Relationship between Bile Reflux and the Severity of Gastric Mucosal Damage 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, prevalent endoscopic observations encompass mucosal erythema, the detection of bile acid on the mucosa, erosion, hyperugosity, and gastric mucosal atrophy. This study aimed to elucidate the association between bile acid levels in gastric fluid and the degree of gastric mucosal damage.*

***Methods:** A cross-sectional investigation involved dyspeptic patients who underwent endoscopy 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). Cohen's kappa analysis, bivariate, and logistic regression analysis was empoyed.*

***Results**: Among the 99 subjects involved, 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; gastric mucosal damage degree*

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

Damage to the gastric mucosa arises from an imbalance between the aggressive and protective elements affecting it. 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 like chemical trauma, medications, and bile acid.[1] 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 documented the occurrence of bile reflux. At Persahabatan Hospital in Jakarta, the incidence of bile reflux gastritis between 1987 and 1989 was noted in 44 patients.[4] In Japan, a substantial 63% of endoscopy patients were found to have bile acid in their gastric fluid.[5] However, when relying on endoscopic observations, the incidence of bile reflux is lower, ranging from 10% to 15%. Conversely, 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 and the extent of damage, inflammation, and significant alterations in cellular structure.[7]

Bile reflux damages gastric mucosa and causes chemical gastritis. Bile reflux 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 those identified with bile acid in their gastric fluid, 33% exhibited 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. 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.

Sample size calculation was calculated with correlational analysis formula. The Zα value used is 1.96. The disease prevalence is 0.63. The desired absolute accuracy level is 0.5. Therefore, the sample calculation is 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 nnmol/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 will be presented as mean ± standard deviation, while categorical scale data will be depicted through frequency distribution. Cohen's kappa analysis was utilized to assess the agreement between two observers. For bivariate analysis, the independent t-test or Mann-Whitney test will be applied. In the case of multivariate analysis, logistic regression analysis will be employed. The odds ratio will serve as the association measure to evaluate relationships. The comprehensive analysis process will be executed using SPSS 24.0 software.

RESULTS

This study involved a total of 99 samples. The mean gastric pH is 2.58 ± 0.84. The dominant samples have normal BMI and were male (58.6%). The characteristics of the research subjects presented in Table 1.

Table 1. Characteristics of study subjects

variables	result (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%)
Normal (< 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 pillory 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%)

BMI: Body mass index; NSAID: Non steroid anti inflammatory drugs; PPI: Proton pump inhibitor

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 ensued, yielding 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 exhibit equivalent reliability in their assessments.

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).

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%)	

Table 3. The result 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)			

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 outcomes of the bivariate analyses for each confounding variable revealed that variables with statistically significant relationships to the degree of mucosal damage include gastric pH (p<0.001), history of H. pylori infection (p<0.001), and history of NSAID consumption (p=0.002). Detailed bivariate analysis results for each variable are presented in Table 4.

Logistic Regression Analysis between Bile Acid Levels in Gastric Fluid and Confounding Variables on the Degree of Gastric Mucosal Damage

To assess the contributory association between bile acid levels in gastric fluid and the extent of mucosal damage, while considering confounding variables, multivariate logistic regression analysis was employed. 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 include bile acid levels in gastric fluid, age, weight, history 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 reveal a statistically significant association between bile acid and the extent of mucosal damage (adjusted odds ratio (AOR): 3.5, p=0.01). Having bile acid levels in gastric fluid exceeding 170.09 µmol/L increases the risk of severe mucosal damage by 3.53 times. Additional variables displaying a statistically significant relationship include gastric pH (p<0.001), history of H. pylori infection (p=0.01), and history of NSAID consumption (p=0.04). Conversely, variables such as age above 45 years (p=0.26) and weight (obese) (p=0.39) do not exhibit a statistically significant relationship.

Table 4. Bivariate analysis between confounding variables and the degree of mucosal damage.

Variable	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 drugs

DISCUSSION

The demographic profile of the subjects in this study indicates that 32% were aged 45 or above, and the gender distribution was almost equal. The majority of subjects exhibited good nutritional status, with 32% reporting alcohol consumption, 48% having a history of NSAID use for over 2 weeks, 43% being smokers, 53% having prior PPI medication use, and a median gastric pH of 2.77. Notably, these subject characteristics align with recognized risk factors for dyspepsia, encompassing, female gender, obesity, smoking, alcohol consumption, a history of medication or herbal remedies with stomach-related side effects (such as NSAIDs and pain relievers), and H. pylori infection.[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 can differ 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 is 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 like erythema, gastritis, and superficial erosions, particularly when their gastric fluid contains 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. In cases where patients display gastric fluid bile acid levels surpassing 200 µmol/L, over 80% exhibit hyperemia during endoscopic examinations. Additionally, when subjected to NBI (Narrow Band Imaging), 20-30% manifest indications of intestinal metaplasia.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] Notably, this current study did not include histopathological observations, implying that the apparently normal mucosal appearance observed during endoscopy might have already undergone cellular-level damage, including 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 A. 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 inhibiti ng 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 backflow of hydrogen ions and prompt mast cells to release histamine, thereby stimulating gastric acid secretion and reducing gastric pH.[18] This hyperacidity in gastric fluid constitutes a significant aggressive factor that amplifies the risk of gastric mucosal damage and exacerbates dyspeptic symptoms.1

This study has several limitations that should be considered. In this research, the concentration of bile acid was observed only once, while the concentration of bile acid in gastric fluid is highly fluctuating. Therefore, further research is needed with a 24-hour examination of bile acid in gastric fluid. Additionally, the examination of mucosal damage was only macroscopic, so it could not observe cellular and tissue levels such as hypertrophy, hyperplasia, atrophy, intestinal metaplasia, or gastritis, which might appear normal in endoscopic images.

Although the results of this study can be used to investigate mucosal damage to understand the role of bile acid in gastric mucosal damage, further research is still needed. Follow-up research with a

design that observes bile acid reflux 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 reseach.

CONCLUSION

Severe mucosal damage was observed in 38% of cases, while mild damage 62%. The average bile acid level in gastric fluid stands at 191.02 μmol/L, with a median value of 170 μmol/L. Cases with elevated bile acid levels (exceeding the median cutoff) was account for 50.5%, whereas those with lower levels was 49.5%. There was an association between the bile acid level in gastric fluid and the extent of gastric mucosal damage.

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