastric histology.

in Los Angeles for radioimmunoassay measurement of serum concentrations of PG I and II (3).

Means, SDs, and medians for PG I and II and the PG I:II ratio were calculated by sex, age, and global histological diagnosis. We also determined the prevalences of the precancerous lesions by PG category.

Results

Histological and serological results were available for a total of 3252 participants, 1713 males and 1539 females. The numbers with global diagnoses of SG, CAG, IM, DYS, and SC, respectively, were 54 (1.7%), 1456 (44.8%), 1060 (32.6%), 669 (20.6%), and 13 (0.4%).

The overall means ± SD of PG I, PG II, and PG I:II ratio were 97.3 ± 48.1 µg/liter, 16.9 ± 10.5 µg/liter, and 7.0 ± 3.3. Within individuals, PG I and PG II concentrations were positively correlated ($r = 0.7$; $P < 0.001$). When PG I exceeded 100 µg/liter, nearly 90% of the PG II values exceeded 12.5 µg/liter, whereas when PG I was below 75 µg/liter, only about 30% of the PG II levels exceeded 12.5 µg/liter. The distributions of each variable tended to be skewed (Fig. 1), so median values are presented in subsequent figures and tables.

Median PG values according to histology status are plotted in Fig. 2. The lowest PG I concentration was found among those with SC, but there was no consistent trend of decreasing PG I level with increasing severity of precancerous lesions. PG II, on the other hand, tended to rise with the severity of precancerous gastric lesions but was not elevated among those with SC. The most marked and consistent trends, however, were for the PG I:II ratios: in subjects with SG, the median PG I:II ratio was 9.1, but the medians decreased monotonically to 7.2 for CAG, 5.7 for IM, 5.4 for DYS, and 3.8 for SC.

We examined the relation between PG levels and several variables after adjusting for the association with

Table 1 Median levels of serum PG I, PG II, and PG I:II according to sex and gastric histology

Histology[a]	Sex	*n*	PG I (μg/liter)	PG II (μg/liter)	PG I:II
SG	Male	30	97.4	13.5	8.3
	Female	24	59.9	6.9	10.0
CAG	Male	702	105.4	14.4	7.5
	Female	754	76.6	11.9	7.0
IM	Male	544	102.8	18.1	5.8
	Female	516	80.8	15.4	5.7
DYS	Male	426	89.5	17.1	5.6
	Female	243	78.7	15.7	5.3

[a] Most severe diagnosis in any biopsy.

Table 2 Median levels of serum PG I, II, and I:II among those with CAG, IM, and DYS by number of biopsy sites with the lesions

No. of biopsies	No.	PG I (μg/liter)	PG II (μg/liter)	PG I:II
With CAG				
1	82	87.3	9.3	8.5
2–3	345	88.1	11.0	8.3
4–5	644	89.9	12.8	7.4
6+	365	95.6	15.2	6.3
With IM				
1	462	96.8	15.8	6.3
2–3	402	91.2	18.0	5.6
4–5	156	80.4	16.8	5.2
6+	40	70.0	17.2	4.0
With DYS				
1	417	87.6	16.5	5.7
2–3	218	82.2	16.4	5.0
4–5	32	76.6	17.0	5.1

gastric histology. Within each diagnostic category, males had higher median levels than females of PG I and PG II, but sex differences in PG I:II ratios were generally small (Table 1).

Smokers tended to have higher PG I and PG II levels, but the distributions of the PG I:II ratios were similar between smokers and nonsmokers and did not vary by amount smoked. PG I tended to fall, PG II to rise, and the PG I:II ratios to decline with age. Persons with blood type A and with a family history of stomach cancer, both risk factors for gastric dysplasia as well as gastric cancer (2, 4), also significantly more often had low PG I:II levels. The prevalence of low (<3.0) PG I:II also was higher among consumers of sour pancakes, a locally favorite fermented food associated with increased risk for stomach cancer (4). No clear associations between PG I:II levels and consumption of fresh vegetables, salted vegetables, or animal foods were detected.

Among those with IM and DYS, PG I levels and PG I:II ratios tended to decline as the number of biopsy sites showing the lesion increased (Table 2). The lowest PG I levels and PG I:II ratios occurred among those with extensive IM. Among those with CAG as the most advanced lesion, there was little trend in PG I, but a marked rise in PG II, with extensiveness of CAG.

Not only the type and extension, but also the anatomic location of the gastric lesions determined the PG levels. If biopsies in the fundus of the stomach were normal or showed only SG, then the PG I levels and PG I:II ratios tended not to be depressed even if DYS were diagnosed in the biopsies in the antrum (Table 3). The fundic diagnoses appeared to be the more important predictors of the PG ratios, with levels dropping to or below 5.0 when dysplasia was detected in the fundus.

Table 4 shows the prevalence of SG/CAG, IM, and DYS according to categories of PG I, II and I:II ratio. The prevalence of DYS increased with decreasing serum PG I concentration, while the prevalence of both DYS and IM increased with increasing PG II. However, the most marked elevations in prevalence of DYS and IM were found with low PG I:II ratios. The prevalence of DYS was nearly 3 times greater among those with PG I:II < 3.0 than among those with PG I:II ≥ 10.0. Although less than 2% of the population had all biopsies as normal or SG, hindering the evaluation of patterns, the PG I:II ratios tended to be higher in this small group than in those with CAG (e.g., only 5.6% of those with SG had PG I:II <5, *versus* 7.9% of those with CAG, 36% of those with IM, and 41% of those with DYS).

We calculated the sensitivity and specificity and false positive and false negative rates associated with using a PG I:II ratio cutoff level of 3.0 as an indicator of DYS. Using this cutoff, only 13% of those with DYS would have been detected, and 64% of the individuals with ratios below 3.0 would have been false positives. Changing the cutoff to 4.0 or 5.0 would have increased sensitivity to 25% and 41%, respectively, but would have decreased specificity and increased the false positive rate even further.

Discussion

Serum PGs have been proposed as markers of gastritis in surveys in North America, Europe, and Japan (5–9). The associations seen in various parts of the world raised the possibility of our using the serological tests as surrogates for endoscopic examinations, at least among those for whom visual inspection of the stomach was not considered clinically essential, in our planned follow-up of the screened population in Linqu. If the serum PG levels could be used to accurately to identify persons with specific precancerous lesions, we could use these serum markers to monitor changes in mucosal status over time. Thus, less invasive and less expensive serological techniques could be used with data on the characteristics of the participants to help evaluate the determinants of mucosal transitions thought to be on the pathway to SC.

The rationale for considering PG levels as markers of gastric mucosal status arose from their physiology. PG I is synthesized primarily by the chief cells in the fundus and corpus gland mucosa, whereas PG II is synthesized both by these cells and by glands in the gastric cardia and antrum. As atrophic gastritis progresses, chief cells in the body and fundus are lost, and thus PG I levels tend to decrease. As intestinal metaplasia progresses, pyloric glands extend proximally and thus PG II levels tend to increase (3). The association between dysplasia and PG levels has not been extensively characterized, but we hypothesized that we might find unusually low PG I and high PG II levels among those with dysplasia.

Low levels of PG I have been documented previously in patients with CAG. In some western countries, CAG typically is a diffuse corporal atrophic gastritis,

Table 3 Median levels of serum PG I, II, and I:II according to type and location (antrum *versus* fundus) of gastric lesion

Antrum		Fundus				
		DYS	IM	CAG	SG	Normal
DYS	*n*	118	179	192	98	8
	PG I	79.0	78.7	91.5	89.5	68.6
	PG II	17.2	16.4	17.9	13.8	8.1
	PG I:II	4.8	4.9	5.8	7.1	9.8
IM	*n*	59	284	415	218	18
	PG I	77.6	81.9	96.9	91.3	84.5
	PG II	15.2	17.7	18.4	14.4	8.2
	PG I:II	5.0	5.2	5.6	6.7	10.7
CAG	*n*	11	108	784	574	85
	PG I	94.2	95.7	94.2	87.9	81.5
	PG II	20.9	16.8	14.9	11.9	7.8
	PG I:II	4.8	5.8	6.6	7.9	11.0
SG	*n*		2	9	41	10
	PG I			84.5	116.2	79.1
	PG II			8.2	16.7	7.5
	PG I:II			10.5	7.0	11.1

Table 4 Prevalence of SG, CAG, IM, and DYS according to categories of PG I, PG II, and PG I:II

	n	Prevalence (%) with		
		SG/CAG	IM	DYS
PG I (μg/liter)				
100+	1295	48	34	18
75–99	821	46	31	23
50–74	754	48	33	19
20–49	330	43	29	28
<20	38	24	42	34
PG II (μg/liter)				
<7.6	626	62	24	14
7.6–12.5	646	53	29	18
12.6–17.5	667	42	33	25
17.6–24.5	667	38	34	24
24.6+	632	38	40	22
PG I:II				
10+	599	63	24	13
7.5–9.9	583	58	27	15
5.0–7.4	1162	48	32	20
3.0–4.9	652	26	45	29
<3.0	242	25	39	36

mostly involving the fundus and corpus, often accompanied by pernicious anemia as the end result. This is the type of CAG commonly seen in Scandinavian countries and is generally associated with PG I levels below 20 μg/liter (5, 10, 11). In China (as well as Japan), however, the typical CAG is multifocal, occurs mostly in the antrum along the lesser curvature, and extends to the corpus and the fundus with increasing age (1, 9). Prior studies among Japanese populations with CAG and IM have also shown depressed PG I levels, although generally not to the extent seen with diffuse fundic CAG (9).

We are not aware of data on PG concentrations from China, but we were nevertheless surprised that in Linqu, where CAG is nearly universal, median PG I levels exceeded 90 μg/liter. In European, North American, and Japanese populations mean and median serum PG I levels among persons without CAG have rarely exceeded 70 μg/liter (5–9). Even for those with fundic dysplasia, median concentrations in Linqu exceeded 70 μg/liter. Differences in assay procedures may contribute, but our laboratory has been involved in studies in other countries (3, 5, 6, 10–12) and, following the same methods, has not previously seen PG I levels as high as those in Linqu. Reasons for the higher PG I levels in Linqu, however, are unclear.

Overall PG II concentrations also tended to be somewhat higher in Linqu than elsewhere. Over 50% of the Linqu population showed evidence of IM in at least one gastric biopsy, however, which likely contributed to the elevated PG II levels. Indeed, PG II levels in Linqu residents without extensive CAG tended to be near or below levels reported in the United States (3) and Europe (6–8).

The strongest indicator of gastric mucosal status was the PG I:II ratio. The overall mean ratio was 7.1 in Linqu, generally higher than reported in Japan, North America, and northern Europe, although nearly equal the average level recently reported among randomly selected adults in Italy (12). The median PG I:II levels declined monotonically with increasing severity of gastric lesion, falling from over 9 in those with SG to below 4 in patients with SC. Furthermore, within pathologic categories, low PG I:II ratios also indicated more extensive lesions. Thus, the PG I:II ratio is a clear biomarker, at the group level, of gastric histology in this Chinese population.

Others have used very low PG I:II ratios as an indicator of severe gastritis in individuals. The cutoff has varied, but levels below 3.0 have been proposed as both sensitive and specific markers (3, 5, 7). We found that using a PG I:II ratio cutoff of 3.0 would have detected only 13% of those with dysplasis and less than 10% of those with IM as the most severe lesion. Hence this strategy would have low sensitivity and not be useful for identifying individuals with these relatively advanced precancerous lesions in Linqu. Furthermore, most persons with ratios of <3.0 did not have dysplasia. Thus, while mean PG I:II ratios can be useful for evaluating averages, the utility of the PG I:II ratio for distinguishing IM or dysplasia at the individual level is questionable.

In summary, this large-scale investigation has characterized the distribution of serum PGs in a population where precancerous gastric lesions are common and rates of SC are exceptionally high. The average levels are among the highest reported worldwide, but these varied by gastric mucosal histology. The marker most predictive of gastric status was the PG I:II ratio, which discriminated between CAG, IM, and DYS at the group level but was not an adequate predictor of an individual's gastric histology.

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