Association Between Bile Reflux and Gastric Mucosal Damage Severity in Patients with Dyspepsia

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ABSTRACT

***Background**: Bile acid reflux stands out as a notable risk factor for dyspepsia. Among patients with bile acid reflux, common endoscopic findings include mucosal erythema, the presence of bile acid on the mucosa, erosions, hyperrugosity, and gastric mucosal atrophy. This study aims to elucidate the association between bile acid levels in gastric fluid and the degree of gastric mucosal damage.*

***Methods:** This cross-sectional study involved dyspeptic patients who underwent endoscopic examination at Prof. Dr. I.G.N.G. Ngoerah Denpasar Hospital. Bile acid analysis was conducted through the enzymatic calorimetric method, while assessment of mucosal damage relied on the Lanza score, evaluated independently by two observers. Mucosal damage severity was categorized as either mild (score 0-2) or severe (score 3-5). Statistical analyses included Cohen's kappa for interobserver agreement, bivariate analysis, and logistic regression.*

***Results**: Of the 99 subjects involved in the study, 58.6% were male. H. pylori antibodies were detected in 21% of the participants, while 48% exhibited a pH below 2.77. Additionally, 48% reported a history of NSAID consumption. The mean bile acid level in gastric fluid was 156.07 µmol/L, with a median of 170.09 µmol/L (categorized as high if ≥ 170.09 µmol/L, and low if < 170.09 µmol/L). During endoscopic examination, mild mucosal damage was observed in 61%, and severe damage in 39% (kappa 1, P < 0.001). A statistically significant relationship between gastric fluid bile acid levels and mucosal damage was evident (P < 0.05).*

***Conclusion:** This study concludes that there was a relationship between the level of bile acid in gastric fluid and the degree of mucosal damage.*

***Keywords:** Bile acid levels, gastric fluid, degree of gastric mucosal damage*

ABSTRAK

***Latar Belakang:** Salah satu faktor risiko dispepsia adalah refluks asam empedu. Temuan endoskopi yang paling umum pada pasien dengan refluks asam empedu termasuk eritema mukosa, adanya asam empedu pada mukosa, erosi, hiperugositas, dan atrofi mukosa lambung. Studi ini bertujuan untuk menentukan hubungan antara kadar asam empedu dalam cairan lambung dan tingkat kerusakan mukosa lambung.*

***Metode:** Penelitian ini merupakan studi potong lintang yang dilakukan pada pasien dispepsia yang menjalani endoskopi di Prof. Dr. I.G.N.G. Rumah Sakit Ngoerah Denpasar. Pemeriksaan asam empedu dilakukan dengan menggunakan metode kalorimetri enzimatik, dan penilaian kerusakan mukosa didasarkan pada skor LANZA yang dievaluasi oleh 2 pengamat.*

Tingkat kerusakan mukosa diklasifikasikan sebagai ringan (skor 0-2) dan parah (skor 3-5). Analisis kappa Cohen, analisis bivariat, dan analisis regresi logistik digunakan pada penelitian ini.

Hasil: *Dari total 99 subjek yang terlibat, sebesar 58 (58,6%) adalah laki-laki. Antibodi H. pylori terdeteksi pada 21% subjek, dan 48% memiliki pH di bawah 2,77; 48% memiliki riwayat konsumsi NSAID. Nilai rata -rata kadar asam empedu dalam cairan lambung adalah 156,07 µmol/L, dengan median 170,09 µmol/L (≥170,09 µmol/L diklasifikasikan sebagai tinggi, <170,09 µmol/L diklasifikasikan sebagai rendah). Selama pengamatan endoskopi, kerusakan mukosa ringan ditemukan pada 61%, dan kerusakan parah ditemukan pada 39% (kappa 1, p <0,001). Terdapat hubungan yang signifikan secara statistik antara kadar asam empedu cairan lambung*

dan kerusakan mukosa (p <0,05).

Kesimpulan: *Studi ini menyimpulkan bahwa terdapat hubungan antara tingkat asam empedu dalam cairan lambung dan tingkat kerusakan mukosa.*

Kata kunci: *Kadar asam empedu; cairan lambung; derajat kerusakan mukosa lambung*

INTRODUCTION

Gastric mucosal damage arises from an imbalance between aggressive and protective factors which affecting the stomach lining. Protective factors encompass blood flow to the submucosa, prostaglandins, the regenerative and differentiative capacities of epithelial cells, tight junctions, and the protective layer. Conversely, aggressive factors involve the pepsin enzyme, gastric acid, and exogenous elements such as chemical trauma, medications, and bile acid. Bile acid is noted to have the potential to harm the gastric mucosa by elevating gastric pH through a specific mechanism.[2] The direct correlation between the concentration of bile acid in gastric fluid and the presence of significant gastric mucosal atrophy, intestinal metaplasia, and the infiltration of inflammatory cells in the basal gastric mucosa is evident. Moreover, the decrease in acidity induced by bile acid is associated with a gradual rise in the incidence of gastric cancer.[3]

Various studies have reported the occurrence of bile reflux. At Persahabatan Hospital in Jakarta, 44 cases of bile reflux gastritis were documented between 1987 and 1989.[4] In Japan, a substantial 63% of patients undergoing endoscopy were found to have bile acid present in their gastric fluid.[5] However, when relying on endoscopic observations, the incidence of bile reflux is lower, ranging from 10% to 15%. In contrast, a higher percentage, specifically 60% of endoscopy patients, was identified with bile acid in their gastric fluid.[6]

Numerous studies have demonstrated a direct link between the concentration of bile acid in gastric fluid with the extent of damage, infla mmation, and signific ant alterations in cellular structure.[7] Bile reflux damages gastric mucosa and causes chemical gastritis. It also stimulates antral G cells' gastrin secretion, promoting gastric acid secretion and inhibiting pyloric sphincter contraction.[8] Typical endoscopic observations in individuals experiencing bile reflux include mucosal erythema, the presence of bile on the mucosa, erosion, hyperugosity, and gastric atrophy. Among individuals with detectable bile acid in their gastric fluid, 33% were also found to have *H. pylori* infection in the gastric mucosa.[9] Supporting this, one study discovered that the observed relative frequency of *H. pylori* infection among patients with bile reflux was 34.82%.[10] Prior research has established a connection between the quantity of bile acid present in gastric fluid and the severity of mucosal damage, encompassing conditions such as erosion, bleeding, inflammation, and even the development of gastric adenocarcinoma.[11] Histopathologically, individuals infected with *H. pylori* exhibit more severe mucosal damage within the bile reflux group. Furthermore, findings from a study offered corroborative evidence that elevated levels of gastric conjugated bile acids were a distinguishing characteristic among gastritis patients with bile reflux.[12] It is noteworthy that there is currently no research confirming the relationship between bile acid levels and the extent of gastric mucosal damage in Indonesia. This study aimed to elucidate the association between bile acid levels in gastric fluid and the degree of gastric mucosal damage.

METHODS

This study utilized a cross-sectional analytic research design conducted in the endoscopy unit of Prof. Dr. dr. I.G.N.G Ngoerah Central General Hospital, Denpasar, from May 2023 to November 2023. The inclusion criteria encompassed patients aged ≥ 18 years, both male and female, who underwent endoscopy at Prof. Dr. dr. I.G.N.G Ngoerah Central General Hospital. Those with a history of stomach and biliary surgery were deliberately excluded from the research. Sample selection was accomplished using a consecutive sampling method.

The sample size calculation was calculated with correlational analysis formula. A Zα value of 1.96 was applied, with a disease prevalence of 0.63 and a desired absolute accuracy of 0.5. Based on these parameters, the calculated sample size was 89, rounded up to 90. Bile acid levels in gastric fluid were assessed utilizing the enzymatic method from Daiichi Pure Chemicals Co., Tokyo, Japan, with results reported in μmol/L units. Collection of gastric fluid for bile acid examination occurred during endoscopy, involving a minimum of 3 ml extraction. The fluid collection was carried out in the morning between 08:00 and 11:00 local time, with patients observing a fasting period of at least 8 hours before undergoing esophagogastroduodenoscopy. Immediate freezing of the gastric fluid was done at a temperature of-20 degrees Celsius. Concurrently, mucosal damage was evaluated during endoscopy, employing the Lanza score system. The scoring system comprised a range from 0 for normal mucosa to 5 for ulcers, with intermediate scores indicating varying degrees of erosions and bleeding in different gastric areas.[13]

A tabular representation was employed for descriptive analysis to illustrate the characteristics of the research subjects. Numerical scale data were expressed as mean ± standard deviation, while categorical scale data were summarized using frequency distribution. Cohen's kappa analysis was utilized to assess the agreement between two observers. For bivariate analysis, either the independent t-test or the Mann–Whitney U test was applied, depending on data distribution. Logistic regression was employed for multivariate analysis, with the odds ratio serving as the measure of association. All statistical analyses were performed using SPSS version 24.0.

RESULTS

This study involved a total of 99 samples. The mean gastric pH was 2.58 ± 0.84. Most subjects had a non-obese BMI (59.6%) and were male (58.6%). The prevalence of *H. pylori* in this study was 21.2%. The use of NSAID and PPI was 48.5% and 53.5%, respectively. The characteristics of the research subjects are presented in **Table 1.**

Gastric Mucosal Damage Examination

Table 2 displays the outcomes of mucosal observations carried out by both Observer 1 and Observer 2. A Cohen's kappa analysis yielded a kappa value of 1.0, signifying a unanimous and highly agreement between the two observers (Kappa=1.00, p=0.001). Consequently, it can be inferred that both Observer 1 and Observer 2 exhibited equivalent reliability in their assessments.

Table 1. Characteristics of Study Subjects

Variables	Results (n=99)
Gastric pH (μmol/L)	
Mean ± SD	2.58 ± 0.84
Median	2.77
BMI (kg/m2)	
Obese (≥ 25 kg/m2)	40 (40.4%)
Non-obese (< 25 kg/m2)	59 (59.6%)
Gender, n (%)	
Male	58 (58.6)
Female	41 (41.4)
Age (years), n (%)	
≥ 45 years	78 (78.8%)
< 45 years	21 (21.2%)
History of alcohol consumption, n (%)	
Yes	32 (32.2%)
No	67 (67.7%)
History of *H. pylori* infection, n (%)	
Yes	21 (21.2%)
No	78 (78.8%)
History of NSAID consumption, n (%)	
Yes	48 (48.5%)
No	51 (51.5%)
History of smoking, n (%)	
Yes	43 (43.4%)
No	56 (56.6%)
History of using PPI, n (%)	
Yes	55 (53.5%)
No	44 (46.5%)

Table 2. Characteristics of Mucosal Damage

Lanza Score		Observer 1	Observer 2	Total
Mild	0	25 (25.3%)	26 (26.2%)	61 (61,6%)
	1	13 (13.1%)	14 (14.1%)	
	2	23(23.2%)	21 (21.2%)	
Severe	3	17 (17.2%)	19 (19.1%)	38 (38.4%)
	4	10 (10.1%)	8 (8.1%)	
	5	11 (11.1%)	11 (11.1%)	
Total		99 (100%)	99 (100%)	

Relationship between Bile Acid Levels in Gastric Fluid and the Degree of Gastric Mucosal Damage

Among the samples, 50 (50.5%) exhibited high bile acid levels (utilizing the median as a cut-off) of ≥ 170.9 μmol/L, while 49 samples (49.5%) displayed low levels below <170.9 μmol/L. In this study, a Chi-square analysis was executed to examine the correlation between varied proportions of gastric fluid bile acid levels and the extent of mucosal damage. To ensure a balanced frequency distribution and enhance precision, the bile acid levels

were categorized into two groups using the median value as a threshold. Individuals with bile acid levels equal to or exceeding 170.09 µmol/L were designated as having high levels, while those with levels below 170.09 µmol/L were categorized as having low levels. The outcomes of the Chi-square test are detailed in **Table 3.**

Among subjects with elevated bile acid levels in gastric fluid, 27 cases (54%) exhibited severe mucosal damage, whereas 23 cases (46%) demonstrated mild damage. This noteworthy difference in prevalence holds statistical significance, pointing to a clear association between the levels of bile acid in gastric fluid and the extent of gastric mucosal damage ($p = 0.001$).

Relationship between Confounding Variables and the Degree of Mucosal Damage Bivariately

In this study, bivariate analyses were performed to illustrate the connections between confounding variables and the extent of mucosal damage in the stomach. The results revealed statistically significant associations for several variables, including gastric pH ($p < 0.001$), history of *H. pylori* infection ($p < 0.001$), and history of NSAID use ($p = 0.002$). Detailed bivariate analysis results for each variable are presented in **Table 4.**

Table 3. The Results of the Chi-Square Test for the Association Between Bile Acid Levels in Gastric Fluid and the Degree of Mucosal Damage

Variables		The degree of mucosal damage		PR	95% CI	p-value
Bile acid levels in gastric fluid, n (%)		Severe	Mild			
	High	27 (54)	23 (46)	4.055	1.69-9.69	0.001*
	Low	11 (22)	38 (78)			

Table 4. Bivariate Analysis Between Confounding Variables and the Degree of Mucosal Damage

Variables	Degree of Mucosal Damage		p-value
	Severe (n=38)	Mild (n=61)	
Age (years)			
≥ 45 Years	33 (42)	45 (58)	0.122
< 45 Years	5 (24)	16 (76)	
Gender, n (%)			
Male (n=58)	23 (40)	35 (60)	0.757
Female (n=41)	15 (37)	26 (63)	
BMI (Kg/m^2)			
Obese	12 (30)	28 (70)	0.158
Normal	26 (44)	33 (56)	
Gastric pH, n%			
Low pH	31 (65)	17 (35)	<0.001*
High pH	7 (14)	44 (86)	
H Pylori Antibody, n%			
Yes	13 (40)	19 (60)	0.751
No	25 (37)	42 (63)	
History of alcohol consumption, n%			
Yes	18 (42)	25 (58)	0.533
No	20 (36)	36 (64)	
History of using NSAID, n%			
Yes	25 (54)	23 (46)	0.007*
No	13 (24)	38 (76)	
History of Using PPI, n%			
Yes	22 (44)	33 (56)	0.271
No	16 (33)	28 (67)	

NSAID: Non steroid anti-inflammatory drugs; PPI: Proton pump inhibitor

Table 5. Logistic Regression Analysis

Variables	Adjusted PR	95% CI	p-value
Blie Acid	3.53	1.05-11.86	0.01*
Gastric pH (Low)	10.28	2.98-35.47	<0.001*
History of H Pylori Infection (yes)	8.76	1.64-46.70	0.01*
History of using NSAID (yes)	3.48	1.05-11.51	0.04*
Age (>45 Years)	2.41	0.51-11.30	0.26
BMI (obese)	0.58	0.16-2.02	0.39

BMI: Body mass index; NSAID: Non steroid anti inflammatory

To assess the contributory relationship between bile acid levels in gastric fluid and the extent of mucosal damage, while accounting for confounding variables, a multivariate logistic regression analysis was performed. The independent and confounding variables integrated into the logistic regression analysis were selected based on a bivariate analysis threshold of p-value < 0.25. These variables included bile acid levels in gastric fluid, of *H. pylori* infection, history of NSAID consumption, and gastric pH. The findings of the logistic regression analysis are detailed in **Table 5.** The results of the logistic regression analysis revealed a statistically significant association between bile acid and the extent of mucosal damage (adjusted odds ratio (AOR): 3.5, p=0.01). Specifically, individuals with bile acid levels ≥170.09 μmol/L were 3.53 times more likely to experience severe mucosal injury. Additional variables that showed significant associations included gastric pH (p < 0.001), history of H. pylori infection (p = 0.01), and NSAID use (p = 0.04). In contrast, variables such as age over 45 years (p = 0.26) and obesity (p = 0.39) did not demonstrate statistically significant relationships with mucosal damage.

DISCUSSION

The subjects in this study were mostly well-nourished, with a balanced gender distribution and a notable proportion aged 45 or older. Common risk factors for dyspepsia were present, including smoking, alcohol use, prolonged NSAID use, prior PPI intake, and a median gastric pH of 2.77. These characteristics are consistent with established risk factors such as female gender, obesity, smoking, alcohol consumption, and use of medications known to affect the stomach.[14]

On the other hand, the occurrence of *H. pylori* infection was determined to be 21%, a finding closely resembling a prior study that noted an *H. pylori* infection prevalence of 22% in Denpasar.[15] This prevalence of *H. pylori* infection vary significantly diff across regions due to geographical conditions, sanitation levels, access to clean water, and ethnic factors. For instance, *H. pylori* infection rates reach 49% in China and 44% in Japan. In Indonesia, the overall prevalence of *H. pylori* infection spans from 5.7% to 68%.[16]

In this study, the average bile acid level in gastric fluid was 191.02 μmol/L, with a median value of 170.09 μmol/L and a range spanning 562.24. These findings exhibit a slight disparity when compared to a Japanese study, which reported an average gastric fluid bile acid level of 431.1 μmol/L, along with a wider range of 1234.3 μmol/L. Notably, the Japanese study revealed a correlation between bile acid levels exceeding 200 μmol/L and an elevated risk of mucosal damage and gastric cancer.[5] This discrepancy in results may be attributed to the substantial influence of dietary patterns, particularly the consumption of fatty foods, on the hepatocyte-driven production of bile acids.[17]

Patients experiencing dyspepsia frequently exhibit endoscopic findings such as erythema, gastritis, and superficial erosions, particularly when their gastric fluids contain elevated levels of bile acid. Among individuals with bile acid concentrations surpassing 200 μmol/L in gastric fluid, the mucosal presentation comprises 64.4% erythema, 22% mucosal thickening, 5% erosions, 12% gastric atrophy, and 8% ulcers.[9] The majority of current studies examining the correlation between bile acid levels in gastric fluid and mucosal damage primarily rely on histopathological assessments for evaluating such damage. Consequently, locating comparable studies employing endoscopic observations to gauge mucosal damage proves challenging. Notably, in patients with bile acid levels above 200 μmol/L, more than 80% exhibit hyperemia during endoscopic examination. Furthermore, Narrow Band Imaging (NBI) reveals signs of intestinal metaplasia in 20–30% of these cases.[5] In contrast, histopathological assessments conducted on individuals aged 50 and above, possessing an average gastric fluid bile acid concentration of 180 μmol/L, revealed 61% with chronic gastritis, 29% with intestinal metaplasia, and 8% diagnosed with gastric

cancer.[6] It is important to note that this current study did not include histopathological evaluation. Therefore, the seemingly normal mucosal appearance observed during endoscopy may mask underlying cellular-level changes, such as inflammation, hyperplasia, mucosal atrophy, or even intestinal metaplasia.

The reflux of bile acid into the stomach initiates the transformation of lecithin and bile salts into lysophospholipids through the action of phospholipase. These lysophospholipids then combine with the phospholipid layer, leading to heightened permeability of the epithelial cell membrane in the gastric mucosa. Bile acids play a role in inhibition nitric oxide enzymes, impeding the sodium-hydrogen exchange, and subsequently inducing DNA damage, early apoptosis, and mutations in epithelial cells. Additionally, bile acids induce the backfl ow of hydrogen ions and prompt mast cells to release histamine, thereby stimulating gastric acid secretion and reducing gastric pH.[18] This resulting hyperacidity in gastric fluid constitutes a significant aggressive factor that amplify the risk of gastric mucosal damage and exacerbates dyspeptic symptoms. This study has several limitations that should be considered. First, bile acid concentration was measured only once, despite its known variability throughout the day. Future research should consider 24-hour monitoring of bile acid levels in gastric fluid to capture more accurate fluctuations. Second, mucosal damage was assessed solely through macroscopic endoscopic observation, which does not reveal cellular or tissue-level changes such as hypertrophy, hyperplasia, atrophy, intestinal metaplasia, or gastritis, conditions that may not be visible on endoscopic imaging but could be present histologically.

Although the findings of this study contribute to understanding the role of bile acids in gastric mucosal damage, further research is warranted. Follow-up research with a design that observes bile acid reflu x over 24 hours can help obtain the average bile acid levels in gastric fluid over a 24-hour period. Therefore, this can depict the overall acidity conditions in the stomach and can be correlated with mucosal damage observed histopathologically, allowing the causal relationship between bile acid in gastric fluid and gastric mucosal damage to be identified. Also, future research using high performance liquid chromatography (HPLC) as a more advanced and precise method for measuring bile acids could be performed. Additionally, focusing on the microbiota of the gastrointestinal tract, which can be considered a component of the innate immune defense, would be beneficial for future research.

CONCLUSION

There is an association between bile acid levels in gastric fluid and the severity of gastric mucosal damage. Higher bile acid concentrations tend to be linked with more extensive mucosal injury, suggesting that bile reflux may play a significant role in the pathogenesis of gastric mucosal damage.

Conflict of Interest:

The authors have no competing interests to disclose.

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Author contribution

All authors contributed significantly to the work and approved the final manuscript.

Data Avaibility

All data have been provided within the manuscript.

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