

## Serum Anti-*Helicobacter pylori* IgG Antibodies and Pepsinogens A and C as Serological Markers of Chronic Atrophic Gastritis<sup>1</sup>

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### Abstract

This study was designed to test the sensitivity and specificity of serum anti-*Helicobacter pylori* IgG antibodies and the ratio of serum pepsinogen A to pepsinogen C (PGA:PGC) in detecting chronic atrophic gastritis (CAG) and intestinal metaplasia. Parallel gastric biopsies and a serum sample were collected from a series of 87 patients aged 20–69 years attending a routine upper endoscopy clinic. The seroprevalence (>10 µg IgG/ml) of anti-*H. pylori* antibodies was 42.7%, and of a low PGA:PGC ratio (<1.5) was 17.7%. A positive *H. pylori* IgG antibody level was more sensitive than the level of PGA:PGC in diagnosing CAG (71.4% and 25.0%, respectively), moderate CAG (86.7% and 26.7%, respectively), and intestinal metaplasia (90.9% and 50.0%, respectively). Anti-*H. pylori* IgG antibody levels were less specific than PGA:PGC levels in diagnosing CAG (90.9% and 93.9%, respectively), moderate CAG (78.3% and 89.1%, respectively), and intestinal metaplasia (72.6% and 92.2%, respectively). A combination of anti-*H. pylori* antibodies and a low PGA:PGC ratio for the detection of CAG resulted in a specificity of 100%, but the sensitivity was 21.4%.

### Introduction

CAG<sup>7</sup> (1, 2) is an inflammatory process of multifactorial etiology predominantly localized in the antral gastric

mucosa and often accompanied by intestinalization of gastric epithelial cells. Both CAG and IM predispose to gastric cancer (3).

Neither CAG nor IM produces distinctive symptoms (4, 5), and diagnosis depends on gastric biopsy (6). Most of our knowledge about these lesions is, therefore, based on patients who present with conditions such as dyspepsia to gastroenterology clinics. It is unclear how representative such patients are of all those with pathological lesions.

Two serological markers, the level of the proenzyme PG and the presence of anti-*Helicobacter pylori* IgG antibodies, may be of value in detecting CAG and/or IM. PG is secreted by glandular cells into the gastric lumen and appears in sera as PGA (PGI) and PGC (PGII) (7, 8). PGA originates mainly from the chief cells and from the neck cells of the oxyntic mucosa. PGC is produced in chief and neck cells of all the gastric mucosa and in the Brunner's glands of the proximal duodenum (8). With increasing gastric atrophy, PGA and the ratio of PGA:PGC both tend to fall. For this reason PGA and the PGA:PGC ratio have been used as screening tools for CAG and early gastric cancer (9). The PGA:PGC ratio is more sensitive and specific in detecting those with CAG than is the level of PGA alone (10).

There is now good evidence from experimental volunteer ingestion and treatment studies that infection with the bacterium *H. pylori* is associated with chronic active gastritis (11, 12). *H. pylori* infection elicits a serum IgG response, which remains raised and constant throughout infection (13). It has been suggested that the presence of such antibodies may be of value in detecting chronic gastritis (14). Over several decades, *H. pylori*-associated gastritis may develop into CAG, and the presence of antibodies, therefore, may also be a marker for this lesion.

This study was designed to examine the association between the PGA:PGC ratio and the presence of anti-*H. pylori* IgG antibodies (both singly and in combination) and histologically defined CAG or IM. If these markers could reliably classify subjects into those with and those without lesions, it would enable the design of more representative epidemiological studies than has hitherto been possible. Improved markers for detecting CAG and IM may also be of value in selecting high-risk populations for endoscopic or radiological screening of early gastric cancer.

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<sup>7</sup> The abbreviations used are: CAG, chronic atrophic gastritis; IM, intes-

tinal metaplasia; PGA, PGC, pepsinogen A and C, respectively; HLO, *Helicobacter*-like organisms.

## Materials and Methods

**Subjects.** Five gastric biopsy specimens were obtained [from distal antrum, lesser curve (antral), lesser curve (corporal), greater curve (corporal), and fundus] from 95 consecutive patients, aged 20–69 years, attending a routine endoscopy clinic. Patients were excluded if they had gastric or esophageal cancer, previous gastric surgery, esophageal varices, liver or kidney disease, or a hemorrhagic diathesis. Biopsy specimens were immediately fixed in formal saline solution. Just before endoscopy, a 10-ml blood sample was obtained. Serum was separated and frozen to  $-20^{\circ}\text{C}$  on the same day.

**Histology.** A Warthin Starry preparation (15) was used to identify HLO in sections from each biopsy specimen. Other sections were stained using hematoxylin and eosin (15) for the classification of the gastric mucosa. Biopsies were classified by site (antrum, fundus) and severity of gastritis into normal, chronic superficial gastritis, and CAG using Whitehead's classification (6). The presence of IM was also recorded. HLO and the grading of gastritis were assessed separately by different histopathologists.

To measure the sensitivity and specificity of *H. pylori* seropositivity and the PGA:PGC ratio in detecting the presence or absence of CAG or IM, subjects were divided into those with or without histological evidence of CAG. The CAG group was further subdivided into those with and without IM. Most analyses were carried out after excluding those subjects who were diagnosed with a peptic ulcer.

**Analytical Procedures.** Serum PGA and PGC levels were measured with an enzyme-linked immunosorbent assay using purified PGA and PGC antigens (10). Subjects with a PGA:PGC ratio less than 1.5 were considered to have a low PGA:PGC level. This level of PGA:PGC was found to optimize discrimination in detecting CAG in a previous study using an identical assay (10). Anti-*H. pylori* IgG serum antibodies were measured with an enzyme-linked immunosorbent assay using an acid-extractable antigen from the surface of *H. pylori* (NCTC 11638) (14, 16). An anti-*H. pylori* IgG antibody concentration greater than  $10.0\ \mu\text{g/ml}$  was considered to be a positive indication of infection. This cutoff point was confirmed by constructing a receiver operating characteristic curve (17) for different antibody cutoff levels. A cutoff of  $10\ \mu\text{g/ml}$  gave a sensitivity of 84.8% and specificity of 92.7% in detecting HLO in any one of five biopsies.

**Statistical Tests.**  $\chi^2$  tests were used to test for associations between dichotomous variables (18). The sensitivity, specificity, and the positive and negative predictive values of single or combined markers were calculated using standard formulae (17).

## Results

Eight of 95 subjects endoscoped (8.4%) were excluded because of inadequate biopsy specimens. Fifty-two (59.8%) of the remaining 87 subjects were men (mean age, 48.3 years; SD = 13.2) and 35 (40.2%) were women (mean age, 47.4 years; SD = 14.1). Twenty-six subjects had ulcers (4 gastric, 21 duodenal, and one with both).

Of the 87 subjects with complete biopsy material, 26 (30.0%) had normal histology and 13 (15.9%) had chronic superficial gastritis. Forty-eight subjects (55.2%) had CAG (25 mild, 22 moderate, and one severe), which

Table 1 Mean values and ranges for PGA, PGC, and PGA:PGC ratio for all subjects and by *H. pylori* serology status

	All (n = 85)	<i>H. pylori</i>		<i>P</i> <sup>a</sup>
		Seropositive (n = 40)	Seronegative (n = 45)	
PGA				
Mean (SD)	49.6 (34.3)	55.9 (34.5)	44.0 (33.5)	0.11
Range	0.0–193.6	0.0–158.4	0.0–193.6	
PGC				
Mean (SD)	19.9 (13.3)	25.1 (14.8)	15.2 (9.7)	0.004
Range	0.5–70.0	9.0–70.0	0.5–48.0	
PGA:PGC <sup>b</sup>				
Mean (SD)	2.8 (1.8)	2.4 (1.2)	3.1 (2.1)	0.065
Range	0.0–13.2	0.0–5.3	0.0–13.2	

<sup>a</sup> From *t* test comparison of seropositive subjects versus seronegative subjects.

<sup>b</sup> Values shown after exclusion of one subject (seronegative) with a PGA:PGC ratio of 62.40.

in 26 cases (29.9%) was confined to antral biopsies and in 3 cases (3.5%) to body biopsies and in 19 cases (21.8%) was present in biopsies from both antrum and body. All three subjects with body CAG also had an ulcer. Fifteen subjects, all with CAG, had IM, and five of these had an ulcer. Forty-six of the 87 subjects (52.9%) on histological examination had HLO at one or more biopsy sites.

Forty-two of the 87 subjects (48.3%) had an anti-*H. pylori* IgG concentration greater than  $10.0\ \mu\text{g/ml}$  and were categorized, therefore, as seropositive. Thirty of the 42 positive subjects had an IgG concentration of  $90.0\ \mu\text{g/ml}$ , which was the upper limit of detection for the assay under these conditions. Three of the remaining 13 positive subjects had concentrations close to the cutoff level (between 10.1 and 12.0), and two of the 45 seronegative subjects had concentrations close to the cutoff level (between 7.1 and 10.0). Fifteen of 85 tested subjects (17.6%) had a PGA:PGC ratio of less than 1.5. Nine of the 15 subjects with a ratio less than 1.5 were *H. pylori* seropositive. PGA, PGC, and PGA:PGC values in relation to *H. pylori* serology status are shown in Table 1. Both PGA and PGC mean levels were elevated in seropositive subjects, although this effect was stronger and only statistically significant for PGC. As a result, the PGA:PGC ratio was lower in seropositive subjects.

Table 2 shows that both *H. pylori* seropositivity and low PGA:PGC ratios were found more frequently in subjects with CAG, especially those who also had IM, than in those with normal mucosa or with superficial gastritis. The trend in the relationship between grade of gastritis and *H. pylori* seropositivity was highly significant ( $P < 0.0001$ ), while that with a low PGA:PGC ratio was of borderline significance ( $P = 0.08$ ).

Table 3 shows the same information as Table 2, restricted to the 61 subjects without peptic ulcers and for whom both sets of serological data were available. This shows again that both serological markers were found more frequently in subjects with CAG, with highly significant trends in relationship to grade of gastritis. Twenty of the 28 subjects (71.4%) with CAG were *H. pylori* seropositive, while only 3 of the 33 subjects (9.1%) without CAG (22 normal and 11 with superficial gastritis) were positive. Seven of the 28 subjects (25.0%) with CAG had a PGA:PGC ratio of less than 1.5 compared

**Table 2** Number and percentage of subjects seropositive for *H. pylori* IgG antibodies and with low (<1.5) PGA:PGC ratios by gastric mucosal histology

Histology	No.	No. (%) positive for	
		<i>H. pylori</i> antibodies <sup>a</sup>	PGA:PGC < 1.5
Normal	26	2 (7.7)	3 (11.5)
Superficial gastritis	13	3 (23.1)	1 (7.7)
CAG	48 <sup>b</sup>	37 (77.1)	11 (23.9)
Without IM	33 <sup>b</sup>	23 (69.7)	6 (19.4)
With IM	15	14 (93.3)	5 (33.3)
Total	87	42 (48.3)	15 (17.6)
$\chi^2$ <sup>c</sup>		38.72 ( $P < 0.0001$ )	4.16 ( $P = 0.25$ )
$\chi^2$ (trend) <sup>c</sup>		37.20 ( $P < 0.0001$ )	3.09 ( $P = 0.08$ )

<sup>a</sup> IgG antibody > 10  $\mu\text{g/ml}$ .

<sup>b</sup> Only 46 subjects with CAG (31 without intestinal metaplasia) were analyzed for pepsinogen.

<sup>c</sup> Normal, superficial gastritis, CAG without IM, CAG with IM.

with 2 of the 33 subjects (6.1%) without CAG. Of the 7 subjects with CAG and a low PGA:PGC ratio, 6 were *H. pylori* seropositive (the one *H. pylori* seronegative subject being in the group without IM). However, neither of the two subjects without CAG but with a low PGA:PGC ratio were *H. pylori* seropositive.

These results can be used to calculate the sensitivities, specificities, and predictive values for using *H. pylori* seropositivity and/or the PGA:PGC ratio as tests for identifying individuals with CAG or with IM. These are shown in Table 4, with predictive values calculated for the prevalence of CAG and IM as actually found in this endoscopy series and for a prevalence assumed to be 10%. Also shown are values of tests for the identification of individuals with moderate CAG (including one subject with severe CAG) compared with other histologies.

The presence of anti-*H. pylori* IgG antibodies was more sensitive than the level of PGA:PGC (<1.5) in identifying subjects with CAG (71.4% and 25.0%, respectively), moderate CAG (86.7% and 26.7%, respectively), and IM (90.0% and 50.0%, respectively). However, anti-*H. pylori* IgG antibody levels were less specific than PGA:PGC levels in identifying CAG (90.0% and 93.9%, respectively), moderate CAG (78.3% and 89.1%, respectively), and IM (72.6% and 92.2%, respectively).

By combining *H. pylori* seropositivity and a low PGA:PGC ratio, all of the subjects without CAG were "correctly" identified, i.e., there were no false positives and specificity was therefore 100%. However, the sensitivity of using both markers in detecting CAG was 21.4%. The specificity and sensitivity of combining *H. pylori* seropositivity and a low PGA:PGC ratio in detecting moderate CAG were 95.7% and 36.4%, respectively, and in detecting IM were 50.0% and 98.0%, respectively.

## Discussion

This study was designed to test the extent to which two serological markers, the presence of IgG antibodies directed against *H. pylori* and the ratio of PGA to PGC, can be used to identify individuals with CAG or intestinal metaplasia, important precursors of gastric cancer. Both markers had, independently, specificities of over 90% in

**Table 3** Number and percentage of subjects seropositive for *H. pylori* IgG antibodies and with low (<1.5) PGA:PGC ratios by gastric mucosal histology (subjects without peptic ulcers)

Histology	No.	No. (%) positive for	
		<i>H. pylori</i> antibodies <sup>a</sup>	PGA:PGC < 1.5
Normal	22	1 (4.5)	1 (4.5)
Superficial gastritis	11	2 (18.2)	1 (9.1)
CAG	28	20 (71.4)	7 (25.0)
Without IM	18	11 (61.1)	2 (11.1)
With IM	10	9 (90.0)	5 (50.0)
Total	61	23 (37.7)	9 (14.8)
$\chi^2$ <sup>b</sup>		27.93 ( $P < 0.0001$ )	12.17 ( $P = 0.007$ )
$\chi^2$ (trend) <sup>b</sup>		26.66 ( $P < 0.0001$ )	7.70 ( $P = 0.006$ )

<sup>a</sup> IgG antibody > 10  $\mu\text{g/ml}$ .

<sup>b</sup> Normal, superficial gastritis, CAG without IM, CAG with IM.

identifying CAG, and in combination the specificity became 100% (Table 3). In other words, there were no individuals without CAG who were *H. pylori* antibody positive and who had a PGA:PGC ratio of less than 1.5. There were, therefore, no false positive identifications. This combination of markers did, however, result in a sensitivity of only 21%, i.e., over three-quarters of individuals with CAG were not correctly identified. For the identification of IM the equivalent specificity and sensitivity were 98% and 50%, respectively.

These results would mean that in a hypothetical CAG screening situation, assuming a disease prevalence of 10%, for every 1000 people screened only 21 of the 100 individuals with CAG would be detected, while of the 979 who tested negative, there would be 79 false negatives. If screening was for IM, again assuming a 10% prevalence, then 50 of the 100 with IM would be detected, and there would be 50 of 932 false negatives and 18 of 68 false positives (although all the false positives should have CAG).

Our results were based on a group of only 61 patients without ulcers, and there would need to be more extensive studies before the above findings could be accepted with certainty. The conclusions are, however, not unreasonable in light of current knowledge about the causes and consequences of CAG. Thus, a PGA:PGC ratio of less than 1.5 sets a stringent criterion for detecting CAG, and the few cases (2 of 33 in this study) who, for whatever reason, have a low PG ratio in the absence of CAG were *H. pylori* seronegative (see Table 3). It is not surprising, therefore, that a combination of markers results in a very high specificity. If it can be confirmed that the specificity for detecting CAG is 100%, this would have important consequences for the practical use of these markers (see below).

It will be important to repeat this type of study in nonpatient populations and in populations with different prevalences of different types of gastritis. This study was carried out in a patient group undergoing endoscopy, and there are obvious difficulties in attempting to generalize from these results to nonclinical populations. Confining the main analysis to those patients without peptic ulcers excludes those patients likely to have the most discordant results. The presence of an ulcer is often associated with both abnormally elevated PGA levels

Table 4 Diagnostic power of various serological tests (subjects without peptic ulcers)

	Histology				Spec.	Sens.	PV+ <sup>b</sup>	PV- <sup>b</sup>	PV+ <sup>c</sup>	PV- <sup>c</sup>
	N/S <sup>a</sup>		CAG							
	Test +ve	Test -ve	Test +ve	Test -ve						
HP IgG > 10 µg/ml	3	30	20	8	90.9	71.4	87.0	79.0	46.6	96.6
PGA:PGC <1.5	2	31	7	21	93.9	25.0	77.8	59.6	31.4	91.9
HP IgG > 10 µg/ml and PGA:PGC <1.5	0	33	6	22	100.0	21.4	100.0	60.0	100.0	92.0
	Other		Mod. CAG							
HP IgG > 10 µg/ml	10	36	13	2	78.3	86.7	56.5	94.7	30.9	98.2
PGA:PGC <1.5	5	41	4	11	89.1	26.7	44.4	78.8	21.6	91.7
HP IgG > 10 µg/ml and PGA:PGC <1.5	2	44	4	11	95.7	36.4	66.7	80.0	48.0	93.1
	IM-		IM+							
HP IgG > 10 µg/ml	14	37	9	1	72.6	90.0	39.1	97.4	26.7	98.5
PGA:PGC <1.5	4	47	5	5	92.2	50.0	55.6	90.4	41.5	94.3
HP IgG > 10 µg/ml and PGA:PGC <1.5	1	50	5	5	98.0	50.0	83.3	90.9	74.0	94.6

<sup>a</sup> N/S, normal or chronic superficial gastritis; Mod. CAG, moderate chronic atrophic gastritis; +ve, positive test; -ve, negative test; Spec., specificity; Sens., sensitivity; PV+, positive predictive value; PV-, negative predictive value; HP, *H. pylori*; IM, intestinal metaplasia.

<sup>b</sup> PV+ and PV- calculated for prevalence rate at endoscopy.

<sup>c</sup> PV+ and PV- calculated for prevalence rate of 10%.

(10) and *H. pylori* infection associated with a diffuse, antral, nonatrophic gastritis. Studies in other populations where *H. pylori* infection is endemic or where *H. pylori*-associated diffuse antral gastritis is common are likely to produce different results for sensitivity and specificity.

The cutoff criteria for the assays used in this study were established in independent validation studies using identical assay procedures (10, 14, 16). For *H. pylori* antibody titre, the cutoff can be validated against an obvious "gold standard," i.e., whether or not there is a *H. pylori* infection in the stomach. In this study we had available histological confirmation of gastric colonization by HLO and so were able to confirm 10.0 µg/ml as the optimum cutoff using receiver operating characteristic curve analysis. The lower sensitivity (84.8%) we obtained in comparison with other studies (16) was probably because the latter used both histopathology and microbiological culture to assess infection status rather than histopathology alone.

The cutoff of 1.5 for the PGA:PGC ratio is more arbitrary in that there is no dichotomous gold standard against which to validate the assay, and while raising the cutoff point would "detect" less severe cases of CAG, it would be at the expense of reducing the specificity. Empirical *post hoc* adjustment of the cutoff in this study did not improve the value of the PGA:PGC ratio in detecting either CAG or IM.

One anomalous feature of these results was the low proportion of patients with chronic superficial gastritis who were *H. pylori* antibody positive (3 of 13). Although there are other causes of superficial gastritis apart from *H. pylori* infection (4), it is now widely accepted that the bacteria is the major cause of "nonspecific" gastritis (11), and a higher proportion of positive patients might have been expected. This means that the specificity we reported for the use of the *H. pylori* antibody test alone in detecting CAG (91%) is likely to be too high in other situations.

In a study of 169 patients from New Orleans, Fox *et al.* (19) reported that 74 of 101 patients with CAG were *H. pylori* antibody positive (i.e., a sensitivity of 73%), while 46 of 68 patients without CAG were also positive (i.e., a specificity of 32%). The large difference in specificity was because 87% of the patients of Fox *et al.* with forms of gastritis other than CAG were *H. pylori* positive. In a population-based survey of 78 subjects in Colombia, South America, Correa *et al.* (20) reported 35 seropositive subjects of 42 with CAG or IM (i.e., a sensitivity of 83%) and 27 seropositive subjects of 36 without either lesion (i.e., a specificity of 25%). The two studies confirm, therefore, that our reported sensitivity of 71% can be replicated in other populations, but our specificity of 91% will not be generally applicable, especially in populations where the background rate of *H. pylori* infection is high.

For the PGA:PGC ratio, we report a sensitivity of 25% and a specificity of 94% in the identification of CAG and 50% and 92% in the identification of IM. This compares with 65% and 83% reported by Westerveld *et al.* (10) using the same assay for the identification of "gastric cancer and its precursors" (CAG/IM). Samloff *et al.* (7), in a study of relatives of patients with pernicious anemia, reported a sensitivity of 84% and a specificity of 70% for the detection of atrophic gastritis using the PGA:PGC ratio with a different assay, while Miki *et al.* (21) reported a sensitivity of 87% and a specificity of 84% for the detection of "open-type gastritis" using a third assay. The wide variation, especially in the sensitivity values, reflects the use of different assay procedures, different criteria for the definition of CAG, and the proportion of subjects with severe CAG in the reference patient population. An assay will be more sensitive if the reference disease group consists of a high proportion of cases with severe disease. In our study, where there was only one patient with severe CAG and a high proportion with mild CAG, the assay is likely to be less sensitive. Comparisons of mod-

erate (and severe) CAG against other histologies, however, did not materially affect the sensitivity (Table 4).

Classification schemes for gastritis have undergone recent revision (2) and remain the subject of unresolved controversy (22). Since the purpose of this study was solely to distinguish the presence or absence of gastric atrophy, the Whitehead classification scheme (6) was thought to be adequate.

To our knowledge, this is the first study to estimate the sensitivity and specificity of using both markers in combination to identify patients with CAG and/or IM. Although there are a number of studies looking at the effect of *H. pylori* infection on PG levels (23, 24), these have not focused on the specific precancerous lesions. In our patient population the combined markers had a high specificity and a low sensitivity.

Could these markers be used for screening individuals at high risk for gastric cancer? All current screening techniques involve direct examination of the stomach (e.g., endoscopic biopsy or radiology) and are thus time consuming and expensive. Preselection, by use of these markers, of a subgroup for such investigations might make more effective use of resources even if only a minority of the subjects with lesions were identified. The combined marker system would correctly identify one-half of all subjects with IM who could then be monitored by more invasive procedures. In the example given above, i.e., assuming a 10% prevalence, there would be an accompanying false positive rate of 26% who would also have to undergo investigation. This false positive rate is dependent on the prevalence and becomes higher as the prevalence decreases. Where the prevalence is high, the false positive rate might be sufficiently low such that the proportion of unnecessary investigations becomes acceptable. Thus, as far as screening is concerned, the use of these markers and subsequent endoscopy/radiology could identify a high-risk group more cheaply than say, endoscopying the entire population. The drawback would be that a substantial proportion of high-risk individuals would be missed.

If these markers are to be used to identify "cases" and "controls," respectively, with and without gastric lesions for subsequent epidemiological comparisons, then there are obvious problems. If the interest were in CAG and the specificity for the detection of this lesion were truly 100% then the "case" group would consist entirely of true cases, while the "control" group would contain false negative cases to an extent determined by the prevalence of the disease (low prevalence being equivalent to a low proportion of false negatives). With a specificity of 100% it would, however, be possible to calculate both the true prevalence rate and the false negative rate, and thus the proportion of false negatives could be estimated. If specificity is, in fact, anything less than 100%, then there will be both false positives and false negatives. Furthermore, a high true prevalence would result in a high proportion of false negatives.

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