

Endoscopic and histological findings in the gastric mucosa of cholecystectomized patients with biliary reflux

Hallazgos endoscópicos e histológicos en la mucosa gástrica de pacientes colecistectomizados con reflujo biliar

Achados endoscópicos e histológicos na mucosa gástrica de pacientes colecistectomizados com refluxo biliar

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ABSTRACT

Introduction: duodenogastric biliary reflux is one of the main factors of gastric mucosal injury, occurring in 80% to 90% of patients undergoing gallbladder surgery. **Objective:** To characterize cholecystectomized patients with biliary reflux and gastric mucosal lesions. **Method:** a cross-sectional descriptive study was conducted in 146 cholecystectomized patients who underwent upper gastrointestinal endoscopy in the Gastroenterology Department of the Hospital General Provincial “Carlos Manuel de Céspedes”, Granma province, Cuba, from October 2019 to May 2022. Data were collected from medical records and a survey form; sociodemographic, clinical, endoscopic, and histological variables were analyzed. Quantitative variables were compared using Student's t-test if they had a normal distribution; The qualitative variables were compared as they were analyzed in contingency

tables, with the Z test for comparing proportions and the Chi-square test to establish dependence between them. **Results:** the mean age was 55.7 years, 53.4% were women, and the mean time since cholecystectomy was 7 years. Sessile polypoid lesions were the most frequently diagnosed endoscopic diagnosis (26.03%), with more than one lesion detected in 17.8%. A total of 41.1% presented pathological elements of chronic superficial gastritis. Men had a higher proportion of cancer compared to women (13.2% vs. 3.8%). **Conclusions:** Chronic superficial gastritis and chronic multifocal gastritis were the main histological findings.

Keywords: bile reflux; cholecystectomy; histology; gastric mucosa

RESUMEN

Introducción: el reflujo biliar duodenogástrico es uno de los principales factores lesivos de la mucosa gástrica, y ocurre entre el 80 % y 90 % de los pacientes operados de vesícula. **Objetivo:** caracterizar a los pacientes colecistectomizados con reflujo biliar y lesiones en la mucosa gástrica. **Método:** se realizó un estudio descriptivo transversal en 146 pacientes colecistectomizados, a los que se les realizó endoscopia digestiva superior en el servicio de Gastroenterología del Hospital General Provincial “Carlos Manuel de Céspedes”, provincia Granma, Cuba, en el período comprendido octubre de 2019 hasta mayo de 2022. Los datos se recopilaron de las historias clínicas y planilla de encuesta; se analizaron variables: sociodemográficas, clínicas, endoscópicas e histológicas. Las variables cuantitativas se compararon con la t de Student si tuvieron una distribución normal; las variables cualitativas se compararon según fueron analizadas en tablas de contingencia, con la prueba Z de comparación de proporciones y el test Ji cuadrado para establecer dependencia entre ellas. **Resultados:** la edad media fue de 55,7 años, el 53,4 % fueron mujeres, el tiempo promedio de la colecistectomía fue de 7 años. Las lesiones polipoideas sésiles fue el diagnóstico endoscópico más empleado (26,03 %), en el 17,8 % se detectó más de una lesión. El 41,1 % presentó elementos anatomopatológicos de gastritis crónica superficial. Los hombres tuvieron una mayor proporción de cáncer con respecto a las mujeres (13,2 % vs. 3,8 %). **Conclusiones:** la gastritis crónica superficial y crónica multifocal constituyeron los principales hallazgos histológicos.

Palabras clave: reflujo biliar; colecistectomía; histología; mucosa gástrica

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RESUMO

Introdução: o refluxo biliar duodenogástrico é um dos principais fatores que causam danos à mucosa gástrica e ocorre em 80% a 90% dos pacientes submetidos à cirurgia da vesícula biliar. **Objetivo:** caracterizar pacientes colecistectomizados com refluxo biliar e lesões da mucosa gástrica. **Método:** foi realizado um estudo transversal descritivo em 146 pacientes colecistectomizados, submetidos à endoscopia digestiva alta no serviço de Gastroenterologia do Hospital General Provincial “Carlos Manuel de Céspedes”, província de Granma, Cuba, no período de outubro de 2019 a maio de 2022. Os dados foram coletados de prontuários médicos e formulários de pesquisa; Foram analisadas as seguintes variáveis: sociodemográficas, clínicas, endoscópicas e histológicas. As variáveis quantitativas foram comparadas com o teste t de Student se tivessem distribuição normal; As variáveis qualitativas foram comparadas conforme analisadas em tabelas de contingência, com o teste Z para comparação de proporções e o teste Qui-quadrado para estabelecer dependência entre elas. **Resultados:** a média de idade foi de 55,7 anos, 53,4% eram mulheres e o tempo médio para colecistectomia foi de 7 anos. Lesões polipoides sésseis foram o diagnóstico endoscópico mais utilizado (26,03%), em 17,8% foi detectada mais de uma lesão. 41,1% apresentaram elementos anatomopatológicos de gastrite superficial crônica. Os homens tiveram uma proporção maior de câncer do que as mulheres (13,2% vs. 3,8%). **Conclusões:** gastrite crônica superficial e multifocal crônica foram os principais achados histológicos.

Palavras-chave: refluxo biliar; colecistectomia; histologia; mucosa gástrica



INTRODUCTION

Laparoscopic cholecystectomy is the treatment of choice for cholelithiasis in approximately 90% of patients.⁽¹⁾ Although it is an effective treatment, late complications can occur, such as post-cholecystectomy syndrome, which occurs more frequently in women and includes the same symptoms that prompted the procedure, or other related symptoms consistent with extrahepatic biliary disease.⁽²⁾

Patients with gallbladder disease are more likely to have bile reflux gastropathy. Bile reflux, or duodenogastric reflux (from the Latin "refluo"), refers to the retrograde flow of duodenal contents, including pancreatic enzymes, into the stomach. Although it can be considered a normal occurrence when the frequency and volume are small, when it increases, it becomes a pathological condition capable of damaging the gastric mucosa, which can cause symptoms.^(3,4)

The diagnosis of bile reflux gastropathy is challenging due to its atypical clinical symptoms and nonspecific diagnostic tests. Patients often complain of abdominal pain, dyspepsia, nausea with bilious vomiting, a bitter taste, loss of appetite, and heartburn, while others are completely asymptomatic. (5)

Gastric mucosal biopsy may show histological features of atrophy and intestinal metaplasia.⁽⁶⁾ As a general rule, endoscopic findings in biliary gastritis are characterized by hyperemia and edema of the mucosa. There are no specific clinical, endoscopic, or histological features of bile reflux gastropathy.^(7,8,9)

All these aspects allow us to characterize patients who have undergone cholecystectomy and bile reflux, and who have had an upper gastrointestinal endoscopy, which is the objective of this study.

METHOD

A descriptive, cross-sectional study was conducted on patients who had undergone cholecystectomy and who were subsequently examined with upper endoscopy at the Gastroenterology Department of the "Carlos Manuel de Céspedes" Provincial General Hospital in Granma, Cuba, between October 2019 and May 2022.

The study included 146 patients who had undergone cholecystectomy and showed endoscopic evidence of biliary reflux. All participants agreed to participate in the study and had no history of gastrointestinal surgery, gastric cancer or polyposis, distal stenosis of the ampulla of Vater, or radiation therapy.

The following variables were analyzed: age, sex, tobacco and alcohol use, comorbidities, time elapsed since cholecystectomy, duration of symptoms, and endoscopic and histological findings.



The analysis was based on descriptive statistics. For qualitative variables, absolute and relative frequencies were calculated; for quantitative variables, the mean and standard deviation, as well as the minimum, maximum, and range were estimated. Quantitative variables were compared using the Student's t-test if they had a normal distribution; otherwise, the Mann-Whitney U test was used. Qualitative variables were compared using contingency tables, with the Z-test for comparing proportions and the chi-square test to determine statistical dependence between them. In all analyses, the p-value was calculated with a significance level of less than 0.05.

The Statistical Package for the Social Sciences (SPSS) version 22 was used for all data processing. The literature search for the study was conducted using the databases LILACS, MEDLINE, BIREME-OPS, PubMed, and Cochrane.

The ethics committee of the participating institution approved the study. The ethical principles of the Declaration of Helsinki were adhered to.

RESULTS

The average age was 55.7 years, with a predominance of females (53.42%, n=78); 46.58% (n=68) were male. The average time since cholecystectomy was 7.7 years, with a minimum of 1 year and a maximum of 20 years. 60.9% (n=89) of the patients had no comorbidities; however, 19.8% were smokers, and 63.01% underwent cholecystectomy due to gallstones (Table 1).

Table 1: Patient characteristics according to age, sex, comorbidities, harmful habits, and reason for cholecystectomy

Variables	Values
Age (years) mean (DE), minimum-maximum	55,7(12,9);22-85
Time since cholecystectomy (years) mean (SD), min-max	7,7(4,3);1-20
Sex (No./%)	
Male	68/46,58 %
Female	78/53,42 %
Comorbidity (No./%)	
None	89/60,96 %
Diabetes mellitus	16/10,96 %
Hypertension	27/18,49 %
Hypertension and diabetes mellitus	14/9,59 %
Harmful habits (No./%)	
Smoking	28/19,18 %
Reason for cholecystectomy (No./%)	
Gallstone	92/63,01 %
Gallbladder polyps	7/4,79 %
Dyspepsia	47/32,19 %

Table 2 summarizes the endoscopic findings. The presence of sessile polypoid lesions (0-Is) accounted for 26.03% (38) of cases, while lesions of type 0-IIb were detected in only 0.68% (1) of cases. Biliary reflux gastropathy was observed in 19 (13.01%) of the 146 cases, and more than one lesion was detected in 26 (17.8%) of the cases.

Table 2: Patients according to endoscopic findings

Findings Values	Values (No./%)
Elevated lesion (0-Is)	38/26,03 %
Multiple findings	26/17,8 %
Bile reflux gastropathy	19/13,01 %
Signs of atrophic gastritis	15/10,27 %
Gastric ulcer	11/7,53 %
Advanced cancer	10/6,85 %
Nodular gastropathy	10/6,85 %
Flat lesion (0-IIa)	7/4,79 %
Elevated lesion (0-Ip)	5/3,42 %
Erosive gastropathy	4/2,74 %
Flat lesion (0-IIb)	1/0,68 %

The main histological findings are shown in Table 3. 41.1% (60) of the cases showed histopathological features of chronic superficial gastritis, followed by multifocal atrophic gastritis, present in 37 of the 146 cases (25.3%).

Malignant diseases, specifically gastric adenocarcinoma and gastric lymphoma, represented 6.16% and 2.05% of the cases, respectively (9 and 3). Normal gastric mucosa (without any histological changes) was reported in 17.12% of all cases (25). Furthermore, hyperplastic and adenomatous polyps were reported as histological findings in 6.85% and 1.37% of all cases, respectively.

Table 3: Patients according to histological findings

Findings	Values (No./%)
Chronic superficial gastritis	60/41,10 %
Multifocal atrophic gastritis	37/25,3 %
Normal mucosa	25/17,12 %
Hyperplastic polyps	10/6,85 %
Adenocarcinoma	9/6,16 %
B-cell lymphoma	3/2,05 %
Adenomas	2/1,37 %

Table 4 shows the characteristics of patients with malignant diseases compared to those with other diagnoses. The mean age of patients with cancer was significantly higher than that of the other group (62.5 vs. 55.1; $p=0.005$), as was the average time to cholecystectomy.

Regarding sex, men had a higher proportion of cancer diagnoses than women did (13.2% vs. 3.8%; $p=0.03$); however, among patients with non-malignant diseases, women were more frequently affected than men were.

Table 4: Patient characteristics according to the presence of malignant neoplasm

Variables	Cancer	Others diagnoses	p
Age, mean (SD)	62,5/10,3	55,1/13	0,005*
Time since cholecystectomy, mean (SD)	11,3/3,2	74/4,3	0,002*
Sex			
Male	9/13,2 %	59/86 %	0,03**
Female	3/3,8 %	75/96,1 %	

Note: *Student's t-test, **Chi-square test

DISCUSSION

Bile reflux, or duodenogastric reflux, is a condition that occurs when bile flows from the duodenum into the stomach and esophagus; in this study, it was more frequent in women than in men, which is consistent with research conducted by Chávez-Mendoza⁽¹⁰⁾ in Peru, where women represented 61.52%, with a mean age of 48.18 ± 16.82 years.

Although cholecystectomy is the definitive treatment for cholelithiasis, the absence of the gallbladder is the main cause of secondary duodenogastric reflux; among the mechanisms involved, the most important is the constant presence of bile in the duodenum.

Gilani⁽¹¹⁾, in a prospective study of 44 patients who had undergone cholecystectomy, found that in 66% of them, symptoms appeared after 5 years, which is similar to the findings of the present study. The authors of this study infer that cholecystectomy induces high levels of cholecystokinin, due to the loss of regulatory mechanisms, which would favor duodenogastric reflux by relaxing the pyloric sphincter muscle.

In a study conducted in the United States by Kolli⁽¹²⁾ with 728 patients of various ethnicities, it was determined that post-cholecystectomy patients who were smokers, hypertensive, or diabetic represented the largest proportion, a result similar to that of this study.

Diabetes was considered a risk factor for bile gastritis due to damage to the vagus nerve, which is crucial for gastric motility, and has been linked to gastroduodenal dysmotility. A considerable proportion of diabetic patients suffer from gastroparesis, which is defined as a deficiency in gastric motility function. It has been described that long-term hyperglycemia can induce autonomic nervous system dysfunction, which reduces gastric tone and slows gastric peristalsis, leading to delayed gastric emptying and abnormal gastropyloric-duodenal dynamics. This prolongs the residence time of bile in the stomach and contributes to the occurrence of duodenogastric reflux.

In addition, diabetic microvascular damage significantly reduces blood flow to the gastric mucosa, which further decreases gastric peristalsis, as experts speculate that this may also be one of the reasons for gastroparesis⁽⁵⁾.

The presence of endoscopic lesions is not specific to bile reflux; however, the deleterious effect of bile on epithelial cells is well documented. Mucosal damage could be attributed to the interaction of bile acids with the M3 subtype of muscarinic receptors on parietal cells, followed by inflammation, intestinal metaplasia, glandular atrophy, focal hyperplasia, redox reactions, and apoptosis. Endoscopic findings in bile reflux gastropathy include erythema, petechiae, and erosions of the gastric mucosa, in addition to the presence of bile.⁽¹³⁾

In the present study, 13.1% of the patients (19/146) presented with bile reflux gastropathy, a result similar to that of the study by Li et al.⁽¹⁴⁾, where this condition was found in only 18.4% of the patients (5118/27807).

Erosive gastropathy was present in 18% of the patients studied by Al-Bayati⁽¹³⁾ in Iraq. In this same study, 2 patients (6.5%) had nodular lesions and 5 patients had peptic ulcers (a lower number than in the present study), and no malignant lesions were reported.

The concentration and duration of exposure to bile have a positive correlation with the incidence rate of cancer. Choi⁽⁶⁾ found in his study that the incidence of cancer in the cholecystectomy group was 9.56 per 1000 person-years, and in the control group, 7.95 per 1000 person-years.

Other prospective studies evaluating the risk of cancer in patients who underwent cholecystectomy found that the incidence was significantly higher compared to the control group (40% vs. 18%; $p=0.003$). There is evidence that deoxycholic acid and lithocholic acid can induce necrosis or promote apoptosis and DNA damage; deoxycholic acid is both mutagenic and carcinogenic⁽¹⁵⁾.

The most common cause of chronic gastritis is *Helicobacter pylori* infection; however, other histological findings, such as intestinal metaplasia, may also be present. In the study by Chang et al.⁽¹⁶⁾ involving patients who had undergone cholecystectomy, intestinal metaplasia was found in 28.4% of the 88 patients with gastro-duodenal reflux, and none of them had normal histological findings. This latter finding does not coincide with the results of the present study. It is well documented that bile reflux increases gastric mucosal damage, and high concentrations of bile acids may have an effect on the progression of intestinal metaplasia in patients with *Helicobacter pylori*-negative chronic gastritis.

Other studies consulted show a lower proportion of patients with intestinal metaplasia. In a study by Erdogan⁽¹⁷⁾ involving 1005 patients, intestinal metaplasia was present in 20.2%, significantly lower than that found in this study ($p=0.002$). In that same study, 39.5% of the patients had atrophic gastritis, a higher proportion than in the present study ($p=0.000$); however, they had a lower incidence of dysplasia (5%).

Stomach cancer is one of the most common malignancies of the digestive tract, with an incidence that ranks fifth among all cancer types. Its etiopathogenic mechanisms are complex; environmental factors (diets low in fruits and vegetables, alcohol consumption), infectious factors (*Helicobacter pylori* colonization), and genetic changes, which play a fundamental role in disease progression, are all implicated. In a systematic review and meta-analysis by Yang et al. ⁽¹⁸⁾ to determine the relationship between cholecystectomy and gastric cancer, a relative risk of 1.11 (95% confidence interval; 1.03-1.20) was found in 26,063 patients; a result similar to ours.

Li et al. ⁽¹⁹⁾, in 2022, conducted a meta-analysis using various databases, primarily Gene Expression and Genome Atlas, including 30 studies involving 4487 patients. The results showed that androgen receptor expression was present in 40% of patients with cancer (95% confidence interval; 29% - 51%); however, in Asian male patients, expression was significantly higher than in Asian women, with a mean difference of 1.33 (95% confidence interval; 0.28-2.39; $p=0.013$); They also found that patients with overexpression of these receptors have a poorer prognosis.

CONCLUSIONS

Female sex and middle age were associated with the highest prevalence of lesions. Sessile lesions and the presence of multiple lesions were the most frequent endoscopic findings. Superficial chronic gastritis and multifocal chronic gastritis were the main histological findings. Patients with malignant neoplasms were older and had a longer duration since their cholecystectomy, with a predominance of males.

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Conflicts of Interests:

The authors declare that there are no competing interests.

Author Contributions:

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