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High Serum Pepsinogen I and Low Seroprevalence of *Helicobacter Pylori* in Chinese Patients with Nonerosive Reflux Disease

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Abstract

The prevalence of gastroesophageal reflux disease (GERD), including nonerosive reflux disease (NERD), is increasing in Asia where *H. pylori* infection is highly endemic. The role of *H. pylori* and pepsinogen (PG) has not been evaluated in most studies of NERD, and whether they play a role in GERD remains controversial. This study aimed to determine the demographic and serologic characteristics of Chinese patients with NERD. We prospectively enrolled 69 consecutive NERD patients, and as controls, 69 age- and gendermatched subjects who received endoscopy as a part of their annual health check-up. Rate of *H. pylori* IgG seropositivity, and serum levels of pepsin precursors (PGI and PGII) and gastrin were measured for each subject. Differences were analyzed using the Chi-square and Mann-Whitney U-test. The *H. pylori* IgG seropositive rate was lower in NERD patients than in controls (26/69, 37.7% vs. 41/69, 59.4%; $p<0.05$). PGI level was higher (144.7 ± 10.7 ng/ml vs. 75.4 ± 6.4 ng/ml; $p<0.001$) and PGI/II ratio (14.4 ± 10.7 vs. 9.1 ± 0.7; $p<0.001$) was higher in NERD patients than in controls, but both groups had similar PGII (12.0 ± 0.8 ng/ml vs. 10.5 ± 1.1 ng/ml, $p=0.466$) and gastrin levels (69.1 ±7.1 pg/ml vs. 81.8 ±9.6 pg/ml, $p=0.318$). Chinese patients with NERD exhibit hyperpepsinogenemia I and a lower seropositive rate of *H. pylori* than age-matched controls. These results indicate a pivotal role of hyperacidity and possible protective role of *H. pylori* in this subset of GERD patients. (J Intern Med Taiwan 2007; 18: 270- 277)

Key Words ： **Gastroesophageal reflux disease, Non-erosive reflux disease, *Helicobacter pylori*, Pepsingen, Gastrin**

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Introduction

Gastroesophageal reflux disease (GERD) is a disorder characterized by recurrent reflux of gastric contents into the esophagus causing heartburn and other symptoms. Two major mechanisms contribute to the pathogenesis of GERD: a defective antireflux barrier and acid secretion adequate to damage the mucosa of the lower esophagus[1]. It is noteworthy that GERD is heterogeneous in terms of endoscopic features and etiologic factors. On the basis of whether mucosal breaks or ulcerations were noted in endoscopic examination, GERD can be classified into erosive esophagitis and non-erosive or endoscopy-negative reflux disease (NERD)[2]. NERD patients tend to have shorter symptom duration at the time of diagnosis, to be mostly female, to be less likely to have concomitant hiatal hernia and more likely to have close to normal esophageal acid exposure, and to rarely progress to severe mucosal injury[3]. Instead of the traditional consideration of GERD as a spectrum of diseases, a recent conceptual framework proposes subdivision of GERD patients into three distinct groups: those with NERD, erosive esophagitis, or Barrett's esophagus.

The prevalence of GERD is high in developed countries and low in developing countries[4]. The contrasting trend of GERD, *H. pylori* prevalence in different geographic areas and the crucial role of *H. pylori* in chronic gastritis suggest that *H. pylori* infection might act through its effect on gastritis and acid secretion to protect patients against the development of GERD[5]. Some reports, using either histologic or serologic examination to detect the presence of *H. pylori* and gastritis, have confirmed this hypothesis[6]. In Asia, GERD was previously thought to be uncommon in comparison with *H. pylori*-related diseases such as gastric malignancies and peptic ulcers. Recent published epidemiologic studies, however, indicate the prevalence of GERD is increasing in Asia[7,8]. Furthermore, data revealed that 80-90% of Asian GERD patients had NERD[7,9]. In Taiwan, we previously demonstrated the increasing prevalence of GERD and that *H. pylori* infection is infrequent in patients with erosive esophagitis[10]. Although data show a relationship between GERD, *H. pylori* infection, and serologic parameters of gastritis such as pepsinogen I/II and gastrin, few studies have centered on NERD[11-13]. In this case-control study, we aimed to investigate the relationship between NERD and *H. pylori* infection as well as serologic profiles of pepsinogen and gastrin in a Chinese population.

Material and Methods

Study population

From January 2003 to June 2003, consecutive patients visiting the out-patient clinic at National Taiwan University Hospital (NTUH), Taipei, Taiwan were evaluated for GERD symptoms. Symptoms suggesting GERD were heartburn, acid regurgitation, and dysphagia at least three episodes per week as evaluated by both a self-reported questionnaire and an internal medicine physician. Patients with NERD (which was diagnosed on the basis of predominant symptoms of heartburn with or without acid regurgitation or dyspeptic symptoms occurring at least twice per week for the previous 6 months but without erosive esophagitis by esophagogastroduodenoscopy [EGD] were included in this study. Those who had peptic ulcers, atrophic gastritis, corpus gastritis at EGD, a history of gastrectomy or vagotomy, and those who were taking proton pump inhibitors or H2-blockers within the previous two weeks were excluded from the study. Control subjects were randomly selected from asymptomatic subjects aged 20 to 60 who visited NTUH for their annual routine health check-ups during the same period. Those who had negative EGD findings were enrolled for study. All subjects enrolled in this study were ethnic Chinese living in Taiwan. Consent to perform EGD and blood analysis was obtained from all NERD patients and control subjects. This study was approved by the institutional review board of NTUH.

Table 1.Seropositivity of *H. pylori* and serum levels of gastrin and pepsinogen compared between NERD patient and controls

	NERD	Control	P-value
H. pylori IgG positivity	26/69 (37.7%)	41/69 (59.4%)	0.017§
Gastrin (pg/ml)	69.1 ± 7.1	81.8 ± 9.6	0.318
Pepsinogen I (ng/ml)	144.7 ± 10.7	75.4 ± 6.4	<0.001á
Pepsinogen II (ng/ml)	12.0 ± 0.8	10.5 ± 1.1	0.466
Pepsinogen ratio *	14.4 ± 0.7	9.1 ± 0.7	<0.001á

§ by Pearson Chi-square test
á by Mann-Whitney *U*-test
* Pepsinogen ratio = pepsinogen I / pepsinogen II

Endoscopy

All enrolled subjects received EGD using electrical panendoscopes (XQ 240, Olympus Optical Co. Ltd., Tokyo, Japan). The mucosal change at esophagus, esophagogastric junction, gastric mucosa, and duodenum was carefully observed and recorded.

The presence of erosive esophagitis was defined as endoscopically visible erosions or ulcerations extending from the gastroesophageal junction. Endoscopic atrophic gastritis was defined as pale gastric mucosa with prominent background vasculature. Endoscopic corpus gastritis was defined as diffuse hyperemic patches located at the gastric body.

Serologic test of *H. pylori* infection

Serum anti-*H. pylori* IgG antibody was measured using a commercial ELISA kit (I B L - Hamburg GmbH, Hamburg, Germany). Seropositivity for *H. pylori* antibody was defined by optical density values according to the manufacturer's protocol.

Serum levels of gastrin and pepsinogens

Serum concentration of gastrin was determined using a commercial RIA kit (Incstar Corp., MN, USA). Serum pepsinogen (PG) I and II concentration was determined using a commercial ELISA kit (Biohit Plc, Helsinki, Finland).

Statistical Analysis

SPSS Version 11.0.1 (SPSS Inc., Chicago, IL, U.S.A.) was used for statistical analysis. Results are demonstrated as mean ± SEM. Mann-Whitney U-test was used for comparison of numerical variables and Chi-square test for categorical variables. A two-sided p value of less than 0.05 was considered as statistically significant.

Results

Sixty-nine NERD patients and 69 controls were enrolled in the study. There were 27 (39.1%) males and 42 (60.9%) females in the patient group (mean age 44.2 ± 13.2 years) and 28 males and 41 females in the control group (mean age was 47.5 ± 10.8 years). Both gender and age were not statistically different between the two groups (p=0.86 and 0.07, respectively).

The prevalence of seropositivity of *H. pylori* antibody was significantly lower in NERD patients (26/69, 37.7%) in comparison with control subjects (41/69, 59.4%) (p=0.017 by Pearson Chi-square test). The serum PG I concentration and PG I/II ratio were significantly higher in NERD subjects (144.7 ± 10.7 vs. 75.4 ± 6.4 ng/ml for PG I ; 14.4 ± 0.7 vs. 9.1 ± 0.7 for PG I/II ratio; both p<0.001 by Mann-Whitney U-test). Serum concentration of gastrin was lower and PG II was higher in NERD subjects but the difference was not statistically significant (p= 0.32 and 0.47, respectively, by Mann-Whitney U-test). (Table 1)

After stratification by *H. pylori* seropositivity, the PG I concentration of *H. pylori*-positive NERD subjects was significantly higher than that in *H. pylori*-positive controls (173.3 ± 22.8 vs. 78.5 ± 6.6 ng/ml, p<0.001 by Mann-Whitney U-test). The ratio of PG I/II of *H. pylori* positive NERD patients was also significantly higher than that in *H. pylori* con-

trols (11.4 ± 0.8 vs. 7.1 ± 0.7; $p<0.001$ by Mann-Whitney U-test). The PG I concentration was significantly higher in NERD patients without *H. pylori* infection in comparison with controls without *H. pylori* infection (127.4 ± 9.4 vs. 71.0 ± 12.6 ng/ml; $p<0.001$ by Mann-Whitney U-test). The PG I/II ratio of *H. pylori*-negative NERD patients was also significantly higher than that of *H. pylori*-negative controls (16.2 ± 0.9 vs. 11.9 ± 1.4; $p=0.013$ by Mann-Whitney U-test).

Discussion

The clinical disease spectrum of *H. pylori* infection ranges from asymptomatic gastritis and peptic ulcer to gastric malignancies. Recently, *H. pylori*-associated diseases have been extended to include GERD, based on the opposing time trends of increased prevalence of acid-reflux associated esophageal disorders and decreased rate of *H. pylori* infection in Western countries[5]. Although controversial data existed, many studies including ours have shown a significantly lower incidence of *H. pylori* infection in patients with erosive esophagitis[6,7]. Labenz et al. first documented that GERD developed in patients cured of *H. pylori* infection[14]. They proposed that *H. pylori* was protective against GERD but did not mention the detailed mechanisms clearly. On the contrary, the population-based HUNT study published in Helicobacter 2007 showed no difference of prevalence of *H. pylori* infection between those individuals with and without reflux symptoms[15]. *H. pylori* infection seems not to provide protection for GERD. They only used questionnaires to evaluate symptoms of heart burn and acid regurgitation; however, all of population in our study received EGD to exclude erosive esophagitis. Later studies reported that the effect could be attributed to the topographical distribution of *H. pylori*-related gastritis with resultant modification of acid secretion[6,7,16]. Acid secretion increases after eradication of *H. pylori via* improvement of corpus gastritis and therefore the preexistent GERD becomes apparent and symptomatic. Corpus gastritis might decrease gastric acid secretion even in the absence of atrophy. Haruma et al. have shown that gastritis at both antrum and corpus was significantly milder in patients with erosive esophagitis, but serum PG I levels (which reflect gastric acid output) was significantly higher than in controls[11]. Koike et al. also reported decreased gastritis score and increased acid secretion after *H. pylori* eradication by measurement of H^+ concentration in gastric fluid before and after *H. pylori* eradication. These results implied that 1) the final denominators of the protection against GERD were decreased gastric acid secretion and the distribution and severity of *H. pylori*-induced gastritis and 2) all played a role in the pathophysiology of erosive esophagitis. Intriguingly, those patients with latent GERD (unmasked after eradication of *H. pylori* via a mechanism of increased gastric acid secretion) was defined as the fourth group of GERD and this description is consistent with the iceberg analogy proposed by Graham[17].

In addition to erosive esophagitis, a recent study from Japan has confirmed that *H. pylori* also plays a protective role in the development of Barrett's esophagus[18]. Results of this case-control study have shown the prevalence of *H. pylori* infection was remarkably lower in NERD patients than in controls. We previously reported a higher seropositive rate of *H. pylori* infection in asymptomatic Chinese in Taiwan, reaching 60-70% at the age of 40 years[19]. The present result of 59.4% in the control group was within that range. CagA-positive strains possess strong inflammation-inducing capability and were inversely associated with the development of GERD and esophageal adenocarcinoma. Previous studies have disclosed that more than 90% of *H. pylori* isolated in Taiwan was cagA-positive strains[20-22]. A similar phenomenon of high prevalence of cagA-positive *H. pylori* was observed in Japan and other Asian countries[23,24]. Collectively, *H. pylori* play a protective role

in different subgroups of GERD patients, including those with NERD, erosive esophagitis, and Barrett's esophagus, irrespective of geographic regions [6,17] Whether the decreasing prevalence of *H. pylori* infection in the young generation of Taiwan explains the increasing prevalence of GERD in Taiwan remains to be clarified.

Microscopic examination of gastric biopsies, despite the possibility of sampling errors due to inhomogeneous distribution of *H. pylori* in the stomachs of atrophic gastritis patients, is the gold standard for diagnosis of gastritis. We did not adopt histologic examination in the present study. Instead, we applied serologic tests to reveal the relationship of gastritis to NERD and *H. pylori*. After the introduction of serological assays of pepsinogen in the beginning of the 1980s, serum pepsinogen level has been considered a handy, inexpensive, and rapid option for non-endoscopic diagnosis of gastritis. There is general agreement that serum pepsinogen levels reflect the morphological and functional state of the gastric mucosa[26-27]. Secreted mainly by the chief cells in the oxyntic glands and mucous neck cells of the gastric corpus, pepsinogen I (PGI) has been used as an indicator of chief cell mass and, indirectly, reflected the gastric secretion of pepsin and acid. Elevated serum PGI levels have been observed to be associated with increased acid output or antral-predominant gastritis in patients with duodenal ulcer[28]. Besides, demographic factors (such as age and *H. pylori* infection) might provoke PGI increase. In patients with erosive esophagitis, hyperpepsinogenemia I was also reported, indicating that either antral predominant gastritis or gastric hypersecretion plays a role in its pathogenesis[12,13]. In this study, PGI level was significantly higher in NERD patients than controls. Because both NERD patients and control subjects in our study were endoscopically negative or only had minimal antral gastritis, the influence of PGI due to antral-predominant gastritis could be considered minimal. In addition, on an age-sex-matched basis, the impact of age on pepsinogen level could also be neglected. Our data showing hyperpepsinogenemia I in NERD patients may thus indicate the crucial role of gastric hypersecretion in the pathogenesis.

On the other hand, PGII is secreted from glands of the entire stomach and also from Brunner's gland in the proximal duodenum. Together with the PGI/PGII ratio, the serum PGII levels provide a useful and even better parameter in assessing gastritis[29]. It has been established that both serum PGI and PGII increased in superficial corpus gastritis. However, the progression of mild-moderate-severe atrophic gastritis results in a gradual reduction of PGI-producing cells, while the PGII cell mass is unaffected. Therefore, a stepwise reduction of serum PGI levels and a low PGI/PGII ratio have been found to be indicative of atrophic gastritis[30]. Previous histologic studies have demonstrated corpus inflammation is mild in patients with erosive esophagitis. Our serologic profiles of high PGI/PGII ratio and no difference in PGII levels were consistent with the findings in erosive esophagitis and suggested that corpus gastritis, if it existed, was also mild in patients with NERD. The data showing no difference in gastrin levels between NERD patients and controls fur-

Table 2.Serum pepsinogen I level and pepsinogen I/II ratio compared between NERD and control subjects with and without *H. pylori* infection

			NERD	Control	P-value[§]
H. pylori IgG	Positive	PG I (ng/ml)	173.3 ± 22.8	78.5 ± 6.6	<0.001[§]
		PG I/II ratio	11.4 ± 0.8	7.1 ± 0.7	<0.001[§]
	Negative	PG I (ng/ml)	127.4 ± 9.4	71.0 ± 12.6	0.001[§]
		PG I/II ratio	16.2 ± 0.9	11.9 ± 1.4	0.013[§]

[§] by Mann-Whitney U-test

ther support this speculation since gastrin levels tend to increase when atrophic gastritis is present.

For further elucidation of the role of *H. pylori* infection, we compared the PGI levels and PGI/II ratio between NERD patients and controls with respect to their *H. pylori* IgG status. PGI level and PGI/II ratio were significantly higher in *H. pylori*-positive NERD subjects in comparison with seropositive controls. A similar tendency was found when NERD patients without *H. pylori* infection were compared to control subjects without *H. pylori* infection. This observation supports the hypothesis that hyperacidity is the most important cause of NERD development, irrespective of *H. pylori* status. We also noticed higher PGI levels in *H. pylori*-positive NERD patients when compared with *H. pylori*-negative NERD patients. This may be well explained by the fact that *H. pylori* infection could lead to antral gastritis and increased PGI secretion.

There are some limitations in our study. First of all, though pepsinogen I is correlated with acid secretion, its correlation is not strong enough to correctly estimate acid secretion in an individual patient. Moreover, intragastric acidity rather acid secretion is more relevant and representative of pathogenic mechanism of NERD. Secondly, NERD has been recently recognized as heterogeneous disorder including mucosal hypersensitivity and emotional or psychological abnormalities in addition to hyperacidity and therefore proton pump inhibitor is less effective in NERD patients compared with erosive esophagitis. Parameters of mechanism other than acid secretion should be elucidated and measured in future study.

In summary, we demonstrated that the prevalence of *H. pylori* infection in Chinese patients with NERD was significantly lower than that of age-and gender-matched asymptomatic controls. High PGI levels and PGI/PGII ratio (but without change in PGII and gastrin levels) indicate mild gastritis in the corpus and suggest gastric hypersecretion might play a pivotal role in the pathogenesis of this subset of GERD patients.

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台灣非糜爛性逆流疾病病患有較高的第一型血清胃蛋白原 (Pepsinogen I) 及較低的幽門螺旋桿菌陽行率

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摘　要

胃食道逆流疾病的流行，包括非糜爛性逆流疾病，正在幽門螺旋桿菌感染高盛行率的亞洲持續增加中。在關於非腐蝕性逆流疾病的大多數研究中並沒有提到幽門螺旋桿菌和pepsinogen(PG)，而且他們在胃食道逆流疾病中扮演的角色仍有爭論。這項研究是希望確定台灣華人非糜爛性逆流疾病病患的人口統計和血清學的特性。我們將連續六十九名到門診就醫的非糜爛性逆流疾病病患，和六十九名於台大醫院接受包含胃鏡的年度健康檢查的健康人做對照比較。吾人分別測量幽門螺旋桿菌 IgG 血清陽性率和血清胃蛋白原 (PGI 和 PGII) 與gastrin 。統計分析方法爲卡方檢定 (Chi-Square Tests) 及獨立樣本 U 檢定 (Mann-Whitney U test)。在非糜爛性逆流疾病的那一組和對照組加以比較，對照組有較高 seropositive IgG pylori 比率 (37.7% v.s 59.4% ；P<0.05)。在非糜爛性逆流疾病的那一組則有較高的 PGI (144.7 ± 10.7 ng/ml v.s 75.4 ± 6.4 ng/ml ；P<0.05) 和 PGI/II 比率 (14.4 ± 10.7 v.s 9.1 ± 0.7 ；P<0.01)；兩組有相似 PGII (12.0 ± 0.8 ng/ml v.s 10.5 ± 1.1 ng/ml ； P=0.466) 和 gastrin (69.1 ± 7.1 pg/ml v.s 81.8 ± 9.6 pg/ml ； P= 0.318)。有非糜爛性逆流疾病的台灣華人病患與對照組比較，他們有比較高的第一型胃蛋白原和較低的幽門螺旋桿菌血清陽性率。這些結果表明酸過多在非糜爛性逆流疾病中扮演的關鍵性的角色和在胃食道逆流疾病中幽門螺旋桿菌可能扮演的保護角色。