Gastric mucosal atrophy, intestinal metaplasia, and *Helicobacter pylori* status in patients with gastritis with or without bile reflux: Is the presence of bile reflux good or bad?

Safra reflüsü bulunan ve bulunmayan gastrit hastalarında gastrik mukozal atrofi, intestinal metaplazi ve *Helicobacter pylori* durumu: Safra iyi mi kötü mü?

Muhammet Fatih AYDIN[1], Şule NAMLI KOÇ[2], Mehmet Akif AYDIN[3], Hüseyin AKYOL[3]

Departments of [1]Gastroenterology and [3]General Surgery, Altınbaş University Bahçelievler Medical Park Hospital, İstanbul
Department of [2]Gastroenterology, Ataşehir Memorial Hospital, İstanbul

Background and Aims: *To investigate the relation between bile reflux and gastric mucosal atrophy, intestinal metaplasia, and Helicobacter pylori status in patients with gastritis.* ***Materials and Methods:*** *A total of 217 patients (mean ± SD; age: 33.2±7.9 years; 51.2% males) with gastritis were divided into two groups: patients with intragastric bile reflux (n = 134; confirmed by pathology in 20 patients) and without bile reflux (control group; n = 83). The status of Helicobacter pylori and presence of intestinal metaplasia and gastric atrophy were evaluated with respect to the presence of bile reflux.* ***Results:*** *A positive Helicobacter pylori status, intestinal metaplasia, and gastric atrophy were observed in 85 (39.2%), 72 (33.2%), and 66 (30.4%) patients, respectively. No significant difference was noted between patients with gastritis with or without bile reflux in terms of a positive Helicobacter pylori status (38.8% vs. 45.8%), intestinal metaplasia (32.8% vs. 33.7%), and gastric atrophy (30.6% vs. 30.1%). However, the pathological confirmation of bile reflux gastritis was associated with a significantly lower rate of Helicobacter pylori positivity (0.0% vs. 45.6%; p = 0.001), intestinal metaplasia (5.0% vs. 37.7%; p = 0.009), and gastric atrophy (0.0% vs. 36.0%; p = 0.003). In patients with bile reflux (n = 134), the intestinal metaplasia and gastric mucosal atrophy rates were similar with respect to the H. pylori status.* ***Conclusion:*** *The rates of Helicobacter pylori positivity, intestinal metaplasia, and gastric atrophy were similar in patients with gastritis with or without bile reflux. However, the frequency of Helicobacter pylori, intestinal metaplasia, and gastric mucosal atrophy was lower in patients with pathologically confirmed biliary gastritis.*

Key words: *Bile reflux gastritis, gastric mucosal atrophy, intestinal metaplasia, Helicobacter pylori status*

Giriş ve Amaç: *Mideye safra asidi reflüsü ve atrofi ile intestinal metaplazi riski çeşitli çalışmalarda ele alınmış ve farklı sonuçlar elde edilmiştir. Bu çalışmanın amacı gastrit hastalarında safra reflüsünün gastrik mukozal atrofi, intestinal metaplazi ve Helicobacter pylori arasındaki ilişkiyi araştırmaktır.* ***Gereç ve Yöntem:*** *Çalışmaya gastrit bulunan toplam 217 hasta dahil edilmiş olup hastalar, intragastrik safra reflüsü bulunan (134 hasta) (n=20 patoloji ile doğrulanmış) ve safra reflüsü bulunmayan 83 hasta kontrol grubu olmak üzere iki gruba ayrılmıştır. Helicobacter pylori durumu ve intestinal metaplazi ile gastrit atrofi varlığı, safra reflüsü ve safra reflüsü gastriti varlığı açısından değerlendirilmiştir.* ***Bulgular:*** *Safra reflüsü bulunan ve bulunmayan gastrit hastaları arasında Helicobacter pylori pozitifliği (%38.8 vs %45.8), intestinal metaplazi (%32.8 vs %33.7) ve gastrik atrofi (%30.6 vs %30.1) açısından anlamlı fark saptanmamıştır. Bununla birlikte safra reflüsü gastritinin patolojik doğrulama eksikliği anlamlı derecede daha düşük Helicobacter pylori pozitifliği (%0.00 vs %45.6, p=0.001), intestinal metaplazi (%5.0 vs %37.7, p=0.009) ve gastrik atrofi (%0.0 vs %36.0, p=0.003) ile ilişkili bulunmuştur.* ***Sonuç:*** *Bulgularımız safra reflüsü bulunan ve bulunmayan gastrit hastaları arasında Helicobacter pylori poizitifliği, intestinal metaplazi ve gastrik atrofi oranlarının benzer olduğunu ortaya çıkarmıştır. Ancak patolojik olarak doğrulanan safra gastriti bulunan hastalarda Helicobacter pylori, metaplazi ve atrofi sıklığının daha az olduğu saptanmıştır.*

Anahtar kelimeler: *Safra reflüsü gastriti, gastrik mukozal atrofi, intestinal metaplazi, Helicobacter pylori*

INTRODUCTION

Bile reflux gastritis occurs due to retrograde movement of bile into the stomach either after gastric or biliary surgery or primary biliary reflux accompanied with gallbladder dysfunction and gastric or duodenal dysmotility (1,2). Recurrent and excessive exposure of gastric mucosa to bile reflux leads to endoscopic and histologic changes that are characteristic for chemical (reactive) gastritis with or without clinical symptoms (2).

Helicobacter pylori (H. pylori) infection and chronic bile reflux are considered amongst the risk factors for intestinal metaplasia. Chronic *H. pylori* infection induces chronic inflammation in the gastric mucosa, which may progress to atrophy and intestinal metaplasia, increasing the risk of gastric adenocarcinoma (3). Unlike to well-known close relationship among *H. pylori* infection, atrophic gastritis, and intestinal metaplasia (4-6), the relati-

Correspondence: Muhammet Fatih AYDIN
Department of Gastroenterology, Altınbaş University Bahçelievler Medical Park Hospital, Kültür Sok. No: 1 Bahçelievler, 34180 İstanbul, Turkey
Faks: +90 212 484 16 90 • E-mail: drmfatih@hotmail.com

Aydın MF, Namlı Koç Ş, Aydın MA, et al. Gastric mucosal atrophy, intestinal metaplasia, and Helicobacter pylori status in patients with gastritis with or without bile reflux: Is the presence of bile reflux good or bad? The Turkish Journal of Academic Gastroenterology 2020;19:49-56. ***DOI: 10.17941/agd.800877***

Geliş Tarihi: 30.07.2020 • **Kabul Tarihi:** 24.08.2020

akademik gastroenteroloji dergisi 2020; 19(2): 49-56

onship between reflux of bile acid into the stomach and risk of atrophy and intestinal metaplasia has only been discussed in a few studies and different results have been obtained (7-12).

Some clinical and experimental studies have shown that bile acids and pancreatic proteolytic enzymes can damage gastric mucosa, therefore reflux of bile and duodenal contents has a possible pathogenetic role in gastritis, gastric ulcer, chronic gastritis, metaplasia and gastric cancer (13). In addition, pancreatic fluid and bile acid cause cancer and ulcer development has been shown in rats (14-18). However, one study revealed no contribution of bile and Helicobacter on metaplasia (19). Some studies have shown that bile reduces *H. pylori* colonization, whereas some other studies reported that bile increases *Helicobacter* colonization (20,21).

The present study was designed to investigate the association of intragastric bile reflux, gastric mucosal atrophy, intestinal metaplasia and *H. pylori* status in a cohort of patients with gastritis.

MARETIALS and METHOD

Study Population

A total of 217 patients (mean±SD age: 33.23±7.87 years, 51.2% were males) diagnosed with gastritis upon their admission to our gastroenterology clinic with complaint of dyspepsia were retrospectively included in this single-center retrospective study conducted between January 2017 and June 2017. Patients with histologically confirmed gastritis were divided into two groups based on endoscopic findings, including those with intragastric bile reflux [n=134; bile reflux gastritis confirmed (n=20) by pathology] and those without bile reflux (control, n=83) (Figure 1). All patients fulfilling the selection criteria during the enrollment period of 6 months were included in the study. Exclusion criteria of the study were patient age over 50 years, presence of gastric or esophageal malignancy and active bleeding, cholecystectomy, gastric operation, ongoing or previous chemotherapy, antibiotic or non-steroidal anti-inflammatory drug therapy and inability to perform gastric biopsy.

The study was conducted in full accordance with local Good Clinical Practice (GCP) guideline and current legislations, while the permission was obtained from our institutional ethics committee for the use of patient data for publication purposes. An ethic commitee approval was obtained from Sakarya University Faculty of Medicine's Non-interventional Ethics Committee (Ethics committee number:71522473/050.01.04/403, date: 10.07.2020).

Study Parameters

Data on patient demographics (age, gender), active smoking, alcohol consumption, family history for gastritis or gastric cancer, gall bladder pathology (previous cholecystectomy, cholelithiasis, polyps), status of pylorus, type of gastritis (antral gastritis, pan-gastritis, corpus-dominant gastritis) were recorded in each patient. *H. pylori* status and presence of intestinal metaplasia and gastric atrophy were evaluated.

Endoscopic and Histopathological Investigation

Diagnosis of bile reflux gastritis was based on endoscopic findings such as erythema of the gastric mucosa, thickened gastric folds, erosions, and the presence of bile

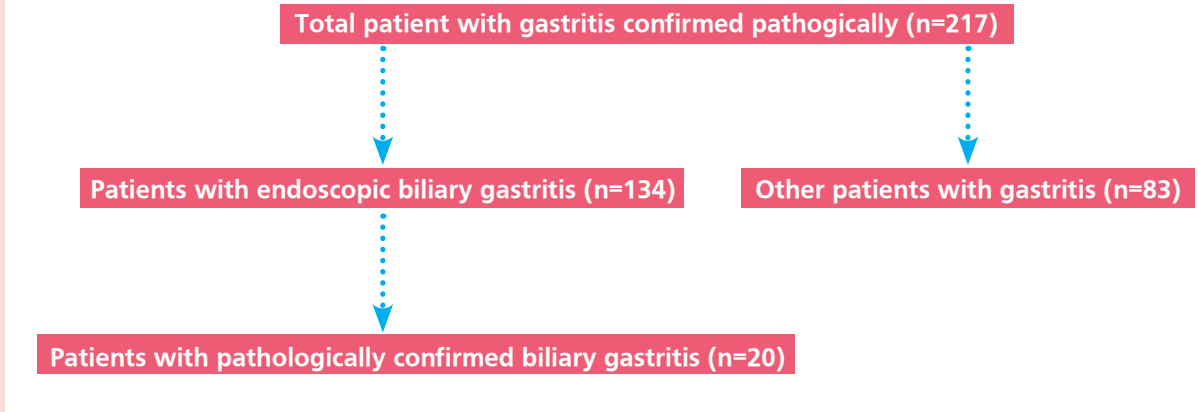

Figure 1. Study design

in the stomach. Samples were taken from the antrum and corpus for pathology. Features of chemical gastritis on pathology included the presence of epithelial foveolar hyperplasia, edema, smooth muscle fibers in the lamina propria, fibrotic bands, cystic dilatation of glands in the lamina propria, minimal or no inflammation in the absence of *H. pylori* positivity. *H. pylori* infection was diagnosed by histochemical examination by giemsa or toloudin blue. The demonstration of active and chronic inflammatory cells in the lamina propria was in favor of the diagnosis. Atrophic gastritis was diagnosed by a decrease in the number of glands in lamina propria. Intestinal metaplasia was diagnosed by the presence of goblet cells within the epithelium of gastric biopsies obtained outside the pyloric canal. Endoscopic and histopathological assessments were performed by the same gastroentorologist and pathologist. Endoscopy reports were transferred to the pathologist before histopathologic evaluation.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY). Chi-square (2) test, Fisher's exact test and Continuity (Yates) Correction were used for the comparison of categorical data, while Student t test was used for analysis of the parametric variables. Data were expressed as mean ± standard deviation (SD) or n (%) as appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics in Patients With Gastritis With and Without Bile Reflux

Endoscopy revealed intragastric bile reflux in 134 (61.8%) of 217 patients with gastritis, while bile reflux gastritis was pathologically confirmed in 20 of 134 (30.8%) patients. History of gall bladder pathology revealed previous cholelithiasis and polyps in less than 5% of patients, while pan-gastritis was the leading type of gastritis (85.0 % and 77.0%, respectively), which was similar in patients with gastritis with and without bile reflux (Table 1).

Table 1. Demographic and clinical characteristics of patients with gastritis with and without bile reflux

			Bile reflux	
		Total (n=217)	**Present (n=134)**	**Absent (n=83)**
Age (year), mean±SD		33.3±7.9	33.3±7.6	33.8 (7.7)
Gender, n (%)				
Female		111 (51.2)	71 (52.9)	40 (48.2)
Male		106 (48.8)	63 (47.1)	43 (51.8)
Active smoking, n (%)		88 (43.3)	51 (38.1)	37 (44.6)
Regular alcohol consumption		46 (22.7)	26 (19.4)	20 (24.1)
Family history for gastritis/gastric cancer		6 (2.8)	3 (2.2)	3 (3.6)
Gall bladder	cholecystectomy	2 (0.9)	2 (1.5)	0 (0.0)
	cholelithiasis	6 (3.4)	5 (3.7)	1 (1.2)
	polyps	11 (6.3)	7 (5.2)	4 (4.8)
Pylorus	normal	33 (15.2)	0 (0.0)	33 (39.8)
	open	171 (78.8)	122 (91.0)	46 (55.0)
	closed	13 (6.0)	11 (8.0)	1 (1.0)
Type of gastritis				
Antral gastritis		16 (7.4)	6 (4.0)	10 (12.0)
Pangastritis		179 (82.5)	114 (85.0)	64 (77.0)
Corpus-dominant gastritis		22 (10.1)	13 (10.0)	9 (11.0)
Bile reflux gastritis	present	134 (61.8)	134 (100.0)	0 (0.0)
	absent	83 (38.2)	0 (0.0)	83 (100.0)
	pathologically confirmed	20 (14.9)	20 (100.0)	0 (0.0)

Associations Between Biliary Gastritis and *H. pylori*, Metaplasia and Atrophy

In patients with biliary gastritis, atrophy was present in 32.8% and metaplasia was seen in 30.6%. In *H. pylori* positive patients, metaplasia was seen in 34% and atrophy was seen in 31% of the patients. Overall, the rates of metaplasia and atrophy were 32.3% and 30.8, respectively. *H. pylori* and bile coexistence did not increase the frequency of metaplasia and atrophy. The incidence of *H. pylori* was 45.8% in those without biliary gastritis and 38.8% in patients with biliary gastritis. Metaplasia, *H. pylori* and atrophy rates were close to zero in pathologically confirmed biliary gastritis and there was significant difference between the *H. pylori* positivity (0.0 vs. 45.6%, p = 0.001), intestinal metaplasia (5.0 vs. 37.7%, p = 0.009) and gastric atrophy (0.0 vs. 36.0%, p = 0.003) rates of pathologically confirmed and negative biliary gastritis groups (Table 2). Complete metaplasia was found in all patients with metaplasia, incomplete metaplasia was not observed, and it was located in the antrum.

In patients with intragastric bile reflux (n=134), there was no significant difference in intestinal metaplasia and gastric atrophy rates with respect to *H. pylori* status or family history for gastritis/gastric cancer (Table 3). In both groups of patients with and without intragastric bile reflux, no significant difference was noted in age and rates for active smoking and alcohol consumption with respect to intestinal metaplasia, gastric atrophy or *H. pylori* status (Table 4).

Table 2. *H. pylori* status, intestinal metaplasia and gastric atrophy with respect to endoscopic and pathological findings

		Bile Reflux on Endoscopy					
	Total (n=217)	**Present (n=134)**	**Absent (n=83)**	**p value**	**Pathologically Confirmed Bile Reflux Gastritis**		**p value**
					Yes (n=20)	**No (n=113)**	
H. pylori, n (%)							
Positive	85 (39.2)	52 (38.8)	38 (45.8)	0.311	0 (0.0)	52 (45.6)	**0.001[1]**
Negative	132 (60.8)	82 (61.2)	45 (54.2)		20 (100.0)	62 (54.4)	
Intestinal metaplasia, n (%)							
Positive	72 (33.2)	44 (32.8)	28 (33.7)	0.891	1 (5.0)	43 (37.7)	**0.009[2]**
Negative	145 (66.8)	90 (67.2)	55 (66.3)		19 (95.0)	71 (62.3)	
Gastric atrophy, n (%)							
Positive	66 (30.4)	41 (30.6)	25 (30.1)	0.941	0 (0.0)	41 (36.0)	**0.003[2]**
Negative	151 (69.6)	93 (69.4)	58 (69.9)		20 (100.0)	73 (64.0)	

[1]Fisher's Exact test, [2]Continuity (Yates) correction

Table 3. Intestinal metaplasia and gastric atrophy with respect to *H. pylori* status and family history for gastritis/gastric cancer in patients with gastritis with bile reflux (n=134)

	***H. pylori* Status**			**Family History for Gastritis/Gastric Cancer**		
	Positive (n=52)	**Negative (n=82)**	**p value**	**Yes (n=3)**	**No (n=131)**	**p value**
Intestinal metaplasia, n (%)						
Positive (n=44)	16 (30.8)	28 (34.1)	0.828	2 (66.7)	42 (32.1)	0.251
Negative (n=90)	36 (69.2)	54 (65.9)		1 (33.3)	89 (67.9)	
Gastric atrophy, n (%)						
Positive (n=41)	18 (34.6)	23 (28.0)	0.541	2 (66.7)	39 (29.8)	0.222
Negative (n=93)	34 (65.4)	59 (72.0)		1 (33.3)	92 (70.2)	

Fisher's Exact test

Table 4. Age, smoking and alcohol status with respect to study parameters in patients with gastritis with and without bile reflux

Patients With Bile Reflux (n=134)					
	Age (year), mean±SD	**Active Smoking, n (%)**		**Alcohol Consumption, n (%)**	
		Yes	**No**	**Yes**	**No**
H. pylori status, n (%)					
Positive (n=52)	34.7±7.2	18 (36.0)	31 (41.3)	7 (26.9)	42 (42.4)
Negative (n=82)	32.4±7.8	32 (64.0)	44 (58.7)	19 (73.1)	57 (57.6)
p value	0.088[1]	0.681[2]		0.224[2]	
Intestinal metaplasia, n (%)					
Positive (n=44)	34.4±7.9	18 (36.0)	21 (28.0)	8 (30.8)	31 (31.3)
Negative (n=90)	32.8±7.4	32 (64.0)	54 (72)	18 (69.2)	68 (68.7)
p value	0.252[1]	0.454[2]		1.000[2]	
Gastric atrophy, n (%)					
Positive (n=41)	34.3±8.1	17 (34)	20 (26.7)	7 (26.9)	30 (30.3)
Negative (n=93)	32.9±7.4	33 (66)	55 (73.3)	19 (73.1)	69 (69.7)
p value	0.322[1]	0.497[2]		0.925[2]	
Cholelithiasis, n (%)					
Present (n=5)	34.8±11.4	2 (4.9)	3 (5.3)	1 (4.3)	4 (5.3)
Absent (n=102)	33.2±7.6	39 (95.1)	54 (94.7)	22 (95.7)	71 (94.7)
p value	0.642[1]	1.000[2]		1.000[3]	
Gall bladder polyps, n (%)					
Present (n=7)	40.0±6.9	5 (12.2)	2 (3.5)	1 (4.3)	6 (8.0)
Absent (n=100)	32.8±7.6	36 (87.8)	55 (96.5)	22 (95.7)	69 (92.0)
p value	**0.015[1]**	0.126[2]		1.000[3]	
Patients without bile reflux (n=83)					
	Age (year), mean±SD	**Active Smoking, n (%)**		**Alcohol Consumption, n (%)**	
		Yes	**No**	**Yes**	**No**
H. pylori status, n (%)					
Positive (n=38)	31.97±8.77	16 (42.1)	18 (45.0)	8 (40.0)	26 (44.8)
Negative (n=45)	34.13±7.9	22 (57.9)	22 (55.0)	12 (60.0)	32 (55.2)
p value	0.242[1]	0.977[2]		0.909[2]	
Intestinal metaplasia, n (%)					
Positive (n=28)	34.79±8.26	17 (44.7)	11 (27.5)	7 (35.0)	21 (36.2)
Negative (n=55)	32.31±8.31	21 (55.3)	29 (72.5)	13 (65.0)	37 (63.8)
p value	0.202[1]	0.177[2]		1.000[2]	
Gastric atrophy, n (%)					
Positive (n=25)	34.92±8.71	14 (36.8)	11 (27.5)	7 (35.0)	18 (31.0)
Negative (n=58)	32.38±8.12	24 (63.2)	29 (72.5)	13 (65.0)	40 (69.0)
p value	0.204[1]	0.522[2]		0.960[2]	
Cholelithiasis, n (%)					
Present (n=1)	27	1 (3.3)	0 (0.0)	0 (0.0)	1 (2.2)
Absent (n=68)	33.28±8.24	29 (96.7)	34 (100)	18 (100.0)	45 (97.8)
p value	-	0.469[3]		1.000[3]	
Gall bladder polyps, n (%)					
Present (n=4)	30.25±2.63	2 (6.7)	1 (2.9)	2 (11.1)	1 (2.2)
Absent (n=65)	33.37±8.41	28 (93.3)	33 (97.1)	16 (88.9)	45 (97.8)
p value	0.465[1]	0.596[3]		0.189[3]	

DISCUSSION

Endoscopic and histological findings in the diagnosis of bile reflux are nonspecific and not well defined. Although not accepted internationally, intense bile and gallbladder sludge during endoscopy with histological changes are sufficient for diagnosis and endoscopic appearance is typical in patients with significant biliary reflux (2). Endoscopic findings include bile and gall sludge, edema of the gastric mucosa, erythema, thickened gastric folds, erosion and some histological changes like foveolar hyperplasia, smooth muscle fibers in lamina propria, active and chronic inflammatory cells. Although the distinction between inflammation due to bile and Helicobacter infections can be made pathologically, this issue is controversial. In our study, the rate of pathologic bile gastritis was 20/134 (30.8%). This low rate indicated that there should be an intense bile reflux into the stomach for a long time to produce histological findings related to bile gastritis (2). Patients who had no pathologically confirmed bile gastritis should be evaluated for newly started alkaline reflux gastritis. The amount of bile reflux increases the amount of edema and erythema in the mucosa (13). In some studies, biliary density devices such as biliary 2000 can be used to quantify reflux, (13) but our study was retrospective and quantitative measurement of bile could not be made because of that. The etiology of chronic gastritis is mostly associated with *H. pylori* (22). Intensity of infection directly affects histological inflammation (23). Biliary gastritis or chemical gastritis should be suspected in chronic gastritis without *H. pylori* (24).

In our study, the frequencies of *H. pylori*, metaplasia and atrophy were not significantly different in patients with and without bile gastritis, whereas *H. pylori* frequency, atrophy and metaplasia were significantly lower in patients with pathologically confirmed chronic bile gastritis. This can be explained by the negative effect of bile on *H. pylori* that has been present in the stomach for a long time and caused histological changes. Previous studies either showed a negative (19) or positive effect of bile on *H. pylori* (21). In one study, the rate of *H. pylori* was found to be 94% in patients with chronic gastritis, while the rate of *H. pylori* in patients with bile gastritis was 16.5% (24).

In our study there was no increase in the frequency of metaplasia and atrophy in patients with both bile gastritis and *H. pylori* positivity compared to those with only bile gastritis or *H. pylori*. In the study conducted by Kubop et al, a negative correlation was found between the bile density and histological activity in *H. pylori* infection (25). Safe et al. observed no effect of *H. pylori* on bile reflux (26). Timocin et al. also showed a negative correlation between *H. pylori* colonization and bile (20,27). Decrease in *H. pylori* colonization may be related to the reduction of gastric mucosal barrier by bile (28).

The decrease in the frequency of metaplasia in patients with pathological biliary gastritis may be related to a decrease in *H. pylori* and thus a decrease in inflammation. Although it has been reported that bile causes gastric metaplasia and cancer in some literature, the opposite was observed in our study. In the literature, it was observed that bile did not have a negative effect on *H. pylori* and metaplasia in the biopsies performed 6 months after cholecystectomy (19). But in another study it was observed that bile decreased *H. pylori* and increased metaplasia (20). In our study, the negative effect on *H. pylori* was observed in patients with pathologically confirmed biliary gastritis, but no increase was observed in metaplasia. Reduction in metaplasia may be related to decreased *H. pylori*. This result may raise the question of whether bile reduces the risk of gastric cancer by reducing *H. pylori* and metaplasia. We think that, different results may have been obtained from the previous studies due to the retrospective nature and low number of patients, Prospective studies are needed to make a conclusion about the treatment of biliary gastritis. If bile increases metaplasia, it should be treated. However, it should not be treated if bile reduces metaplasia as we observed in our patients with pathological confirmed biliary gastritis. Ursodeoxycholic acid (UDCA) or surgical treatment are currently used in the treatment of bile reflux. In one study, it was shown that UDCA provided histological and symptomatic improvement in patients with biliary gastritis (29). Another question is about the duration of UDCA treatment, because bile gastritis especially after cholecystectomy lasts long.

Among patients with gastritis with bile reflux, no significant difference in intestinal metaplasia and gastric atrophy rates were noted with respect to *H. pylori* status or family history for gastritis/gastric cancer. Since the incidence of metaplasia was higher in patients over 50 years of age, they were excluded from the study (30). In our study, patient age, active smoking or alcohol consumption had no significant impact on the rates of intestinal metaplasia, gastric atrophy or *H. pylori* status in patients with gastritis with or without bile reflux.

While smoking has been associated with higher incidence of duedonogastric reflux in some studies (31,32), the rate of active smoking was not higher in our patients with bile acid reflux compared to those with gastritis due to other etiologies. Our findings revealed no significant

impact of smoking on intestinal metaplasia rates regardless of the etiology of gastritis.

The current study had some limitations. First, due to the retrospective single center design, establishing the temporality between cause and effect as well as generalizing our findings to overall gastritis population seems difficult. Second, the presence of pathological diagnosis only in a small group of patients is another important limitation. Despite these certain limitations, given the paucity of the solid information available on this area, our findings represent a valuable contribution to the literature.

As a result, in our study, we found no difference between the patients with endoscopic biliary gastritis and *H. pylori* in terms of intestinal metaplasia and atrophic gastritis rates. *H. pylori* frequency, metaplasia and atrophy rates were significantly lower in patients with pathologically confirmed biliary gastritis. Bile had a negative effect on *H. pylori*, metaplasia and atrophy.

Acknowledgment: *The authors would like to thank pathology specialist Dr. Guray Kilic from Private Ekin Pathology Laboratory, Istanbul for his assistance in histopathological assessment.*

Conflicts of Interest: *The authors declare that they have no conflict of interest.*

Source of Funding: *None*

Sakarya University Faculty of Medicine Dean's Office Non-interventional Ethics Committee,

Ethics committee number:71522473/050.01.04/403, ethics committee date: 10.07.2020

REFERENCES

1. Testoni PA, Fanti L, Passaretti S, et al. Interdigestive motility pattern in subjects with duodenogastric bile reflux. Scand J Gastroenterol 1987;22:757-62.
2. McCabe ME, Dilly CK. New causes for the old problem of bile reflux gastritis. Clin Gastroenterol Hepatol 2018;16:1389-92.
3. Tang SJ, Wu R, Bhaijee F. Intestinal Metaplasia of the Stomach. VJGIEN 2013;1:187-9.
4. Kekki M, Siurala M, Varis K, et al. Classification principles and genetic of chronic gastritis. Scand J Gastroenterol Suppl 1987;141:1-28.
5. Misiewicz JJ, Price AB, Tytgat GNJ, et al. The Sydney System. A new classification of gastritis. J Gastroenterol Hepatol 1991;6:207-52.
6. Watari J, Chen N, Amenta PS, et al. *Helicobacter pylori* associated chronic gastritis, clinical syndromes, precancerous lesions, and pathogenesis of gastric cancer development. World J Gastroenterol 2014;20:5461-73.
7. Park YH, Kim N. Review of atrophic gastritis and intestinal metaplasia as a premalignant lesion of gastric cancer. J Cancer Prev 2015;20:25-40.
8. Liu KS, Wong IO, Leung WK. Helicobacter pylori associated gastric intestinal metaplasia: Treatment and surveillance. World J Gastroenterol 2016;22:1311-20.
9. Sobala GM, O'Connor HJ, Dewar EP, et al. Bile reflux and intestinal metaplasia in gastric mucosa. J Clin Pathol 1993;46:235-40.
10. Nakamura M, Haruma K, Kamada T, et al. Duodenogastric reflux is associated with antral metaplasic gasiritis. Gastrointest Endosc 2001; 53:53-9.
11. Matsuhisa T, Tsukui T. Relation between reflux of bile acids into the stomach and gastric mucosal atrophy, intestinal metaplasia in biopsy specimens. Takeshi J Clin Biochem Nutr 2012;50:217-21.
12. Matsuhisa T, Arakawa T, Watanabe T, et al. Relation between bile acid reflux into the stomach and the risk of atrophic gastritis and intestinal metaplasia: a multicenter study of 2283 cases. Dig Endosc 2013;25:519-25.
13. Lee Y, Tokunaga A, Tajiri T, et al. Inflammation of the gastric remnant after gastrectomy: mucosal erythema is associated with bile reflux and inflammatory cellularinfiltration is associated with Helicobacter pylori infection. J Gastroenterol 2004;39:520-6.
14. Kondo K, Suzuki H, Nagayo T. The influence of gastro-jejunal anastomoisis on gastrocarcinogenesis in rats. Jpn J Cancer Res 1984;75:362-9.
15. Kaminishi M, Sadatsuki H, Joshima Y, Oohara T, Kondo Y. A new method for production of chronic gastric ulcer by duodenogastric reflux in rats. Gastroenterology 1987;92:1913-8.
16. Mason RC, Taylor PR, Filipe MI, McColl I. Pancreatoduodenal secretions and genesis of gastric stump carcinoma in rat. Gut 1988;29:830-4.
17. Seto Y, Kobori O, Shimizu E, Morioka Y. The role of alkaline reflux in esophageal carcinogenesis in rats. Int J Cancer 1991;49:758-63.
18. Miwa K, Fujimura T, Hasegawa H, et al. Is bile or are pancreaticoduodenal secretions related to gastric carcinogenesis in rats with reflux through pylorus? J Cancer Res Clin Oncol 1992;118:570-4.
19. Bayram G, Ödemiş B, Çiçek B, et al. Effect on alkalen reflux gastritis, histology on the antral mucosa and Helicobacter pylori colonization of cholecystectomy. Akademik Gastroenterology Dergisi 2005;4:13-7.
20. Atak I, Ozdil K, Yücel M, et al. The effect of laparoscopic cholecystectomy on the development of alkaline reflux gastritis and intestinal metaplasia. Hepatogastroenterology 2012;59:59-61.
21. Chen SL, Mo JZ, Cao ZJ, Chen XY, Xiao SD.Effectt of bile reflux on gastric mucosal lesions in patient with dyspepsia or chronic gastritis. World J Gastroenterol 2005;11:2834-7.
22. Morris A, Nicholson G. Ingestion of Campylobacter pyloridis causes gastritis and raised fasting gastric PH. Am J Gastroenterol 1987;82:192-9.
23. Stolte M, Eidt S, Ohnsmann A. Differences in *Helicobacter pylori* associated gastritis in the antrum and body of the stomach. Z Gastroenterol 1990;28:229-33.
24. Sobala GM, O'Connor HJ, Dewar EP, et al. Bile reflux and intestinal metaplasia in gastric mucosa. J Clin Pathol 1993;46:235-40.
25. Kubo M, Sasako M, Gotoda T, et al. Endoscopic evaluation of the remnant stomach after gastrectomy: proposal for a new classification. Gastric Cancer 2002;5:83-9.
26. Safe AF, Nwose OM, Sheehan L, Mountford RA. Spontaneous bile reflux in the elderly. Gerontology. 1993;39(6):338-345.

27. Tomtitchong P, Onda M, Matsukura N, et al. *Helicobacter pylori* infection in the remnant stomach after gastrectomy: with special reference to the difference between Billroth I and II anastomoses. J Clin Gastroenterol 1998;27(Suppl 1):S154-8.
28. Kuipers EJ, Thijs JC, Festen HP. The prevalence of Helicobacter pylori in peptic ulcer disease. Aliment Pharmacol Ther 1995;9(Suppl 2):59-69.
29. Gad Elhak N, Abd Elwahab M, Nasif WA, et al. Prevalence of *Helicobacter pylori,* gastric myoelectrical activity, gastric mucosal changes and dyspeptic symptoms before and after laparoscopic cholecystectomy. Hepatogastroenterology 2004;51:485-90.
30. Jiang JX, Liu Q, Zhao B, et al. Risk factors for intestinal metaplasia in a southeastern Chinese population: an analysis of 28,745 cases. J Cancer Res Clin Oncol 2017;143:409-18.
31. Muller-Lissner SA. Bile reflux is increased in cigarette smokers. Gastroenterology 1986;90:1205-9.
32. Giacosa A, Cheli R. Smoke and chronic gastritis. Mt Sinai J Med 1982;49:475-8.