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Assessment of Gastric Acidity by Conventional Endoscopy With Serological Gastric Markers

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Abstract

Background: Gastric acidity could determine *Helicobacter pylori* (*H. pylori*)-associated gastritis patterns. In reverse, *H. pylori* infection could lead disturbance in gastric acid secretion. We attempted to elucidate gastric acid status by conventional endoscopy with pepsinogen test.

Methods: A total of 196 subjects who visited our health promotion center were consecutively enrolled and evaluated by conventional endoscopy, and blood examinations with pepsinogen I, II, and fasting serum gastrin were conducted. As a Japanese study suggested that in *H. pylori*-positive subjects the cutoff value was PG I/II ratio ≤ 2.7 for hypochlorhydia, PG I/II ratio ≥ 3.3 for hyperchlorhydria. Based on these serological data, we compared conventional endoscopic images with each acid level.

Results: It showed that for hypoacidity, older age, and most of the *H. pylori*-associated endoscopic appearances featuring mucosal inflammation and more atrophy of corpus or antrum were in favor of hypoacidity in closed type. Mucosal appearances showing severe corpus atrophy and remnant gastritis with advanced background atrophy determine hypoacidity in open type. For hyperacidity, mucosal appearances featuring intact mucosa and less severe atrophy were associated with hyperacid status. Male gender, antrum camouflage were also involved in hyperacidity.

Conclusions: Conventional endoscopy with pepsinogen test could be useful in gastric acid assessment.

Keywords: Gastric acid secretion; Serum pepsinogen; *Helicobacter pylori*

Introduction

The level of gastric acidity is associated with various upper gastrointestinal tract diseases, and high or normal acid status is correlated with duodenal ulcerations or gastroesophageal reflux diseases [1, 2]. On the contrary, low or profoundly low acid secretion is frequent in gastric ulcerations or gastric cancers [3, 4]. A major component that could influence gastric acid secretion is *Helicobacter pylori* (*H. pylori*) infection in stomach. Furthermore, local acid production is a determining factor for prevalence of corpus-predominant gastritis with *H. pylori* infection [5], and acidity of affected subject can determine topographic patterns of *H. pylori*-associated gastritis, which result in different upper gastrointestinal diseases. Antral-predominant gastritis is a predominant pattern in duodenal ulcer patients with high acid secretion, and severity of corpus gastritis caused by *H. pylori* proportionally decreases gastric acid output leading to corpus-predominant atrophic gastritis in patients with low acid production [6]. Based on these findings, assessing acid level in subjects with *H. pylori*-associated gastritis is important to anticipate future upper gastrointestinal diseases like peptic ulcer or gastroesophageal reflux or even gastric cancer (GC). Uemura et al revealed importance of corpus dominant gastritis as a GC risk factor [7], and Correa suggested that *H. pylori* caused chronic gastritis, and especially corpus gastritis that was associated with loss of parietal cell mass resulting in hypochlorhydria or achlorhydria which was involved in production of carcinogenic compounds [8]. Consequently if we could sort out subjects with disturbed acid secretion based on conventional endoscopic findings, it might be a helpful guidance to identify the subjects with future gastrointestinal diseases including gastric cancer, especially for physicians in Korea, who perform biennial endoscopic gastric cancer screening. Ijima et al revealed the correlation between specific cutoff serum pepsinogen (PG) values and gastric acidity based on endoscopic gastrin test [9]. The authors showed that in *H. pylori*-positive subjects the cutoff value was PG I/II ratio ≤ 2.7 for hypochlorhydria, PG I/II ratio ≤ 2.2 for profound hypochlorhydria, and PG I/II ratio ≥ 3.3 for hyperchlorhydria; and they proved usefulness of PG test in assessing gastric acidity. Nomura et al [10, 11] revealed various conventional endoscopic appearances of *H. pylori*-infected gastric mucosa, which were correlated well with histological features like a mucosal inflammation or atrophy. Cho et al [12] showed three representative forms of *H. pylori* infected gastric mucosa (body type A, B and C). Kimura and Takemoto demonstrated that increased level of endoscopic atrophic border (EAB) was associated with decreased tendency of acid secretion [13]. EAB and various endoscopic appearances featuring mucosal inflammation or atrophy could be useful in anticipating gastric

Figure 1. Representative mucosal findings of antrum. (A-1) Normal antrum-in angle and proximal antrum lesser curvature side, RAC could be seen (A-1-a), RAC in proximal antrum greater curvature side also could be seen in right sided image (A-1-b). (A-2) Normal antrum vessel structure might be seen in remote (A-2-a), but RAC could be found between vessels in close up image (right sided image (A-2-b)). (A-3) Antrum visible vessel (A_VV) (A-3-a)-there are not any RAC between vessels (right sided close up image (A-3-b)). (A-4) Antrum visible vessel break (A_VV_B)-visible mucosal differences in thickness and color between antrum and low body greater curvature side (A-4-a) and no RAC on right sided close up view (A-4-b). (A-5), (A-6) Two representative figures of antrum camouflage (A_CAM)-mosaic like mucosal change with peripheral white grooves (A-5-a, A-6-a), both right sided close up views clearly show peripheral white grooves, and some erythematous mucosal change could enhance detection of CAM (A-5-b, A-6-b). (A-7) Excluded form of similar A_CAM-mosaic like mucosal image similar to A-5 or A-6 (A-7-a), however in close up view no peripheral white grooves (A-7-b). (A-8) Antrum mucosal edema (A_ME)-soft swelling of mucosa with mosaic pattern accompanying dark peripheral grooves (A-8-a, A-8-b). (A-9) Antrum intestinal metaplasia-whitish plaques were scattered on the mucosal surface. (A-10) Antrum diffuse erythema (A_DE)-any dark or light red colors scattered diffusely on the mucosa.

acidity. Based on these endoscopic and serological findings, we attempted to find conventional endoscopic images corresponding to each acid level.

Materials and Methods

Subjects and endoscopic examinations

A total of 196 subjects, who visited our health promotion center from January 2016 to September 2016 for screening endoscopy and had *H. pylori*-associated gastric mucosal appearances mainly based on findings of Nomura et al and Cho et al [10-12] were consecutively enrolled for the present study. All of them showed positive *H. pylori* test (rapid urea test using CLO Helicobacter-detection kits (Asan Pharm Co., Ltd., Seoul, Korea), sample for CLO test were taken from low body greater curvature side of stomach). Each representative

mucosal finding is shown in Figures 1 and 2. Subjects were excluded from the study if they had history of *H. pylori* eradication or if they had been taking any medicine influencing gastric mucosal appearance (any acid suppressive medicines or non-steroidal anti-inflammatory agent) within 8 weeks prior to examination; also we excluded subjects with any past or ongoing medical illness like liver or heart problem or malignant diseases. Because we explore gastric mucosal abnormalities only by visual images, subjects having no discernible EAB with normal looking gastric mucosa and *H. pylori* test positive were excluded. All the subjects had already been requested for *H. pylori* test and PG study for GC screening in a prequestionnaire. They were examined with conventional white light endoscopy using a GIF-Q150 (Olympus Co., Tokyo, Japan) and endoscopic mucosal images were collected for each individual with each type of EAB suggested by Kimura and Takemoto [13] (Table 1). All the endoscopic procedures were performed by the main author to avoid inter-observer variability. This study was approved by Korea National Institute
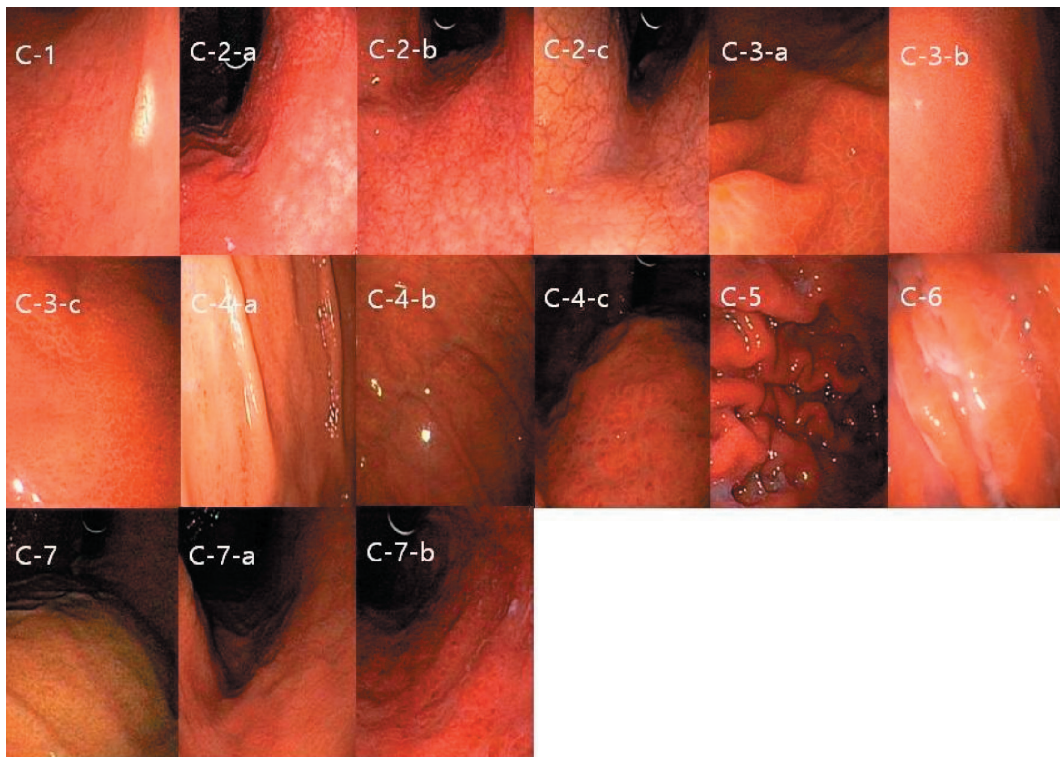
Figure 2. Representative mucosal findings of corpus. (C-1) Body xanthoma(B_XAN)-yellow white spot on the gastric mucosa. (C-2) Body visible vessel (B_VV)-graded as 3 when prominent and clear vessel marking in body lesser curvature side (C-2-c), and 2 when visible vessel mingled with irregular mucosa (C-2-b), 1 when only visible mucosal change in body LC side (C-2-a). (C-3) Body type A, B, and C (B_typeA, B_type B and B_type C)-A: mosaic-like appearance (C-3-a); B: diffuse homogenous redness (C-3-b); C: untypical (C-3-c). (C-4) Body spotty erythema (B_SE)-multilple red spots on the mucosa, graded as 1 when it could be seen only in body greater curvature (C-4-a) and 3 when clearly seen in fundus and body (C-4-c), and 2 when observed but neither 1 nor 3 (C-4-b). (C-5) Body rugal hyperplastic gastritis (B_RHG)-when gastric fold width was equal or over 5mm with the aid of opening width (7 mm) of biopsy forcep despite sufficient aeration. (C-6) Body exudate (B_EXU)-white mucinous fluid sticking to the mucosa. (C-7) Body regular arrangement of collecting venule (B_RAC). (C-7-a), (C-7-b) Body diffuse erythema (B_DE)-erythematous mucosal change graded as 1 when it could be identified by close-up observation of mucosa due to light red color (C-7-a) and 2 when easily identified at some distance due to dark red color (C-7-b).

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Serum pepsinogen and gastrin levels

Fasting blood samplings for serum PG test and gastrin were done before each endoscopy session, and the samples were centrifuged immediately at 4 °C. Serum concentrations of PG I and II were measured by a latex-enhanced turbidimetric immunoassay (HBI Co., Anyang, Korea), and PG I to PG II (PG I/II) ratio was calculated. Each centrifuged serum for gastrin was stored frozen at -20 °C until further assay and measured by GASTRIN (^{125}I) Radioimmunoassay Kit (MP Biomedicals Korea, MP bio). Gastric acid status was classified as PG I/II ratio ≤ 2.7 for hypoacid, PG I/II ratio > 2.7 or < 3.3 for normoacid, PG I/II ratio ≥ 3.3 for hyperacid [9].

Data analysis

All the endoscopic characteristics were graded as scores like EAB as 1 to 6, body visible vessel as 0 to 3, body spotty erythema as 0 to 3, body diffuse erythema as 0 to 2, and others were as 0 to 1. We categorized the subjects into groups based on acid status (hypoacid, normoacid and hyperacid). The statistical differences between each endoscopic parameter between the groups were assessed by one-way ANOVA with Tukey multiple comparison test. All P-value < 0.05 were considered as statistically significant. We used SPSS version 18.0 for Windows Software (SPSS Inc., Chicago, IL, USA), and performed binary logistic regression analysis with an enter method in univariate and with a forward method in multivariate analyses to obtain odds ratios (OR) of each endoscopic findings for hypoacid or hyperacid group. The data were further analyzed based on EAB like closed and open type. We designated body visible vessel, body spotty erythema, body diffuse erythema and EAB as continuous variables and the other parameters as categorical variables. As a forward method in binary logistic regression only reports meaningful results in the last step of variables in the equation table, we showed the same report in the multivariate analyses. We consider OR (> 1) as risk factor and OR (< 1) as protective feature. Protec-

Table 1. Endoscopic Parameters

Endoscopic feature	Biology of feature	Scales	Note
Body xanthoma (B_XAN)	Suggestive of *H. pylori*-associated gastritis with surrounding more atrophic mucosa	Grade 0: do not exist; Grade 1: exist	Yellow white spot on the gastric mucosa
Body visible vessel (B_VV)	Atrophy of body mucosa	Grade 0: do not exist; Grade 1: only visible mucosal change in body lesser curvature; Grade 2: visible vessels mingled with irregular mucosa; Grade 3: when prominent, and clear vessels marking in body lesser curvature side	
Body type A (B_type A)	Highly accurate mucosal pattern of *H. pylori* infection. Higher degree of atrophy (B > A,C) and IM (A,B) than normal RAC pattern	Grade 0: do not exist; Grade 1: exist	Mosaic-like appearance
Body type B (B_type B)			Diffuse homogenous redness
Body type C (B_type C)			Untypical-irregular redness with groove
Body spotty erythema (B_SE)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: when it could be seen only in body greater curvature; Grade 3: when clearly seen in fundus and body; Grade 2: when observed but neither 1 or 3	
Body rugal hyperplasia (B_RHG)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: exist	Gastric fold width was equal or over 5mm with the aid of opening width (7 mm) of biopsy forcep despite sufficient air inflation of stomach
Body regular arrangement of collecting venule (B_RAC)	Usually *H. pylori* free gastric mucosa.	Grade 0: do not exist; Grade 1: exist	
Body exudate (B_EXU)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: exist	White mucinous sticky fluid on the gastric mucosa
Body diffuse erythema (B_DE)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: when it could be identified by close-up observation of mucosa due to light red color; Grade 2: when easily identified at some distance due to dark red color	
Endoscopic atrophic border (EAB)	Degree of atrophy extent	Closed type 1 - 3 (C 1 – 3) (cardia saved from atrophic front); open type 1 - 3 (O 1 - 3) (cardia involved with atrophy)	As suggested by Kimura and Takemoto[13]
Antrum visible vessel break (A_VV_B)	Atrophy of antral mucosa with features suggestive of more inflammatory change in body side	Grade 0: do not exist; Grade 1: exist	Visible differences in mucosal thickness and color between antrum and low body greater curvature side
Antrum visible vessel (A_VV)	Atrophy of antral mucosa	Grade 0: do not exist; Grade 1: exist	
Antrum camouflage (A_CAM)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: exist	Mosaic like mucosal change with peripheral white grooves, some erythematous mucosal change could enhance detection
Antrum mucosal edema (A_ME)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: exist	Soft swelling of mucosa with mosaic pattern but accompanied with dark peripheral grooves
Antrum intestinal metaplasia (A_IM)	Metaplastic antral mucosa	Grade 0: do not exist; Grade 1: exist	When whitish plaques were scattered on the mucosal surface
Antrum diffuse erythema (A_DE)	Suggestive of *H. pylori*-associated gastritis	Grade 0: do not exist; Grade 1: exist	

Table 2. Characteristics of Subjects

	Total	Closed type	Open type
Number	196	151	45
Age (years ± SD)	50.6 ± 9.0	49.8 ± 9.0	53.5 ± 8.8
Sex (male : female)	144 : 52	112 : 39	32 : 13
Hyperacidity(number)	78	72	6
Hypoacidity (number)	73	37	36
Normoacidity (number)	45	42	3

tive feature means risk reducing factor for corresponding acid status. Consequently, various acid statuses would be possible if risk factors and protective factors are coexisted.

Results

Characteristics of the subjects

In 196 subjects, there were 144 males and 52 females; the mean age of the subjects was 50.6 ± 9.0 years (the mean ± standard deviation (SD)). Totally 151 subjects were in the closed type and 45 were in the open type. In 151 subjects with closed type, 72 were in the hyperacid state, 37 were in the hypoacid state, and 42 were in the normoacid state. In open type subjects, six were in the hyperacid state, 36 were in the hypoacid state, and three were in the normoacid state. Hypoacidity was observed to be the dominant form of disturbed acid status in the subjects with open type; and hyperacidity or normoacidity were observed as the dominant form in the closed type (Table 2).

Characteristics of the subjects and serological markers subsequent to classification into subgroups

The mean age of the subjects in the hypoacid group was higher than the subjects in the hyperacid group, but showed no difference between hypoacid and normoacid group. PG I and sex showed no differences between the groups, but PG II and gastrin showed high level in the order of hypoacid, normoacid and hyperacid group (Table 3).

Scores of endoscopic parameters (in multiple comparison test, = means no difference, > means higher score than comparing group)

Endoscopic features that showed higher score in hypoacid group were body xanthoma (= normoacid, > hyperacid), body visible vessel (> normoacid, > hyperacid), body type B (> normoacid, > hyperacid), body rugal hyperplasia (> normoacid, > hyperacid), body exudate (> normoacid, > hyperacid), body diffuse erythema (= normoacid, > hyperacid), EAB (> normoacid, > hyperacid), and antrum visible vessel (= normoacid, > hyperacid). And mucosal appearances that showed higher score in hyperacid group were body type A (= normoacid, > hypoacid), antrum camouflage (CAM) (= normoacid, > hypoacid) and body RAC (= normoacid, > hypoacid). The score of body type C was higher in normoacid group, but no difference was shown between hypoacid and hyperacid groups (Table 4).

Univariate and multivariate analyses for disturbed acid status

Univariate analyses for hyperacid

Overall body RAC (OR: 4.444, P = 0.003), body type A (3.921, P < 0.001), male sex (2.171, P = 0.029), and antrum CAM (2.080, P = 0.015) were the significant risk factors for hyperacid. However, age, body visible vessel, body type B, body rugal hyperplasia, body exudate, body diffuse erythema, antrum visible vessel, and EAB were the protective features against hyperacid.

In closed type, body RAC (OR: 4.131, P = 0.018), body type A (3.297, P = 0.001), and antrum CAM (2.303, P = 0.015) were the risk factors for hyperacid; age, body type B, body rugal hyperplasia, body exudate, body diffuse erythema, and antrum visible vessel were protective against hyperacid.

In open type, body RAC (OR: 9.250, P =0.049) was the only risk factor for hyperacid. Body type B and body exudate were the protective factors (Table 5).

Table 3. Demographic and Serological Data of Hypoacid, Normoacid and Hyperacid

	Total	Hypoacid	Normoacid	Hyperacid	P-value (hypoacid vs. normoacid vs. hyperacid)
Number	196	73	45	78	
Age (years ± SD)	50.6 ± 9.0	53.4 ± 8.5	49.9 ± 9.3	48.4 ± 8.7	0.002
Sex (male : female)	144 : 52	50 : 23	30 : 15	64 : 14	0.085
Pep_I	65.1 ± 25.6	60.9 ± 24.6	64.1 ± 23.1	69.5 ± 27.5	0.116
Pep_II	22.2 ± 10.8	28.6 ± 11.6	21.4 ± 8.0	16.6 ± 7.9	0.001
Gastrin	73.0 ± 37.7	94.3 ± 49.9	64.1 ± 22.8	58.3 ± 16.5	0.001
I/II ratio	3.2 ± 1.2	2.1 ± 0.4	3.0 ± 0.2	4.4 ± 0.9	0.001

Pep_I: pepsinogen I; Pep_II: pepsinogen II.

Table 4. Scores of Endoscopic Appearances of Hypoacid, Normoacid and Hyperacid

	Total	Hypoacid	Normoacid	Hyperacid	P-value (hypoacid vs. normoacid vs. hyperacid)
Number	196	73	45	78	
B_XAN	0.06 ± 0.23	0.11 ± 0.32	0.04 ± 0.21	0.01 ± 0.11	0.033
B_VV	1.31 ± 0.87	1.66 ± 0.87	1.22 ± 0.82	1.04 ± 0.78	0.001
B_type A	0.34 ± 0.48	0.15 ± 0.36	0.33 ± 0.48	0.53 ± 0.50	0.001
B_type B	0.45 ± 0.50	0.78 ± 0.48	0.40 ± 0.50	0.17 ± 0.38	0.001
B_type C	0.10 ± 0.30	0.03 ± 0.16	0.20 ± 0.41	0.12 ± 0.32	0.009
B_SE	0.63 ± 0.98	0.59 ± 0.92	0.87 ± 1.16	0.53 ± 0.89	0.160
B_RHG	0.17 ± 0.38	0.30 ± 0.46	0.11 ± 0.32	0.08 ± 0.27	0.001
B_RAC	0.11 ± 0.31	0.04 ± 0.20	0.07 ± 0.25	0.19 ± 0.40	0.006
B_EXU	0.47 ± 0.50	0.71 ± 0.46	0.40 ± 0.50	0.29 ± 0.46	0.001
B_DE	0.97 ± 0.97	1.16 ± 0.97	1.02 ± 0.97	0.77 ± 0.95	0.041
EAB	3.04 ± 1.02	3.66 ± 1.03	2.78 ± 0.74	2.60 ± 0.87	0.001
A_VV_B	0.21 ± 0.41	0.25 ± 0.43	0.18 ± 0.39	0.21 ± 0.41	0.658
A_VV	0.33 ± 0.47	0.49 ± 0.50	0.31 ± 0.47	0.18 ± 0.39	0.001
A_CAM	0.38 ± 0.49	0.30 ± 0.46	0.33 ± 0.48	0.49 ± 0.50	0.047
A_ME	0.20 ± 0.40	0.21 ± 0.41	0.20 ± 0.41	0.21 ± 0.41	0.997
A_IM	0.18 ± 0.38	0.25 ± 0.43	0.11 ± 0.32	0.15 ± 0.36	0.135
A_DE	0.47 ± 0.50	0.42 ± 0.50	0.58 ± 0.50	0.46 ± 0.50	0.262

B_XAN: body xanthoma; B_VV: body visible vessel; B_type A: body type A; B_type B: body type B; B_type C: body type C; B_SE: body spotty erythema; B_RHG: body rugal hyperplasia; B_RAC: body regular arrangement of collecting venule; B_EXU: body exudate; B_DE: body diffuse erythema; EAB: endoscopic atrophic border; A_VV_B: antrum visible vessel break; A_VV: antrum visible vessel; A_CAM: antrum camouflage; A_ME: antrum mucosal edema; A_IM: antrum intestinal metaplasia; A_DE: antrum diffuse erythema.

Multivariate analyses for hyperacid

Overall male sex (OR: 2.389, P = 0.032) was the only significant risk factor for hyperacid.

In closed type, antrum CAM (OR: 2.527, P = 0.018) was the only risk factor for hyperacid. Age, body type B, and body diffuse erythema were the protective factors against hyperacid.

In open type, no significant risk factors for hyperacid were found, and body exudate was the only significant protective factor against hyperacid (Table 6).

Univariate analyses for hypoacidity

Overall body type B (OR: 10.573, P < 0.001), body exudate (4.952, P < 0.001), body xanthoma (4.923, P = 0.022), body rugal hyperplasia (4.392, P < 0.001), EAB (3.346, P < 0.001), antrum visible vessel (3.301, P < 0.001), body visible vessel (2.215, P < 0.001), body diffuse erythema (1.382, P = 0.036), and age (1.061, P = 0.001) were the risk factors for hypoacidity. However, body type A, body type C, and body RAC were the protective factors against hypoacidity.

In closed type, body type B (OR: 10.025, P < 0.001), body xanthoma (6.788, P= 0.031), body rugal hyperplasia (4.495, P = 0.001), body exudate (3.052, P = 0.004), antrum visible vessel (2.408, P = 0.033), body diffuse erythema (2.026, P = 0.001), and age (1.088, P = 0.001) were the significant factors

for hypoacidity. Body type A and antrum CAM were the protective factors for hypoacidity.

In open type, body exudate (OR: 6.250, P = 0.023), body type B (5.179, P = 0.038), and body visible vessel (3.593, P = 0.039) were the significant risk factors for hypoacidity. There were no significant protective factors against hypoacidity (Table 7).

Multivariate analyses for hypoacidity

Overall body type B (OR: 6.391, P < 0.001), body rugal hyperplasia (3.417, P = 0.013), EAB (2.756, P < 0.001), and age (1.066, P = 0.008) were significant factors for hypoacidity. None of the factors exhibited any significant protective aspect.

In closed type, body xanthoma (OR: 127.603, P = 0.002), body type B (12.517, P < 0.001), body rugal hyperplasia (5.205, P = 0.019), body diffuse erythema (2.667, P= 0.002), and age (1.134, P = 0.001) were risky parameters for hypoacidity. Antrum diffuse erythema showed protective aspect.

In open type, body exudate (OR: 10.671, P = 0.026) was the only risk factor for hypoacidity. None of the factors exhibited any significant protective aspect (Table 8).

Meaning of camouflage appearance

As shown in Table 9, comparison of CAM group with non-

Table 5. Risk Factors for Hyperacid in Univariable Analysis

Number(hyper)	Overall 196 (78)			Closed type 151 (72)			Open type 45 (6)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	0.954	0.923 - 0.987	0.006	0.956	0.920 - 0.993	0.019	1.008	0.912 - 1.114	0.877
Sex	2.171	1.083 - 4.352	0.029	1.918	0.904 - 4.068	0.090	3.728×10^8	B	0.999
B_XAN	0.140	0.018 - 1.119	0.064	0.208	0.024 - 1.829	0.157	0.000	B	0.999
B_VV	0.523	0.363 - 0.752	0.000	0.733	0.485 - 1.108	0.141	0.264	0.062 - 1.119	0.071
B_type A	3.921	2.105 - 7.304	0.000	3.297	1.660 - 6.550	0.001	5.500	0.890 - 33.994	0.067
B_type B	0.115	0.057 - 0.232	0.000	0.143	0.066 - 0.313	0.000	0.129	0.020 - 0.835	0.032
B_type C	1.269	0.500 - 3.220	0.616	0.883	0.343 - 2.273	0.797		A	
B_SE	0.832	0.614 - 1.128	0.235	0.867	0.626 - 1.200	0.390	0.000	B	0.998
B_RHG	0.281	0.110 - 0.717	0.008	0.332	0.123 - 0.895	0.029	0.000	B	0.999
B_RAC	4.444	1.642 - 12.031	0.003	4.131	1.280 - 13.330	0.018	9.250	1.010 - 84.732	0.049
B_EXU	0.287	0.156 - 0.528	0.000	0.444	0.227 - 0.871	0.018	0.109	0.017 - 0.720	0.021
B_DE	0.693	0.513 - 0.936	0.017	0.601	0.427 - 0.846	0.003	1.111	0.466 - 2.652	0.812
A_VV_B	0.913	0.453 - 1.841	0.800	0.960	0.439 - 2.098	0.918	0.667	0.069 - 6.470	0.727
A_VV	0.298	0.150 - 0.590	0.001	0.368	0.166 - 0.814	0.014	0.625	0.111 - 3.509	0.593
A_CAM	2.080	1.153 - 3.753	0.015	2.303	1.178 - 4.502	0.015	1.786	0.317 - 10.061	0.511
A_ME	1.011	0.497 - 2.054	0.976	0.950	0.427 - 2.117	0.901	1.937	0.300 - 12.532	0.487
A_IM	0.751	0.349 - 1.614	0.463	2.057	0.762 - 5.554	0.155	0.000	B	0.998
A_DE	0.917	0.517 - 1.627	0.768	0.863	0.455 - 1.639	0.653	2.105	0.345 - 12.861	0.420
EAB	0.436	0.303 - 0.627	0.000						

A: There were not any cases; B: indefinite; B_XAN: body xanthoma; B_VV: body visible vessel; B_type A: body type A; B_type B: body type B; B_type C: body type C; B_SE: body spotty erythema; B_RHG: body rugal hyperplasia; B_RAC: body regular arrangement of collecting venule; B_EXU: body exudate; B_DE: body diffuse erythema; EAB: endoscopic atrophic border; A_VV_B: antrum visible vessel break; A_VV: antrum visible vessel; A_CAM: antrum camouflage; A_ME: antrum mucosal edema; A_IM: antrum intestinal metaplasia; A_DE: antrum diffuse erythema. CI: confidence interval; OR: odds ratio.

CMA group revealed the significantly lower level of PG II in CAM group, no significant other serological or demographic differences were observed.

Discussion

It was reported that the distribution of *H. pyori* was even in the entire gastric mucosa [14, 15]. However, intrinsic gastric acidity has been known to determine the outcome of the subject with *H. pylori* infection by either promoting corpus gastritis or not. For example, high acid secretion maintains *H. pylori*-associated gastritis in the antrum [2], and low acid state could be involved in corpus dominant gastritis. Also the severity of *H. pylori*-associated gastric inflammation could inversely influence gastric acid secretory disturbance resulting in various adverse outcomes such as peptic ulcer diseases, reflux esophagitis, or even gastric cancers.

Based on endoscopic findings, we attempted to find the clues about gastric acid status with the aid of serological information. As one of the most discernible endoscopic findings is EAB, we first divided subjects into two groups as the closed type and open type and revealed each dominant type was hypoacidity in open type and hyperacidity or normoacidity in

closed type. This similar observation was originally described in the study by Kimura and Takemoto [13].

The hypoacid group had higher PG II and gastrin level than normoacid or hyperacid group, this was comparable to the findings that PG II could be a surrogate marker of corpus inflammation [16], and corpus gastritis was correlated with disturbance in gastric acid secretion [17, 18]. Referring to these results we would cautiously conclude that in our subjects hypoacidity was mainly dependent on severity of gastritis.

Statistical analyses revealed that in the case of hypoacidity, antrum visible vessel, and most of the *H. pylori*-associated endoscopic parameters representing mucosal inflammation and more atrophy of corpus like body type B [12] were correlated with hypoacidity in overall and closed type. These results were similar in both univariate and multivariate analysis. However, in open type, body exudate, body type B, and body visible vessel contributed to hypoacidity in univariate analysis and only body exudate was meaningful in multivariate analysis. These findings probably mean that in closed type, the severity of gastritis and more atrophic body type might have an influence on the decrease in gastric acid secretion. On the other hand, in open type, the severity of atrophy and persistent inflammation caused by the relatively high amount of *H. pylori* in the exudate [19] with advanced background atrophy might

Table 6. Risk Factors for Hyperacid in Multivariable Analysis

Number (hypo)	Overall 196 (78)			Closed type 151 (72)			Open type 45 (6)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age				0.951	0.970 - 0.995	0.028			
Sex	2.389	1.076 - 5.301	0.032						
B_XAN									
B_VV									
B_type A									
B_type B	0.154	0.074 - 0.322	0.000	0.164	0.072 - 0.372	0.000			
B_type C									
B_SE									
B_RHG									
B_RAC									
B_EXU							0.109	0.017 - 0.720	0.021
B_DE				0.654	0.444 - 0.966	0.033			
A_VV_B									
A_VV									
A_CAM				2.527	1.169 - 5.463	0.018			
A_ME									
A_IM									
A_DE									
EAB	0.536	0.357 - 0.805	0.003						

B_XAN: body xanthoma; B_VV: body visible vessel; B_type A: body type A; B_type B: body type B; B_type C: body type C; B_SE: body spotty erythema; B_RHG: body rugal hyperplasia; B_RAC: body regular arrangement of collecting venule; B_EXU: body exudate; B_DE: body diffuse erythema; EAB: endoscopic atrophic border; A_VV_B: antrum visible vessel break; A_VV: antrum visible vessel; A_CAM: antrum camouflage; A_ME: antrum mucosal edema; A_IM: antrum intestinal metaplasia; A_DE: antrum diffuse erythema; CI: confidence interval; OR: odds ratio.

determine gastric acid secretion.

For hyperacidity, mucosal appearances showing less atrophy or relatively intact state (body type A, body RAC) were involved in hyperacid state in univariate analysis. Newly added antrum CAM was involved in hyperacidity in univariate and multivariate analysis.

Body findings, such as body xanthoma and RHG probably denoted hypoacidity derived from active inflammation, similar to the report previously published [20, 21]. Body diffuse erythema means interstitial inflammatory cell infiltration in the atrophy background [11, 22]. Body type B represents more histological atrophy than body type A or C [12], of course, body RAC means intact body mucosal state secreting gastric acid normally.

As antrum aspects, antrum diffuse erythema was associated with protective effect in multivariate analysis for closed type hypoacidity, this might be due to the fact that antrum diffuse erythema was one of the representative features of mononuclear cell infiltration related to antral gastric (G) cell hyperfunction resulting in increase in gastric acid by hypergastrinemia [11, 23]. Antrum CAM was involved in overall and closed type hyperacidity, however only PG II level was lower in antrum CAM group than in non-antrum CAM group and no other serological differences were observed, which mean that considering PG II as a corpus inflammatory sur-

rogate marker, contribution of antrum CAM for hyperacidity might be a secondary change caused by increased body acid (Table 9). As antrum CAM basically consists of some component of erythema, we could not exclude the possibility of antrum hyperfunction in antrum CAM, hence further study is required. In only univariate analysis, antrum visible vessel was related to overall hypoacidity, and antrum IM in open type hypoacidity. As antral atrophy progresses, corpus migration of *H. pylori* could be accelerated and this may cause aggravation of corpus gastritis resulting in decrease in gastric acid [24-26]. This antral induced hypoacidity might partly support the retrospective-case control study suggesting that atrophic gastritis of the antrum and body of the stomach are independent risk factors for GC [27]. And a study by Shiotani et al [28] that showed higher frequency of IM and inflammation at the antrum was associated with GC could also be supported by our result.

Male gender was correlated with hyperacidity and aging was related to hypoacidity similar to the results of previous study [29].

It could be hypothesized that in western countries or in subjects with plenty of gastric acid, hypoacidity could possibly be induced by advanced antrum pathology plus disturbed acid secretion by acquired factors like cigarette or salt, low intake of fresh vegetables, which might allow *H. pyori* to mi-

Table 7. Risk Factors for Hypoacid in Univariable Analysis

Number (hypo)	Overall 196 (73)			Closed type 151 (37)			Open type 45 (36)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.061	1.024 - 1.099	0.001	1.088	1.036 - 1.144	0.001	0.937	0.854 - 1.028	0.170
Sex	0.671	0.352 - 1.279	0.225	0.770	0.338 - 1.754	0.533	0.250	0.028 - 2.237	0.215
B_XAN	4.923	1.263 - 19.197	0.022	6.788	1.190 - 38.720	0.031	1.000	0.098 - 10.219	0.000
B_VV	2.215	1.521 - 3.225	0.000	1.211	0.757 - 1.937	0.425	3.293	1.070 - 12.072	0.039
B_type A	0.212	0.102 - 0.442	0.000	0.231	0.089 - 0.596	0.002	0.202	0.040 - 1.018	0.053
B_type B	10.573	5.314 - 21.034	0.000	10.025	4.215 - 23.839	0.000	5.179	1.097 - 24.457	0.038
B_type C	0.164	0.037 - 0.730	0.018	0.305	0.067 - 1.381	0.123		A	
B_SE	0.937	0.693 - 1.265	0.670	0.866	0.584 - 1.284	0.474	1.566	0.578 - 4.244	0.377
B_RHG	4.392	1.982 - 9.735	0.000	4.495	1.778 - 11.363	0.001	5.592×10^{8}	B	0.999
B_RAC	0.250	0.071 - 0.881	0.031	0.170	0.022 - 1.330	0.091	0.206	0.025 - 1.719	0.144
B_EXU	4.952	2.637 - 9.302	0.000	3.052	1.421 - 6.556	0.004	6.250	1.287 - 30.349	0.023
B_DE	1.382	1.022 - 1.869	0.036	2.026	1.324 - 3.099	0.001	0.773	0.367 - 1.627	0.498
A_VV_B	1.350	0.674 - 2.703	0.397	1.272	0.528 - 3.064	0.592	2.667	0.292 - 24.345	0.385
A_VV	3.301	1.770 - 6.155	0.000	2.408	1.075 - 5.395	0.033	1.257	0.287 - 5.499	0.761
A_CAM	0.570	0.308 - 1.053	0.073	0.426	0.185 - 0.985	0.046	0.707	0.161 - 3.105	0.646
A_ME	1.014	0.495 - 2.078	0.970	1.154	0.464 - 2.867	0.758	0.483	0.096 - 2.423	0.376
A_IM	2.041	0.975 - 4.271	0.058	0.326	0.072 - 1.484	0.147	7.27×10^{8}	B	0.998
A_DE	0.726	0.405 - 1.301	0.282	0.542	0.251 - 1.168	0.118	0.800	0.184 - 3.473	0.766
EAB	3.346	2.204 - 5.082	0.000						

A: there were not any cases; B: indefinite; B_XAN: body xanthoma; B_VV: body visible vessel; B_type A: body type A; B_type B: body type B; B_type C: body type C; B_SE: body spotty erythema; B_RHG: body rugal hyperplasia; B_RAC: body regular arrangement of collecting venule; B_EXU: body exudate; B_DE: body diffuse erythema; EAB: endoscopic atrophic border; A_VV_B: antrum visible vessel break; A_VV: antrum visible vessel; A_CAM: antrum camouflage; A_ME: antrum mucosal edema; A_IM: antrum intestinal metaplasia; A_DE: antrum diffuse erythema; CI: confidence interval; OR: odds ratio.

grate into corpus more easily. Also this western type might be atrophy dependent rather than gastritis in reducing gastric acid [30]. In contrast, in oriental area like Japan, hypoacidity could mainly occur due to rapid corpus migration of *H. pylori* by a genetically determined shortage of acid reservoir and additional harmful environmental factors, which might be dependent on the severity of gastritis in determining gastric acidity, although additional atrophy could further aggravate gastric acid shortage. Consequently many possible combinations of western and oriental type could exist and population with oriental type might benefit from *H. pylori* eradication for the recovery of acid secretion except for the severe corpus atrophy [4, 24].

Considering all these facts, awareness about hypoacidity would be a great tool in proper management of patient. During endoscopy session, if closed type EAB encountered, most cases would be normoacid or hyperacid state. However, when any one of hypoacid features like body xanthoma, body type B, body rugal hyperplasia or body diffuse erythema was accompanied, we should consider early *H. pylori* eradication to prevent ongoing hypoacid state. Of course in open type EAB, we should take into account *H. pylori* eradication and environmental factor correction like smoking cessation or low salt diet etc.

Antrum CAM could be a useful parameter for recovery of acid secretion after eradication if it is secondary change of hyperacid as our study. When antrum CAM was accompanied with closed type EAB, one might consider hyperacid related disease like duodenal ulcer or reflux esophagitis.

Hematin was a predictive endoscopic finding for hyperacidity, swelling of areae gastricae and open type gastric atrophy were the endoscopic findings for hypoacidity in a Japanese study [31]. However, we used other various endoscopic findings and disclosed explainable mechanism for endoscopic parameters in disturbed acid status.

This study had several limitations. Histologic confirmation to support endoscopic finding was omitted, however this study was focused on evaluating functional aspect of stomach by endoscopy and most of endoscopic parameters were histologically verified in previous studies. Of course newly added antrum CAM was used only in our center, we are seriously considering multicenter study to correct this drawback in near future. Also we did not depend on direct measurement of gastric acid. However, reference value of pepsinogen test was the same (positive finding of PG test were PG I/II ratio ≤ 3.0 and PGI ≤ 70 ng/mL) as Japan, which means that our serological results were not different from the Japanese study [9]. Additionally, there existed an inevitable bias to implement

Table 8. Risk Factors for Hypoacid in Multivariable Analysis

Number (hypo)	Overall 196 (73)			Closed type 151 (37)			Open type 45 (36)		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Age	1.066	10.170 - 1.118	0.008	1.134	1.056 - 1.217	0.001			
Sex									
B_XAN				127.603	5.867 - 2775.034	0.002			
B_VV									
B_type A									
B_type B	6.391	2.953 - 13.831	0.000	12.517	3.944 - 39.722	0.000			
B_type C									
B_SE									
B_RHG	3.417	1.289 - 9.056	0.013	5.205	1.319 - 20.543	0.019			
B_RAC									
B_EXU							10.671	1.324 - 86.018	0.026
B_DE				2.667	1.423 - 4.997	0.002			
A_VV_B									
A_VV									
A_CAM									
A_ME									
A_IM									
A_DE				0.161	0.047 - 0.554	0.004			
EAB	2.756	1.717 - 4.424	0.000						

B_XAN: body xanthoma; B_VV: body visible vessel; B_type A: body type A; B_type B: body type B; B_type C: body type C; B_SE: body spotty erythema; B_RHG: body rugal hyperplasia; B_RAC: body regular arrangement of collecting venule; B_EXU: body exudate; B_DE: body diffuse erythema; EAB: endoscopic atrophic border; A_VV_B: antrum visible vessel break; A_VV: antrum visible vessel; A_CAM: antrum camouflage; A_ME: antrum mucosal edema; A_IM: antrum intestinal metaplasia; A_DE: antrum diffuse erythema; CI: confidence interval; OR: odds ratio.

Japanese results directly on our subjects, because of different sexual and age distributions even if there was a similar ethnic background. Actually most of our subjects were employees of regional companies, being younger and male dominant. Nevertheless, we showed that several aspects of our results, such as EAB, male gender, age, etc. were similar to the previous studies using direct measurement of gastric acid, this might be an evidence that PG level in our study could be an alternative to direct measurement of gastric acid.

Needless to state that when a physician wishes to evaluate specific diseases it should be practical to employ each coun-try's specific and easily available methods, such as a pepsinogen test in Japan and endoscopy in Korea for screening GC. This was our main aim to conduct this study. We could have obtained more detailed and exact results if there had been Korea-specific data based on direct measurement of gastric acidity. In near future, nation-wide study is needed.

Conflict of Interest

There is no conflict of interest.

Table 9. Serological and Demographic Meaning of Antrum Camouflage

	Total	CAM	Non-CAM	P-value (CAM vs. non-CAM)
Number	151	75	121	
Age (years ± SD)	49.8 ± 9.0	50.5 ± 7.9	50.7 ± 9.7	0.873
Sex (male : female)	112 : 39	54 : 21	90 : 31	0.536
Pep_I	68.4 ± 24.6	61.3 ± 22.4	67.4 ± 27.3	0.103
Pep_II	21.7 ± 10.4	19.8 ± 9.5	23.7 ± 11.3	0.015
Gastrin	68.2 ± 32.4	70.0 ± 35.8	74.9 ± 38.8	0.382
I/II ratio	3.5 ± 1.1	3.4 ± 1.2	3.1 ± 1.2	0.067

Pep_I: pepsinogen I; Pep_II: pepsinogen II.

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