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BRIEF ARTICLE

Gastric juice acidity in upper gastrointestinal diseases

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Abstract

AIM: To search the independent factors determining gastric juice acidity and to investigate the acidity of gastric juices in various benign and malignant upper gastrointestinal diseases.

METHODS: Fasting gastric juice acidity of 165 healthy subjects and 346 patients with esophageal ulcer (n = 21), gastric ulcer (n = 136), duodenal ulcer (n = 100) or gastric cancer (n = 89) were measured and compared. Additionally, gastric specimens were taken from the antrum and body for rapid urease test and histological examination.

RESULTS: Multivariate analysis revealed that bile stain of gastric juice, high acute inflammatory score of the corpus, and atrophy of the corpus were independent risk factors for the development of gastric hypoacidity with odds ratios of 3.1 (95% CI: 1.3-7.3), 3.1 (95% CI: 1.2-7.9) and 3.5 (95% CI: 1.3-9.2). Esophageal ulcer and duodenal ulcer patients had a lower pH level (1.9 and 2.1 *vs* 2.9, both $P < 0.05$) of gastric juices than healthy subjects. In contrast, gastric ulcer and gastric cancer patients had a higher pH level (3.4 and 6.6 *vs* 2.9, both $P < 0.001$) than healthy controls. Hypoacidity existed in 22%, 5%, 29%, 5% and 88% of healthy subjects, esophageal ulcer, gastric ulcer, duodenal ulcer and gastric cancer patients, respectively.

CONCLUSION: Bile reflux, atrophy and dense neutrophil infiltrate of the corpus are three independent factors determining the acidity of gastric juice.

Key words: Acidity; Gastric juice; Gastric cancer; Peptic ulcer; Esophageal ulcer

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INTRODUCTION

Gastric juices are liquids found in the stomach. They contain numerous compounds, including hydrochloric acid (HCl), pepsin, lipase, mucin, intrinsic factor, peptides, nucleic acids and electrolytes[1]. Additionally, they may also contain salivary constituents due to swallowing, bile due to gastroduodenal reflux and inflammatory mediators or blood from damaged gastric walls[2]. In their normal state, gastric juices are usually clear in color.

HCl is an important component in gastric juice. It is a strong acid produced by the parietal cells in the corpus generating a gastric pH of 2-3[1]. Activation of pepsin and absorption of nutrients relies on an acidic pH in the stomach. HCl is also important in protecting the stomach and intestines from pathogens. Increased gastric pH induced by disease process, reflux of bile or pharmaceuticals allows for bacterial overgrowth in the stomach[3]. These pathogenic bacteria in the hypochlorhydria stomach can produce nitrite and nitroso-compounds, which act as one of the triggers in the atrophy-metaplasia-dysplasia-carcinoma pathway[4].

Helicobacter pylori (*H. pylori*) infection is an important biological factor which can induce marked alterations in gastric acid secretion of hosts[5,6]. In subjects with an antrum-predominant gastritis following *H. pylori* infection there is increased release of gastrin and consequently increased acid secretion. Such subjects have an increased risk of developing duodenal ulcers (DU)[7,8]. In contrast, the infection induces a corpus-predominant gastritis with hyposecretion of acid in some subjects. These infected subjects have an increased risk of developing gastric cancer (GC)[9,10]. Gastric juices can lead to mucosal damage when they enter the esophagus. Patients with gastroesophageal reflux diseases (GERD) may develop esophageal breaks, along with damage to the enamel of the teeth caused by the high acidity of the stomach contents[11].

Since the acidity of gastric juice is one of the crucial factors in the development of most upper gastrointestinal diseases, we designed this study to search the independent factors determining gastric juice acidity and to investigate the acidity of gastric juices in various upper gastrointestinal diseases.

MATERIALS AND METHODS

Subjects

One hundred and sixty-five consecutive healthy subjects (HSs), 21 patients with esophageal ulcer (EU), 136 patients with gastric ulcer (GU), 100 patients with DU and 89 patients with GC participated in the study. The HSs recruited from our health examination clinics had no clinical history of gastrointestinal diseases, and their endoscopic findings were normal or showed mild gastritis only. The diagnoses of EU, GU and DU were confirmed by endoscopic examination. An EU was defined as a well-defined mucosal break present in the lower esophagus[12]. A gastric or duodenal ulcer was defined as a circumscribed mucosal break 5 mm or more in diameter, with a well-defined ulcer crater in the stomach or duodenum, respectively[13]. The size of ulceration was measured by opening a pair of biopsy forceps of known span in front of the ulcer. The diagnosis of GC was confirmed by histology. Additionally, GC was classified as intestinal (n = 50), diffuse (n = 31) and mixed (n = 8) according to the Lauren's classification[14]. The patient exclusion criteria included (1) the use of proton pump inhibitors or H2-receptor antagonists within 4 wk prior to the study; (2) coexistence of two kinds of gastroduodenal lesions; (3) presentation with upper gastroduodenal bleeding; and (4) coexistence of severe systemic diseases. The study was approved by the Medical Research Committee of the Kaohsiung Veterans General Hospital. All patients and controls gave informed consent.

Clinical methods

Endoscopies were performed with the Olympus GIF XV10 and GIF XQ200 (Olympus Co., Tokyo, Japan) after patients had fasted overnight. Immediately after insertion of the scope into the stomach, 5 mL of gastric fluid was aspirated through the suction channel of the endoscope and collected in a sterile trap placed in the suction line for acidity assay and color assessment. Routine inspection of the upper gastrointestinal tract was then performed. Additionally, gastric specimens were taken for rapid urease test (one specimen from the antrum) and histological examination (two specimens from the antrum and another two from the body)[15].

To adjust for clinical characteristics, the following data were recorded for each subject: age, sex, family history of gastric cancer, smoking, alcohol drinking, coffee consumption, tea consumption.

Acidity and color of gastric juice

The pH of gastric juice was measured just after collection with a glass-electrode pH meter. Hypoacidity was defined as pH level of gastric juice greater than 3.5[16]. The color of gastric juice was carefully assessed, and bile stain of gastric juice was defined as yellowish or greenish discoloration of the gastric juices.

Rapid urease test

The rapid urease test was performed according to our previous studies[17]. Each biopsy specimen was placed immediately in 1 mL of a 10% solution of urea in deionized water (pH 6.8) to which two drops of 1% phenol red solution had been added and incubated at 37℃ for up to 24 h. If the yellowish color around the area of inserted specimen changed to bright pink within the 24-h limit, the urease test was considered positive. In our laboratory, the sensitivity and specificity of the rapid urease test were 96% and 91%, respectively.

Histological assessment

A histological examination of the stomach was carried out for the subjects who provided informed consent for topographical histopathological study. The biopsy specimens were fixed in 10% buffered formalin, embedded in

Table 1 Baseline characteristics of healthy subjects and patients with gastric esophageal ulcer, gastric ulcer, duodenal ulcer and gastric cancer *n* (%)

	HS (*n* = 165)	EU (*n* = 21)	GU (*n* = 136)	DU (*n* = 100)	GC (*n* = 89)
Age (yr)	51 ± 14	54 ± 12	63 ± 15[c]	54 ± 15	67 ± 14[c]
Sex (M/F)	83/82	17/4[b]	75/61	67/33[b]	63/26[b]
Smoking	20 (12)	6 (29)[a]	39 (29)[c]	37 (37)[c]	12 (13)
Alcohol drinking	12 (8)	2 (10)	4 (3)	9 (9)	6 (7)
Helicobacter pylori infection	68 (41)	6 (28)	76 (56)[a]	75 (75)[c]	45 (51)[a]

[a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$ *vs* healthy subjects. HS: Healthy subjects; EU: Esophageal ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; GC: Gastric cancer.

paraffin, and sectioned. The sections were stained with a haematoxylin and eosin stain and a modified Giemsa stain as previously described[18]. Sections were examined blinded to the patient's clinical diagnosis. The scores of acute inflammation (neutrophil infiltrate), chronic inflammation (mononuclear cell infiltrate), glandular atrophy, intestinal metaplasia and *H. pylori* density were graded from 0 to 3 as described by the updated Sydney system[19].

Statistical analysis

Statistical evaluations were performed using the SPSS program (version 10.1, Chicago, Illinois, USA). The differences in gastric juice acidity between HSs and patients with EU, GU, DU or GC were assessed by Student's *t*-test. The chi-square test with or without Yate's correction for continuity and Fisher's exact test, when appropriate, were applied to analyze the categorized variables. Differences were considered to be significant at $P < 0.05$. A multivariate analysis with logistic regression method was carried out to assess the independent factors influencing gastric acidity of gastric juices. The studied variables included the following: age (< 60 years or ≥ 60 years), gender, family history of gastric cancer (presence or absence), history of smoking (< 1 pack/wk or ≥ 1 pack/wk), history of alcohol consumption (< 80 g/d or ≥ 80 g/d), history of tea consumption (< 1 cup/d or ≥ 1 cup/d), coffee consumption (< 1 cup/d or ≥ 1 cup/d), bile stain of gastric juice, *H. pylori* status (presence or absence) and parameters of histological gastritis.

RESULTS

Table 1 shows the demographic characteristics of HSs and patients with EU, GU, DU and GC. Patients with GU and GC were significantly older than HSs (63 ± 15, 67 ± 14 years *vs* 54 ± 12 years, both $P < 0.001$). Additionally, the EU, DU and GC patient groups had higher male-to-female ratios than the HS group (all $P < 0.05$). No significant differences in history of alcohol consumption were identified between groups. However, the rates of cigarette smoking in EU, GU and DU patients were significantly higher than that of HSs ($P < 0.05$, 0.05 and 0.01, respectively). Furthermore, the rates of *H. pylori* infection in GU, DU and GC patients were also significantly higher than that of HSs ($P < 0.05$, < 0.001 and < 0.05, respectively).

Independent factors determining the acidity of gastric juice

Univariate analysis of 15 clinical and histological factors demonstrated that the following nine factors were significantly associated with hypoacidity: old age ($P < 0.001$), family history of GC ($P < 0.05$), bile reflux ($P < 0.001$), *H. pylori* infection ($P < 0.05$), intestinal metaplasia of the antrum ($P < 0.01$), and acute inflammatory score, chronic inflammatory score, atrophy and intestinal metaplasia of the corpus (all *P* values < 0.001, Table 2). Smokers had a lower frequency of gastric hypoacidity than non-smokers, and alcohol drinkers also had less hypoacidity than drinkers. However, the differences concerning smoking and drinking did not reach statistical significances ($P = 0.258$ and 0.100, respectively). Multivariate analysis with a stepwise forward logistic regression method disclosed only bile reflux, high acute inflammatory score of the corpus, and atrophy of the corpus were independent risk factors for the development of gastric hypoacidity with odds ratios of 3.1 (95% CI: 1.3-7.3), 3.1 (95% CI: 1.2-7.9) and 3.5 (95% CI: 1.3-9.2, Table 3).

The subjects with *H. pylori* infection had higher frequencies of high acute inflammatory score (76% *vs* 37%, $P < 0.001$) and high chronic inflammatory score (96% *vs* 74%, $P < 0.001$) in the antrum than those without *H. pylori* infection. Additionally, they also had higher frequencies of high acute inflammatory score (50% *vs* 31%, $P = 0.018$), high chronic inflammatory score (80% *vs* 60%, $P = 0.006$) and gland atrophy (38% *vs* 21%, $P = 0.028$) in the corpus than uninfected subjects.

Acidity of gastric juices in HSs and upper gastrointestinal diseases

Table 4 showed the pH levels of gastric juices in benign and malignant gastrointestinal diseases. EU and DU patients had a higher gastric acidity than HSs (1.91 ± 0.28 and 2.09 ± 0.09 *vs* 2.90 ± 0.16, both $P < 0.05$). In contrast, GU and GC patients had a lower gastric acidity than HSs (3.42 ± 0.20 and 6.62 ± 0.22 *vs* 2.90 ± 0.16, both $P < 0.001$). Overall, hypoacidity existed in 22%, 5%, 29%, 5% and 88% of HSs, EU, GU, DU and GC patients, respectively.

DISCUSSION

This work demonstrated the differences in acidity of

Table 2 Univariate analysis for clinical and histological factors related to the hypoacidity of gastric juice

Principal parameters	*n*	Rate of hypoacidity (%)	*P* value
Clinical factors			
Age (yr)			< 0.001
< 60	282	24.8	
⩾ 60	229	39.7	
Sex			0.496
Female	206	29.6	
Male	305	32.5	
Family history of gastric cancer			0.048
-	497	31.0	
+	14	50.0	
Smoking			0.259
-	396	33.3	
+	115	25.2	
Alcohol consumption			0.100
-	478	32.6	
+	33	15.2	
Bile stain of gastric juice			< 0.001
-	301	20.9	
+	210	46.7	
Helicobacter pylori infection			0.013
-	241	25.7	
+	270	36.7	
Histological factors			
Antrum			
Acute inflammatory score			0.476
Low (grade 0, 1)	61	44.3	
High (grade 2, 3)	91	38.5	
Chronic inflammatory score			0.292
Low (grade 0, 1)	20	30.0	
High (grade 2, 3)	132	42.4	
Atrophy			0.195
-	43	32.6	
+	109	44.0	
Intestinal metaplasia			0.006
-	91	31.9	
+	61	54.1	
Corpus			
Acute inflammatory score			< 0.001
Low (grade 0, 1)	88	28.4	
High (grade 2, 3)	64	57.8	
Chronic inflammatory score			< 0.001
Low (grade 0, 1)	43	18.6	
High (grade 2, 3)	109	49.5	
Atrophy			< 0.001
-	106	28.3	
+	46	69.6	
Intestinal metaplasia			< 0.001
-	126	34.9	
+	26	69.2	

Table 3 Multivariate analysis for independent factors determining hypoacidity of gastric juice

Risk factors	Coefficient	SE	OR (95% CI)	*P* value
Bile reflux	1.116	0.446	3.1 (1.3-7.3)	0.012
Acute inflammatory score of the corpus	1.115	0.488	3.1 (1.2-7.9)	0.022
Atrophy of the corpus	1.245	0.497	3.5 (1.3-9.2)	0.012

gastric juices among patients with upper gastrointestinal diseases. EU and DU patients had a higher gastric acidity than HSs. In contrast, GU and GC patients had a lower gastric acidity than HSs. This study is the first to verify higher gastric acidity in EU patients compared with HSs. In this study, only 5% of EU patients possessed hypoacidity of gastric juice, whereas gastric hypoacidity existed in 22%, 29% and 88% of HSs, GU and GC patients, respectively. The data imply that normal or higher acidity of gastric juice is an important factor for the development of GERD besides lower esophageal pressure abnormalities, hiatal hernia and delayed gastric emptying[20].

Several histological studies also showed chronic atrophic gastritis present in 80%-90% of GC patients[21]. In this study, gastric hypoacidity existed in 88% of the patients with GC. This finding indicates atrophic gastritis with gastric hypoacidity is a crucial step for the development of gastric adenocarcinoma. *H. pylori* infection, old age and cagA and vacA m1 positivity have been identified as independent risk factors for the development of atrophic gastritis[22]. We propose that the high prevalence of *H. pylori* infection, advanced age, some bacterial virulent factors and susceptible host factors may contribute to the development of gastric atrophy and hypoacidity of the GC patients in this study.

The current work also showed that DU patients had a higher gastric acidity than HSs. This result supported previous observations demonstrating increased basal and stimulated acid secretion by the body of the stomach and increased acid load in the duodenum in patients with DU[23]. On the contrary, GU patients in this study had a lower gastric acidity than HSs, suggesting that mucosal defensive impairments are more important than increased acid load in the pathogenesis of GU. The findings were consistent with previous reports[24] revealing that the majority of gastric ulcers do not have increased gastric acid secretion.

Multivariate analysis in this study revealed that bile stain of gastric juice, high acute inflammatory score and atrophy of the corpus were independent factors for the development of gastric hypoacidity. The atrophy of the corpus was the most important factor for gastric hypoacidity with an odds ratio of 3.5. Since gastric acid is secreted by the parietal cells in the corpus, gland atrophy of the corpus leading to hyposecretion of acid and gastric hypoacidity is logical.

In 1988, Correa *et al*[25] proposed a human model of gastric carcinogenesis that gastric cancers develop through a complex sequence of events from normal mucosa to superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia and finally to intestinal-type adenocarcinoma[21,26,27]. Gland atrophy resulting in hypochlorhydria is a key step in this theory and accounts for gastric bacterial colonization, reduction of dietary nitrates to nitrites and the formation of potentially carcinogenic N-nitroso compounds[4,25]. In this study, *H. pylori*-infected patients had higher frequencies of gland atrophy in the corpus (38% *vs* 21%) and gastric hypoacidity (37% *vs* 26%) than uninfected subjects. Additionally, they also had stronger acute and chronic inflammation in the corpus than uninfected

Table 4 pH levels of gastric juices in upper gastrointestinal diseases *n* (%)

pH of gastric juice	HS (*n* = 165)	EU (*n* = 21)	GU (*n* = 136)	DU (*n* = 100)	GC (*n* = 89)
Level					
pH < 2	82 (50)	19 (91)	33 (24)	55 (55)	5 (5)
2 ≤ pH < 3.5	46 (28)	1 (5)	63 (46)	40 (40)	6 (7)
3.5 ≤ pH < 4.0	6 (4)	0 (0)	5 (4)	2 (2)	5 (6)
4.0 ≤ pH < 5.0	5 (3)	0 (0)	7 (5)	0 (0)	5 (6)
5.0 ≤ pH < 6.0	5 (3)	0 (0)	3 (2)	1 (1)	2 (2)
6.0 ≤ pH < 7.0	2 (1)	0 (0)	2 (2)	1 (1)	9 (10)
7 ≤ pH	19 (12)	1 (5)	23 (17)	1 (1)	57 (65)
mean ± SE	2.90 ± 0.16	1.91 ± 0.28[a]	3.42 ± 0.20[b]	2.09 ± 0.09[a]	6.62 ± 0.22[b]

[a]$P < 0.05$, [b]$P < 0.001$ *vs* healthy subjects. HS: Healthy subjects; EU: Esophageal ulcer; GU: Gastric ulcer; DU: Duodenal ulcer; GC: Gastric cancer.

subjects. These findings suggest that *H. pylori* infection is an important factor contributing to the development of atrophic gastritis in the corpus and hypo-secretory status of the stomach.

Primary duodenogastric reflux may occur due to antroduodenal motility disorder or incompetent pyloric sphincter[28]. The retrograded bile and duodenal contents can induce damage of the gastric mucosa[29]. It has been observed that duodenogastric reflux plays a crucial role in the pathogenesis of alkaline gastritis and GU[29]. Since the presence of bile in the gastric juice implies retrograde passage of alkaline duodenal contents into the stomach, it is reasonable to expect increased pH levels of gastric juice in the subjects with bile in gastric juice.

A higher degree of acute inflammation was the other histological factor predicting gastric hypoacidity in this study. Currently, we have no definite rationale to explain the association between dense neutrophil infiltrate and increased pH level in gastric juices, but dense neutrophil infiltrates may reflect the high density of *H. pylori* in the stomach[30], and have also been reported as one of the important factors related to the progression of atrophic gastritis[26].

In this study, smokers had a trend of less hypoacidity than non-smokers. The finding was supported by previous studies showing that nicotine increases acid secretion and decreases prostaglandin synthesis[31]. It is interesting to note that alcohol drinkers also had a trend of less hypoacidity than nondrinkers. The reasons for this finding remain unclear, but some studies demonstrated that fermented and nondistilled alcoholic beverages increase gastrin levels and acid secretion[32]. Additionally, succinic and maleic acid contained in certain alcoholic drinks also stimulate acid secretion[32].

In conclusion, bile reflux, atrophy and neutrophil infiltration of the corpus are three independent factors determining the acidity of gastric juices. Gastric acidities in patients with various upper gastrointestinal diseases are quite different. EU and DU patients have a higher gastric acidity whereas GU and GC patients have a lower gastric acidity compared with HSs.

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COMMENTS

Background

The acidity of gastric juice is one of the crucial factors in the development of most upper gastrointestinal diseases.

Research frontiers

The authors designed this study to search the independent factors determining gastric juice acidity and to investigate the acidity of gastric juices in various upper gastrointestinal diseases.

Innovations and breakthroughs

This study is the first to verify higher gastric acidity in esophageal ulcer patients compared with healthy subjects. The results showed that bile stain of gastric juice, high acute inflammatory score and atrophy of the corpus were independent factors for the development of gastric hypoacidity.

Applications

Results of this study are helpful for understanding the pathogenesis of upper gastrointestinal diseases and the factors influencing the acidity of gastric juice.

Terminology

The updated Sydney System is a schema for the classification and grading of histological gastritis established by an International Workshop on the Histopathology of Gastritis, Houston 1994.

Peer review

The study shows evidence collected in large population, however, there is lack of the definite conclusion in this paper. Instead of that, the authors made a comment in conclusion on the results, not providing the idea about the potential mechanism of changes in the acidity of gastric secretion in different group of patients. The Discussion is too general and not always linked to results obtained.

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