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Relation of Gallbladder Function and *Helicobacter pylori* Infection to Gastric Mucosa Inflammation in Patients with Symptomatic Cholecystolithiasis

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Key Words
Cholecystolithiasis · Gallbladder function · Gastric mucosa · *Helicobacter pylori*

Abstract
Background: Inflammatory alterations of the gastric mucosa are commonly caused by *Helicobacter pylori* (Hp) infection in patients with symptomatic gallstone disease. However, the additional pathogenetic role of an impaired gallbladder function leading to an increased alkaline duodenogastric reflux is controversially discussed. ***Aim:*** To investigate the relation of gallbladder function and Hp infection to gastric mucosa inflammation in patients with symptomatic gallstones prior to cholecystectomy. ***Patients:*** Seventy-three patients with symptomatic gallstones were studied by endoscopy and Hp testing. ***Methods:*** Gastritis classification was performed according to the updated Sydney System and gallbladder function was determined by total lipid concentration of gallbladder bile collected during mainly laparoscopic cholecystectomy. ***Results:*** Fifteen patients revealed no, 39 patients mild, and 19 moderate to marked gastritis. No significant differences for bile salts, phospholipids, cholesterol, or total lipids in gallbladder bile were found between these three groups of patients. However, while only 1 out of 54 (<2%) patients with mild or no gastritis was found histologically positive for Hp, this infection could be detected in 14 (74%) out of 19 patients with moderate to marked gastritis. ***Conclusion:*** Moderate to marked gastric mucosa inflammation in gallstone patients is mainly caused by Hp infection, whereas gallbladder function is not related to the degree of gastritis. Thus, an increased alkaline duodenogastric reflux in gallstone patients seems to be of limited pathophysiological relevance.

Introduction

Inflammatory alterations of the gastric mucosa are common in patients with symptomatic gallstone disease [1–3]. In studies that included histological evaluation and controlled for *Helicobacter pylori* (Hp), the prevalence of gastritis ranged from 32 to 88% with mean or median age ranging from 42 to 58 years [4–7]. In comparison, gastric mucosal alterations in asymptomatic persons or control groups as determined by endoscopy alone were observed in about 20% [8, 9], but were significantly increased to 37% [10], over 60% [11] or even 70% [7] when gastritis was defined histologically. Mean or median age was 48, 58 and 46 years, respectively [7, 10, 11].

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Apart from the established role of an increased duodenogastric reflux (DGR) in the clinical entity of postgastrectomy alkaline reflux gastritis [12–15], there is also evidence that an impaired function of the sphincter of Oddi could induce an increased DGR and gastritis [7]. In investigations regarding patients after cholecystectomy (CHE), an increased DGR was shown with scintigraphy, aspiration and analysis of gastric contents, 24-hour pH monitoring and the Bilitec device [7, 16–23]. Still, some studies failed to show any increased DGR after CHE, again utilizing scintigraphy [7, 24] or the Bilitec device [25]. Whether an increased DGR after CHE is also causing histologically evident gastritis is controversially discussed, as is whether an increased DGR (after CHE or per se) is causing symptoms [7, 16, 20–22, 26, 27]. Increased DGR has also been shown to a lesser degree in patients with gallstones, but without a correlation to symptoms or histologically proven gastritis [7, 18–20, 22, 23, 28]. It appears that mostly gallstone patients without functioning gallbladders had an increased DGR, suggesting a spillover effect as the mechanism behind DGR [23, 28].

Our objective was to assess histologically defined gastritis in patients with symptomatic cholecystolithiasis prior to CHE and to investigate its relation to Hp infection and gallbladder function.

Patients and Methods

Patients

The study included 73 consecutive patients, with a mean age ± SD of 49.6 ± 15.5 years; 17 men (mean age ± SD 48.2 ± 13.5 years) and 56 women (mean age ± SD 50.4 ± 16.2 years). All patients underwent upper gastrointestinal endoscopy and biopsy prior to laparoscopic CHE for symptomatic cholecystolithiasis. The patients' records included a history of nicotine, alcohol, nonsteroid anti-inflammatory drugs, proton pump inhibitors (PPI), antacids, and antibiotics use.

We excluded 2 patients that were endoscopied without being biopsied, 1 patient that was biopsied only in the fundus/cardia, and 6 patients that underwent additional surgical procedures.

Collection of Bile and Analysis of Bile Lipid Composition

All patients gave informed consent after a detailed explanation of the procedure required for intraoperative bile collection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was accepted by the ethics committee of the institution. During laparoscopic surgery, the gallbladder was punctured and a flexible probe with side ports was inserted; bile was aspirated as completely as possible because of the known stratification of human gallbladder bile. For the analysis of bile composition, duplicate aliquots of bile samples after ultracentrifugation (1 h at 100,000 *g*) were stored at –30°C prior to determination. Cholesterol was determined colorimetrically with the Liebermann-Burchard reaction after double extraction of a 1-ml methanolic bile sample with petroleum ether. Phospholipids were measured as total biliary phosphate after hydrolysis at 150°C with sulfuric acid using the colorimetric assay of Fiske-Subbarow, and total bile salts were determined by a modified 3α-hydroxysteroid dehydrogenase method. Total lipids were calculated by converting millimoles per liter to grams per deciliter and adding the values for cholesterol, phospholipids, and total bile salts.

Gastritis Classification

For the classification of gastritis, we used the pathological investigations of the biopsies. The classification of gastritis was based on pathologic reports according to the updated Sydney System [14]. We examined the morphology, which is described in the updated Sydney System with the use of 5 graded (0–3) variables and other nongraded variables. For our morphological classification, we utilized 2 of the graded variables (active and chronic inflammation). We examined the presence of Hp, which is the 3rd graded variable, with Giemsa (or, in 1 patient, toluidine blue) staining of the biopsy specimens. We finally noted the presence of intestinal metaplasia (IM; the 4th graded variable), which was controlled for with Alcian blue staining, of the 5th graded variable, i.e. atrophy, and of foveolar hyperplasia (FH), which is a nongraded variable of the updated Sydney System. We divided the patients into three groups as follows: (1) patients with no gastritis that did not show an inflammatory infiltrate in the biopsy; (2) patients with mild gastritis that had chronic inflammatory infiltrate without active inflammation; (3) patients with moderate to marked gastritis that had chronic and active inflammation in either the antrum, the corpus, or both. The examining pathologist was blinded with respect to our investigation. We also examined the topology of gastritis qualitatively in order to differentiate antrum- or corpus-predominant patterns of gastritis.

Statistical Analysis

Since the distribution of the parameters was not normal and the case numbers in the different gastritis groups were rather small, 2-tailed nonparametrical tests (Mann-Whitney test, Kruskal-Wallis test and χ^2 test) were performed using the SPSS statistical software package; $p < 0.05$ was regarded as statistically significant, $p < 0.1$ as indicative.

Results

Distribution of Patient Characteristics in the Different Gastritis Groups

Fourteen patients had a history of smoking (past or present smokers); 4 of them showed moderate to marked, 5 mild, and 5 no gastritis. Fourteen patients had a history of alcohol consumption; 5 of them showed moderate to marked, 4 mild, and 5 no gastritis. As far as the combined history of smoking and alcohol consumption is concerned, we found that out of the 6 patients with such a history, 3 belonged to the no, 2 to the mild and 1 to the moderate to marked gastritis group. Three patients had a

history of nonsteroid anti-inflammatory drug use (including low-dose aspirin), 2 of whom belonged to the mild, and 1 to the moderate to marked gastritis group. One patient had a history of PPI use (mild gastritis group) and 1 had used antibiotics (no gastritis group).

Upper Gastrointestinal Endoscopy

There were no patients with active gastric or duodenal ulcers found, but 3 of the patients had gastric erosions. Five patients showed endoscopic evidence of duodenal inflammation. Eight patients had small (<3 cm) and 4 patients large (≥ 3 cm) axial hernias. Twenty-five patients revealed cardiac insufficiency, which coincided with an axial hernia in 5 of them. One patient had esophageal varices of <5 mm. Fourteen patients suffered from esophageal inflammation, which was associated with an axial hernia or cardiac insufficiency in 10 of them. Finally, endoscopy detected gastric polyps in 3 patients and a duodenal polyp in 1.

Gastritis Classification and Evaluation of Gastric Pathology

We distinguished three groups of patients: (1) no gastritis (n = 15); (2) mild gastritis (n = 39), and (3) moderate to marked gastritis (n = 19) according to the inflammatory infiltration of the gastric mucosa. Patients from the no gastritis group were all Hp negative and only 1 patient from the mild gastritis group was Hp positive. On the contrary, 74% (14/19) from the moderate to marked gastritis group were Hp positive and 26% (5/19) negative (fig. 1), 3 of them having microscopic evidence of lymphoid follicles. Lymphoid follicles were also observed in 6 Hp-positive patients with moderate to marked gastritis and 2 Hp-negative patients with mild gastritis. Hp was detected in both antrum and corpus samples in Hp-positive patients.

There were no major topological patterns (marked antrum or corpus predominance) observed. However, 9 patients displayed minor topological patterns. Two of them showed a corpus predominance pattern, 1 having an Hp-negative moderate to marked gastritis and 1 having a mild gastritis with the pathological diagnosis of chemical corpus gastritis. The remaining 7 patients demonstrated antrum predominance patterns. Six of these patients belonged to the moderate to marked gastritis group and 1 to the mild gastritis group. All 7 patients with an antrum predominance pattern were Hp positive in the antrum samples.

Atrophy was observed in 8 patients, 4 of them with moderate to marked gastritis (3 Hp positive, 1 Hp negative) and 4 with mild gastritis (Hp negative). Mucosa atrophy never reached a marked extent. Atrophy was predominantly found in the antrum, but in 2 patients with moderate to marked gastritis (1 Hp positive and 1 Hp negative) in both antrum and corpus samples. IM was observed in 10 patients. Six of them had mild gastritis (1 Hp positive), 3 moderate to marked gastritis (all Hp positive), and 1 no gastritis. IM was not marked in any of the cases. It was observed only in the antrum samples in nearly all patients apart from 1 with mild, Hp-positive gastritis, where it was reported in both antrum and corpus samples. FH was observed in 20 patients. Eight of these patients had moderate to marked gastritis (5 being Hp positive), 8 mild gastritis (1 being Hp positive) and 4 patients no gastritis. FH was not marked in any of the cases. FH was mainly seen in the antrum samples except in 2 patients (both belonged to the moderate to marked gastritis group, 1 being Hp positive). In one it was also found in corpus samples and in the other one (Hp negative) only in corpus samples. A reflux (chemical) gastritis was diagnosed in just 1 patient (the diagnosis regarded the corpus and not the antrum sample). Still, 7 Hp-negative patients did combine chronic inflammatory infiltrates and IM or FH in the antrum while the corpus samples showed less chronic inflammation and no FH or IM.

Three patients had nonmalignant gastric polyps.

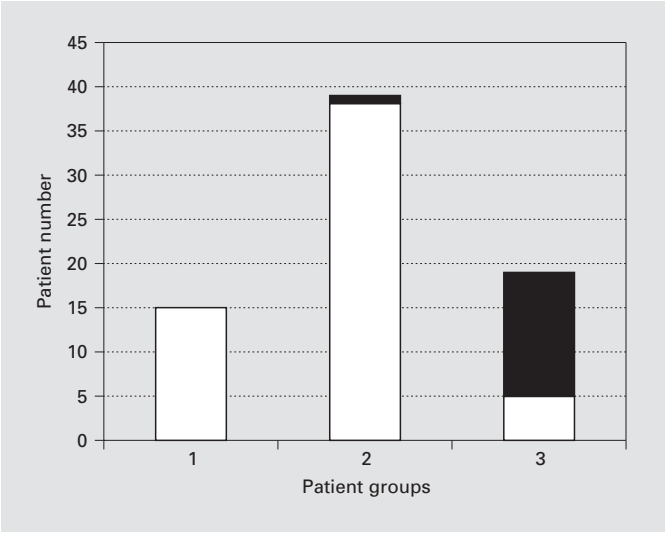

Fig. 1. Distribution of inflammatory alterations of the gastric mucosa and Hp prevalence in 73 patients with symptomatic cholecystolithiasis. 1 = No gastritis; 2 = mild gastritis; 3 = moderate to marked gastritis; dark color = Hp positive; light color = Hp negative.

Table 1. Bile lipid composition (mean ± SD) and age of 73 patients with symptomatic gallstones in relation to gastric mucosa inflammation

	No gastritis (n = 15)	Mild gastritis (n = 39)	Moderate to marked gastritis (n = 19)
Total bile salts, mmol/l	83.0 ± 23.7	75.2 ± 42.4	80.1 ± 44.4
Phospholipids, mmol/l	39.6 ± 13.4	32.5 ± 26	36.2 ± 21.6
Cholesterol, mmol/l	15.5 ± 6	13.8 ± 15.6	14.9 ± 10.1
Total lipids, g/dl	8.1 ± 2.2	7.2 ± 4.3	7.5 ± 4.1
Age, years	40.1 ± 11	55.8 ± 12.4*	50.4 ± 17*

* $p < 0.05$ compared to left column ($p = 0.035$ for mild gastritis vs. no gastritis and $p = 0.01$ for moderate to marked gastritis vs. no gastritis).

Table 2. Bile lipid composition (mean ± SD) and age of 73 patients with symptomatic gallstones in relation to Hp infection

	Hp negative (n = 58)	Hp positive (n = 15)
Total bile salts, mmol/l	83.0 ± 38.8	65.7 ± 43.2
Phospholipids, mmol/l	38.6 ± 20.7	25.6 ± 21.6*
Cholesterol, mmol/l	15.2 ± 8.9	12.9 ± 17.4**
Total lipids, g/dl	7.9 ± 3.7	6.2 ± 4.1
Age, years	48.3 ± 15.9	55.7 ± 12.9**

* $p < 0.05$, compared to left column ($p = 0.022$). ** $p < 0.1$, compared to left column ($p = 0.052$ for cholesterol and $p = 0.074$ for age).

Composition of Gallbladder Bile

We compared the values of total bile salts, phospholipids, cholesterol, and total lipid concentration in the three groups with different inflammatory infiltration of the gastric mucosa. Neither the Kruskal-Wallis nor the Mann-Whitney test showed a statistically significant difference between the three groups for any of the four parameters, but there were statistically significant differences for age both in the Mann-Whitney (table 1) and in the Kruskal-Wallis test ($p = 0.009$).

We then compared the patients who had Hp-positive biopsies with those without. These comparisons showed significantly lower phospholipid concentrations and a nonsignificant trend to lower bile salt, cholesterol and total lipid concentrations in the gallbladder bile of patients with a positive test for Hp infection (table 2).

We controlled for differences in sex within the gastritis or Hp groups, but found no significant differences (data not shown).

Discussion

The use of PPI or antibiotics prior to upper gastrointestinal endoscopy was unlikely to contribute to a significant alteration of Hp detection. The endoscopies discovered no active peptic ulcers, constricting their prevalence to 0%, which is even lower than the prevalence of peptic ulcers in asymptomatic persons or controls (4–6%) [8, 9, 11] or in patients with symptomatic cholecystolithiasis (0.5–4%) [1–3].

The overall prevalence of gastritis in our investigation was 79% (58/73). This is higher than the endoscopic estimate of gastritis prior to CHE [1, 3] and the prevalence of histologically proven gastritis in asymptomatic persons or control groups [7, 10, 11], but within the range of histologically proven gastritis in patients with symptomatic cholecystolithiasis [4–7]. However, since most of our patients had chronic mild gastritis and chronic gastritis is a common finding in control groups [8, 11] and since gastritis was asymptomatic in our patients, the finding of an elevated gastritis prevalence in our patients with symptomatic cholecystolithiasis is of limited clinical relevance.

After classifying the patients, we observed that an Hp infection was present in the gastric mucosa in 74% (14/19) of gallstone patients with a moderate to marked inflammatory infiltrate. The remaining 26% (5/19) with a negative Hp status showed active (granulocytic) inflammatory infiltrates and often lymph follicles in the pathologic examination which does not exclude false-negative Hp testing [14, 29]. Still if existing, Hp infiltration might be less dense in these patients. It should be noted that patients in the mild gastritis group had no lymph follicles in the pathologic examination apart from 2. These results agree with previous observations [30], where the most common cause of gastritis in patients with cholelithiasis was Hp. The overall Hp prevalence in our study was 21% (15/73),

which is lower compared to results previously observed both in asymptomatic persons or controls [7, 10, 31], and furthermore in patients with symptomatic cholecystolithiasis prior to CHE (32–80%) [4–7, 27, 30]. These comparisons lack the exact sex and age matching a control group would offer but cannot be explained with age differences. Apart from its prevalence, the Hp infection was rather asymptomatic since the primary symptom of the patients was biliary pain caused by their gallbladder stones.

Reflux gastritis was only diagnosed once from one corpus sample. One would rather expect such a diagnosis from antrum samples [13, 32]. One should be aware that there are several histological criteria for reflux gastritis and the pathologic effect of DGR [13, 15, 32, 33], taking active and chronic inflammatory infiltrates into account in an opposite way. This means that some authors believe that the presence of active and chronic inflammatory infiltrates is one among several indicators of reflux gastritis and DGR, whereas others think that the paucity of chronic (lymphocytic) and especially active (granulocytic) infiltrates is an indicator (along with other pathologic features) of reflux gastritis. FH and IM in the antrum have also been discussed as possible indicators of reflux gastritis or DGR [13, 32, 34] and atrophy has also been suggested as another pathologic feature [35, 36]. On the other hand, a lack of correlation of IM and atrophy with DGR has also been demonstrated [7]. In search of possible pathological DGR or reflux gastritis indicators, we were not able to observe a major topological predominance pattern in our patient sample. The minor topological patterns observed were either patterns of corpus predominance or, if antrum predominance existed, this was Hp associated. Secondly, although FH, IM, and atrophy where mostly observed in the antrum, they were proportionally more frequent findings in the moderate to marked gastritis group, justifying the comment that they are unspecific pathological indications of any kind of gastritis [14]. Thirdly, the 7 patients that did combine chronic inflammatory infiltrate and IM or FH in the antrum without an Hp infection, as much chronic inflammation, or any sign of IM/FH in the corpus, were not diagnosed with reflux gastritis but also had a normal gallbladder function (data not shown). Of these 7 patients, 3 also showed atrophy in the antrum samples but again were not diagnosed with reflux gastritis and did not have impaired gallbladder function (data not shown).

To summarize, most cases of moderate to marked gastritis were in fact accompanied by an Hp infection. As far as the mild gastritis group is concerned, the analysis of the composition of gallbladder bile and its statistical evaluation did not reveal an impaired gallbladder function in this group. All of the above-mentioned observations lead to the conclusion that the higher chronic (mild) and consequently overall, histologically proven gastritis prevalence cannot be explained by a spillover effect, a DGR and reflux gastritis. DGR was not directly quantified but rather assumed based on previous studies and indirectly estimated through its possible association with impaired gallbladder function. The investigation of a control group without gallstone disease was not possible, since we used total lipid concentration of gallbladder bile as a marker of gallbladder function.

The statistical analysis did not reveal statistically significant differences in values of total bile salts, phospholipids, cholesterol, or total lipid concentration between the gastritis groups. However, when Hp-positive and Hp-negative patients were compared, significantly lower concentrations for phospholipids and a trend to lower concentrations of bile salts, cholesterol and total lipids in gallbladder bile were observed in Hp-infected patients. Since lower concentration of bile lipids could express an impaired concentrative ability of the gallbladder and thus an impaired function, one could speculate that the Hp infection might affect gallbladder function. There is evidence that Hp (or other *Helicobacter* spp.) can infect the gallbladder, since its presence has been detected in gallbladder tissue of patients with cholelithiasis using the highly sensitive PCR method [37] or induce DGR, as clinically shown [38]. It is more likely that DGR contributed to chronic, mild gastritis than to active Hp gastritis. We also confirmed that mild and especially moderate to marked gastritis is more common with increasing age because the gastritis patients (especially the moderate to marked gastritis patients) were older than the ones with normal pathology.

In conclusion, moderate to marked gastric mucosa inflammation in gallstone patients is mainly caused by Hp infection whereas gallbladder function is not related to the degree of gastritis. Thus, an increased alkaline DGR in gallstone patients seems to be of limited pathophysiological relevance.

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