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Gastrointestinal defects in gallstone and cholecystectomized patients

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Abstract

Background and aim: Several gallstone patients complain of dyspeptic symptoms, irrespective of the presence of typical colicky pain. Symptoms often persist after a cholecystectomy. Systematic studies on dyspepsia and dynamic gastrointestinal motor function are missing in gallstone patients with preserved gallbladder or after a cholecystectomy.

Materials and methods: Forty-six gallstone patients (age 55 ± 2 years; 15M, 31F) and 24 cholecystectomized patients (age 57 ± 2 years; 6M, 18F) (no difference in type and volume of gallstones between the two groups) were compared against a group of 65 healthy controls (age 51 ± 2 years; 30M, 35F). Dyspepsia occurring in the prior months was assessed by a questionnaire, gastric and gallbladder emptying by functional ultrasonography and orocecal transit time by a hydrogen breath test using a lactulose-enriched standard liquid meal.

Results: Gallstone patients had significantly greater dyspepsia, fasting and residual gallbladder volumes, and slower gallbladder emptying, gastric emptying and small intestinal transit time than controls. In cholecystectomized patients, gastric emptying further delayed, compared to gallstone patients and controls.

Conclusion: Gallstone patients with the gallbladder "in situ" or after a cholecystectomy display dyspeptic symptoms. Symptoms are associated with multiple gastrointestinal motility defects involving the gallbladder, stomach and small intestine. After cholecystectomy, gastric emptying worsens.

KEYWORDS
breath test, cholelithiasis, dyspepsia, motility, orocecal transit time, small intestine, ultrasonography

1 | INTRODUCTION

Gallstone patients are amongst the most admitted patients to European hospitals,[1] and the socioeconomic costs of symptomatic uncomplicated or complicated gallstone disease are always on the rise. In developed countries, about 20% of adults have gallstones,[2] and the incidence rate increases by 0.60%-1.39% per year.[3] Gallstone prevalence increases along with aging and is higher in women than in men.[4] Cholesterol gallstones are mainly made of cholesterol monohydrate crystals, and in the Western society, they account for approximately 75%-80% of the gallstones.[4–6] In the remaining 20%-25%, gallstones are a black pigment formed by polymerized calcium bilirubinate or brown pigment stones growing in the gallbladder or in the infected extrahepatic or intrahepatic bile ducts, respectively.[7]

Di Ciaula and Molina-Molina equally contributed.

Cholesterol gallstones frequently include several metabolic abnormalities, ranging from insulin resistance, visceral adiposity expansion, overweight, obesity, type 2 diabetes, or metabolic syndrome,[8,9] coronary heart disease,[10] risks for cardiovascular disease and cancer. Other abnormalities are independent of the aforementioned risk factors.[10–12]

Appropriate therapy, either medical or mainly surgical (cholecystectomy), is necessary in about 20% of those who suffer from gallstones, because of colicky pain or complications (such as acute cholecystitis, gallbladder empyema and acute pancreatitis)[13,14] developing during a lifetime. Gallstone patients may also complain of vague or specific dyspeptic symptoms, likely unrelated to the physical presence of gallstones.[4] Instead, dyspeptic symptoms might originate from a different mechanism including motility defects (ie intestine, stomach and oesophagus), food intolerance, changes of gut microbiota, self-perception, etc.

Nonspecific gastrointestinal symptoms can also appear in about 10% of patients after cholecystectomy, but the origin of these disturbances is still unclear.[15] The aim of this study was therefore to evaluate the coexistence of motor disorders of the gastrointestinal tract along with dyspeptic symptoms, in patients with a gallbladder "in situ" and in a group of matched patients after a cholecystectomy.

2 | MATERIALS AND METHODS

2.1 | Subjects

The study comprised 46 gallstone patients with the gallbladder "in situ" and 24 cholecystectomized patients operated for symptomatic gallstone disease. A group of 65 matched healthy subjects served as the control group. The three subgroups were homogeneous for age and body mass index (Table 1). Epidemiological and clinical features and ultrasonographic appearance of gallstones stones were highly suggestive of cholesterol cholelithiasis.

Gallstones in the group with the gallbladder "in situ" were small and occupied invariably less than 30% of the fasting gallbladder volume, a safe condition that prevents major mechanical obstructions during postprandial gallbladder motility studies.[16–19] Invariably, fasting gallbladder volume has to be greater than 12 mL, a safe cut-off ruling out hypoplasic, contracted, severely or chronically inflamed gallbladders.[20] In addition, the gallbladder wall thickness had to be less than 3 mm to rule out ongoing inflammatory changes, and the gallbladder shape had to be regularly pear-shaped, to simplify volume measurements.

TABLE 1 Clinical characteristics of enrolled subjects

	Control subjects	Gallstone patients	Cholecystectomized patients
Number	65	46	24
Age (y)	51 ± 2	55 ± 2	57 ± 2
Males:Females	30:35	15:31	6:18
BMI (kg/m^2)	25.0 ± 0.3	26.4 ± 0.6	25.4 ± 0.8

BMI, body mass index.
Data expressed as mean ± standard error.

All gallstone patients (either with gallbladder "in situ" or cholecystectomized) had been symptomatic, that is, describing one or more episodes of typical colicky pain in the last 18-24 months.[13,21] None of the gallstone patients had developed pain in the last eight weeks (a condition potentially able to interfere with motility studies, due to a persisting inflamed gallbladder wall). Cholecystectomized patients had undergone a laparoscopic cholecystectomy within 18-24 months before recruitment. The macroscopic analysis of stones, as well as the microscopic analysis of bile, confirmed that stones were mainly made of cholesterol.[22]

None of enrolled patients had diabetes or any other clinical or pharmacological condition potentially able to influence the indices of gallbladder, gastric and intestinal motility examined in the study.

Healthy subjects had a negative record for major surgeries, for drug intake in the last week capable of modifying the gallbladder and gastrointestinal motor function, and pregnancy was absent in all women.

All participants signed a written informed consent before entry. The studies had approval of the Human Subjects Committees at the Bari University Medical School (Bari, Italy), as per the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 | Assessment of dyspepsia

Dyspepsia was quantified by a specific questionnaire according to Buckley et al[23] with a score describing severity, frequency and duration of four different symptoms: pain, epigastric burning, belching and a sense of postprandial fullness (maximum score = 48). The score referred to the worst perception of symptoms over the past 12 months in control, gallstone patients and cholecystectomized patients. In gallstone patients, the description of the symptom score was independent on episodes of colicky pain (if any). The value of 8 represented a normal upper limit.[24]

2.3 | Test meal

The standard test meal (Nutridrink®; Nutricia, Milano, Italy) consisted of 200 mL liquid suspension containing 12 g (20%) protein, 11.6 g (19%) fat and 36.8 g (61%) carbohydrates for a total of 300 kcal, 1260 kJ, 455 mOsm/L, energy density 1.5 Kcal/mL, pH 6.5.

2.4 | Ultrasonographic studies of gallbladder and gastric emptying

The ultrasound equipment consisted of a 3.5 MHz convex probe (AU 450, Ansaldo-Hitachi, Genoa and *Noblus* Hitachi, Japan). The study included the simultaneous examination of gallbladder and gastric emptying.[18,25–29] Subjects had to fast for at least 12 hours, and measurements were taken in a seated position for 120 minutes. Immediately before and during the examination, subjects could not smoke and drink coffee or soft drinks to avoid interference with the gallbladder and gastric kinetics.

The gallbladder volume was measured according to the ellipsoid formula[30,31] as fasting gallbladder volume, postprandial volumes taken every 10-15 minutes and minimum residual volume during 120 minutes. Gallbladder half-emptying time was the time when the gallbladder reached 50% emptying.

For the stomach, the fasting antral area was measured (mean of two measurements at times −5 and 0 minutes before the start of the meal). Postprandial antral areas were calculated immediately after ingestion of the test meal and then at regular time intervals (5-15 minutes) for 120 minutes. Gastric half-emptying time was the time when the stomach reached 50% emptying and calculated from the emptying curve (area/time).[26–29]

2.5 | Orocecal transit time

Subjects followed a diet restricted in fermentable foods and were in "wash-out" for at least 10 days from drugs or manoeuvres (ie enemas) that could interfere with the intestinal microbiota or intestinal kinetics. A portable detector (EC60 *Gastrolyzer*®, Bedfont, UK) was used to measure the values of hydrogen (H_2) in the fasted breath and at 10 minutes intervals up to 240 minutes after ingestion of 10 g of crystalline lactulose contained in 15 mL *Duphalac*® (Mylan, Milano, Italy), dissolved in the standard liquid meal. Orocecal transit time (OCTT) was the time required to observe an increase in H_2 in the expired air by at least 10 parts per million (ppm) on the minimum H_2 fasting level, and for at least three consecutive time points.[27,32–34]

2.6 | Statistical analysis

The results are mean ± standard errors (SEM). The one-way ANOVA followed by the Fisher's LSD multiple comparison test was used to assess the differences between control, gallstone patients and cholecystectomized patients. Student's *t* test compared gallbladder motility between control and gallstone patients. Significant differences were considered with a probability (*P*) of less than 0.05.[35] Calculations were performed with the NCSS 10 Statistical Software (2015) (NCSS, LLC. Kaysville, UT, USA, ncss.com/software/ncss).

3 | RESULTS

3.1 | Dyspeptic symptoms

The score of dyspepsia in gallstone patients and cholecystectomized patients was almost threefold increased and significantly ($P < 0.0001$) greater than the score of the control group, but comparable between the two groups of patients (Table 2).

The ingestion of the test meal was uneventful, and during the motility studies, the compliance was excellent in all subjects

3.2 | Gallbladder motility

The functional ultrasonographic study of time-dependent changes of gallbladder volume in the groups of gallstone patients and control showed that both fasting and postprandial volumes increased continuously by about 33% in gallstone patients throughout the emptying curve. Consequently, the residual (minimal) volume increased by 66% (absolute value) and 29% (normalized value) and half-emptying time almost doubled, as compared to the controls (Table 2**,** Figure 1A-C).

3.3 | Gastric motility

The functional ultrasonographic study of time-dependent changes of antral areas appears in Table 2**,** Figure 2A-C. Fasting antral areas were comparable across the three groups (mean range 3.4-3.6 cm^2). Following the ingestion of the 200 mL liquid test meal, antral dilation invariably occurred within 5 minutes and was comparable across groups (mean range 11.7-12.2 cm^2). Gastric emptying was incomplete, delayed throughout the 120 minutes in both gallstone and cholecystectomized patients, as compared to the control group. However, the gastric emptying defects were more evident in cholecystectomized patients. Overall, in patients the score of dyspeptic symptoms was unrelated to the timing of antral emptying (half-emptying time, data not shown).

3.4 | Orocecal transit time

For the small intestine, concentrations of H_2 in expired air showed a progressive time-dependent increment in the three groups. This finding is a reliable marker of bacterial fermentation of lactose in the distal gut. However, the extent of H_2 production by gut microbiota was greater in the control group rather than gallstone and cholecystectomized patients (Figure 3). OCTT was 50%-59% delayed in gallstone and

TABLE 2 Results from the questionnaire for dyspepsia and gastrointestinal motility

	Control subjects	Gallstone patients	Cholecystectomized patients
Number	65	46	24
Dyspepsia score	5.6 ± 0.3	14.9 ± 1.3*	15.2 ± 2.0*
Gallbladder motility			
Fasting volume (mL)	23.6 ± 0.9	31.6 ± 2.2*	—
Residual volume (mL)	6.4 ± 0.4	10.4 ± 0.9*	—
Residual volume (%)	27.1 ± 1.3	34.7 ± 2.7*	—
Half-emptying time (T50, min)	22.7 ± 0.9	44.3 ± 3.1*	—
Stomach (antrum) motility			
Fasting area (cm^2)	3.6 ± 0.1	3.4 ± 0.2	3.4 ± 0.1
Max. postprandial area (cm^2)	12.2 ± 0.3	12.1 ± 0.3	11.7 ± 0.4
Residual postprandial area (%)	4.8 ± 1.2	12.8 ± 2.0*	24.2 ± 4.3*,#
Half-emptying time (T50, min)	28.5 ± 1.3	44.3 ± 3.1*	69.2 ± 14.8*#
Small intestine motility			
OCTT (min)	111.4 ± 5.5	166.1 ± 9.2*	176.8 ± 11.1*

OCTT, orocecal transit time.

Data expressed as mean ± standard error. Significantly different from control: $*P < 0.05$; significantly different from gallstone $^{\#}P < 0.05$.

cholecystectomized patients, as compared to healthy controls (Table 2**,** Figure 3A, B). A trend towards a progressively reduced area under curve (AUC) of H_2 levels in exhaled air was recorded between controls, gallstone and cholecystectomized patients, although the difference between the three subgroups was not significant (Figure 3C).

4 | DISCUSSION

The present study shows that gallstone patients often complain of dyspeptic symptoms, while exhibiting diffuse motility defects, as compared to healthy subjects. The dysmotility profile involves the gallbladder, the stomach and the small intestine, and deteriorates in cholecystectomized patients, even years after surgery.

The extent of dyspeptic symptoms occurring in the previous year was similar in gallstone patients with or without "in situ" gallbladder. Moreover, we confirm that the mean score of dyspepsia is extremely low in control subjects, as shown in previous studies.[24,36]

The ingestion of the liquid test meal was not associated with dyspeptic symptoms (especially fullness) throughout the observation time. Likely, the moderate volume (215 mL) and the isosmotic/fat composition of the test meal (11.6 g = 19%) fat, 300 kcal was not sufficient to trigger upper gastrointestinal symptoms in these groups of subjects. Larger volumes, higher caloric content, fat content or meal type (ie semisolid vs liquid), might explain the symptomatic response of a test meal.[27] This was the case in chronic alcoholic patients,[36] scleroderma patients and dyspeptic patients without dyspepsia.[24]

The delayed gastric emptying can explain only in part these findings. In fact, the extent of dyspepsia (as measured by a score) and the timing of postprandial gastric emptying (ie, half-emptying time) were apparently unrelated in the present group of patients. Additionally, cholecystectomized patients showed the worst indices of gastric emptying, as compared with gallstone patients, although the score of dyspepsia was similar in the two subgroups. In line with these findings, and in accordance with international guidelines, this study confirms that dyspepsia is not specifically related to the presence of gallstones.[7,13,37,38] Furthermore, studies conducted on the general population found no greater prevalence of dyspepsia in gallstone patients.[4,39] Dyspeptic symptoms might rather originate from multiple coexisting motility defects in gallstone patients, likely persisting after a cholecystectomy. This is the case in this study and in another study, which examined gallstone patients before and after a cholecystectomy.[40] Indeed, dyspepsia persisted in a consistent number of patients. Indirectly, we confirm that the colicky pain is a specific symptom clinically linked to the presence of uncomplicated gallstones, and it should be considered in a group of patients who are scheduled for a cholecystectomy.

On the other hand, a study found that cholecystectomy is associated with a series of nonspecific gastrointestinal symptoms, especially in the first three years after surgery. Findings include a wide panel of gastric disorders such as peptic ulcer, hiatus hernia and gastro-oesophageal reflux. Misdiagnosis of some pre-existing diseases, however, is possible.[15]

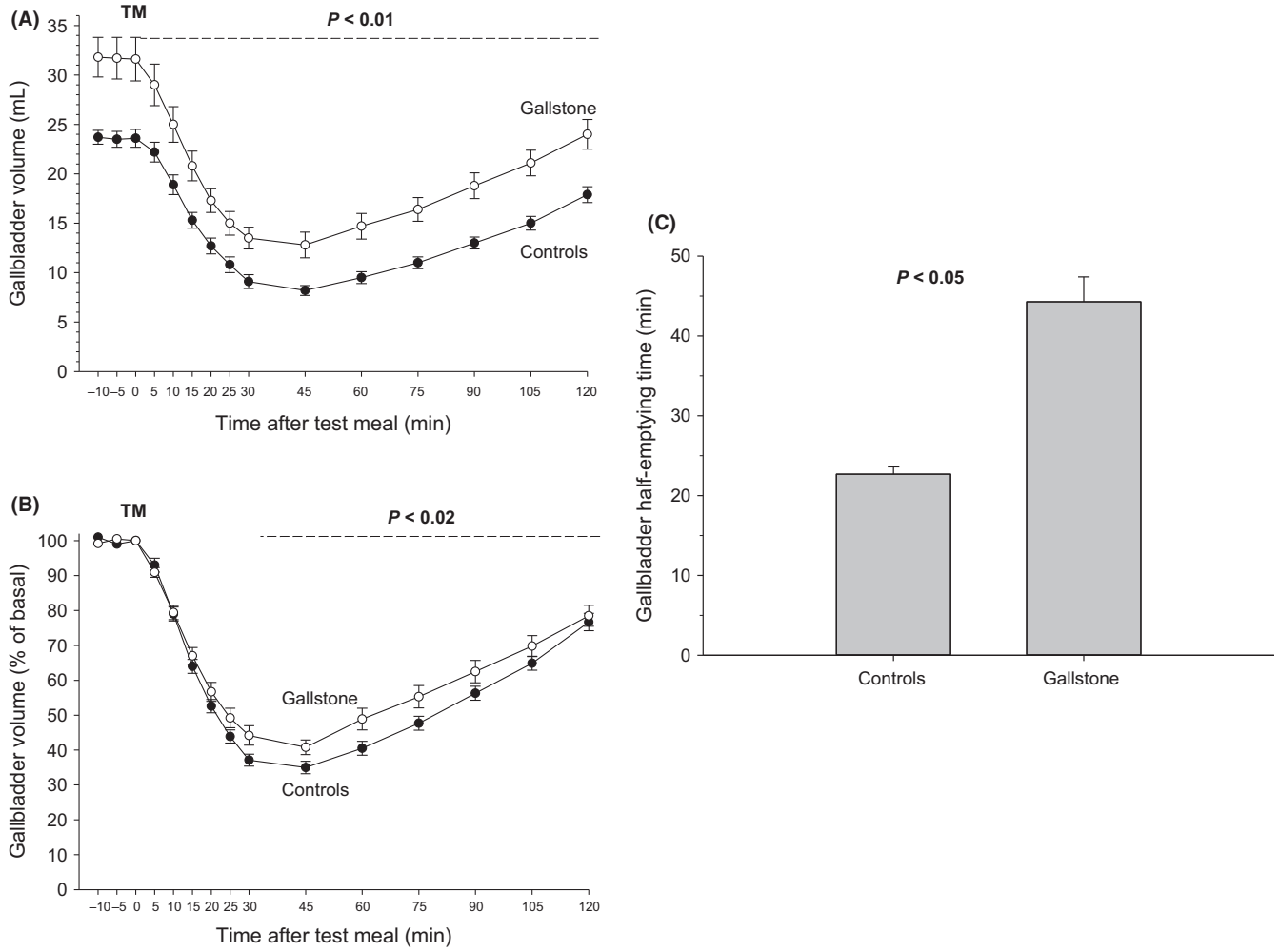

FIGURE 1 Gallbladder motility studies. Time-dependent changes of fasting and postprandial gallbladder volumes and half-emptying time in 46 gallstone patients and 65 control healthy subjects. Symbols indicate means, and vertical lines are standard errors. TM = test meal administered. A, Absolute values in mL with significant difference ($P < 0.01$) between the two curves between 0 and 120 min; B, Percentage of fasting gallbladder volume with significant difference ($P < 0.02$) between 30 and 75 min; C, Half-emptying time in min. Significant difference ($P < 0.05$) between groups

The presence of an altered postprandial gastric emptying occurs either with or without "in situ" gallbladder, suggesting that this defect is independent of the physical presence of gallstones, and possibly linked with mechanisms, which also influence gastrointestinal motility at different levels of the gastrointestinal tract.[41] The extent and timing of gastric emptying worsen after gallbladder removal, pointing to the presence of altered pathways involving bile flow and/or signalling molecules. At variance with the present study, an early report found improved gastric emptying following cholecystectomy.[40] Differences in selection and number of patients, characteristics of study design (ie two separate groups in this study vs pre-postcholecystectomy in the study by Ibrarullah[40]) and duration of follow-up might account for such differences.

The possibility exists, however, that some significant findings found in the present series of cholecystectomized patients could be partly due to cholecystectomy itself involving neuro-hormonal and anatomic changes. Post-operative ileus, for example, is a predictable, self-terminating event, occurring after most general anaesthetic procedures.[42] However, cholecystectomy might induce effects in the medium- and long-term period but studies are somewhat heterogeneous. Symptoms of postcholecystectomy syndrome are likely not related to increased duodenogastric reflux after surgery.[43] Cholecystectomy, however, may cause an exaggerated meal-stimulated cholecystokinin (CCK) response, a factor involved in relaxation of the lower oesophageal sphincter and likely increased incidence of gastro-oesophageal reflux.[44] In the dog, fed-state motility (but not fasted gastrointestinal motility) was the only parameter improving after laparoscopic cholecystectomy, compared to open cholecystectomy.[45] In a small, short-term study performed in five women at baseline, and six months after surgery, laparoscopic cholecystectomy suppressed the normal inhibitory effect of pharmacological doses of CCK

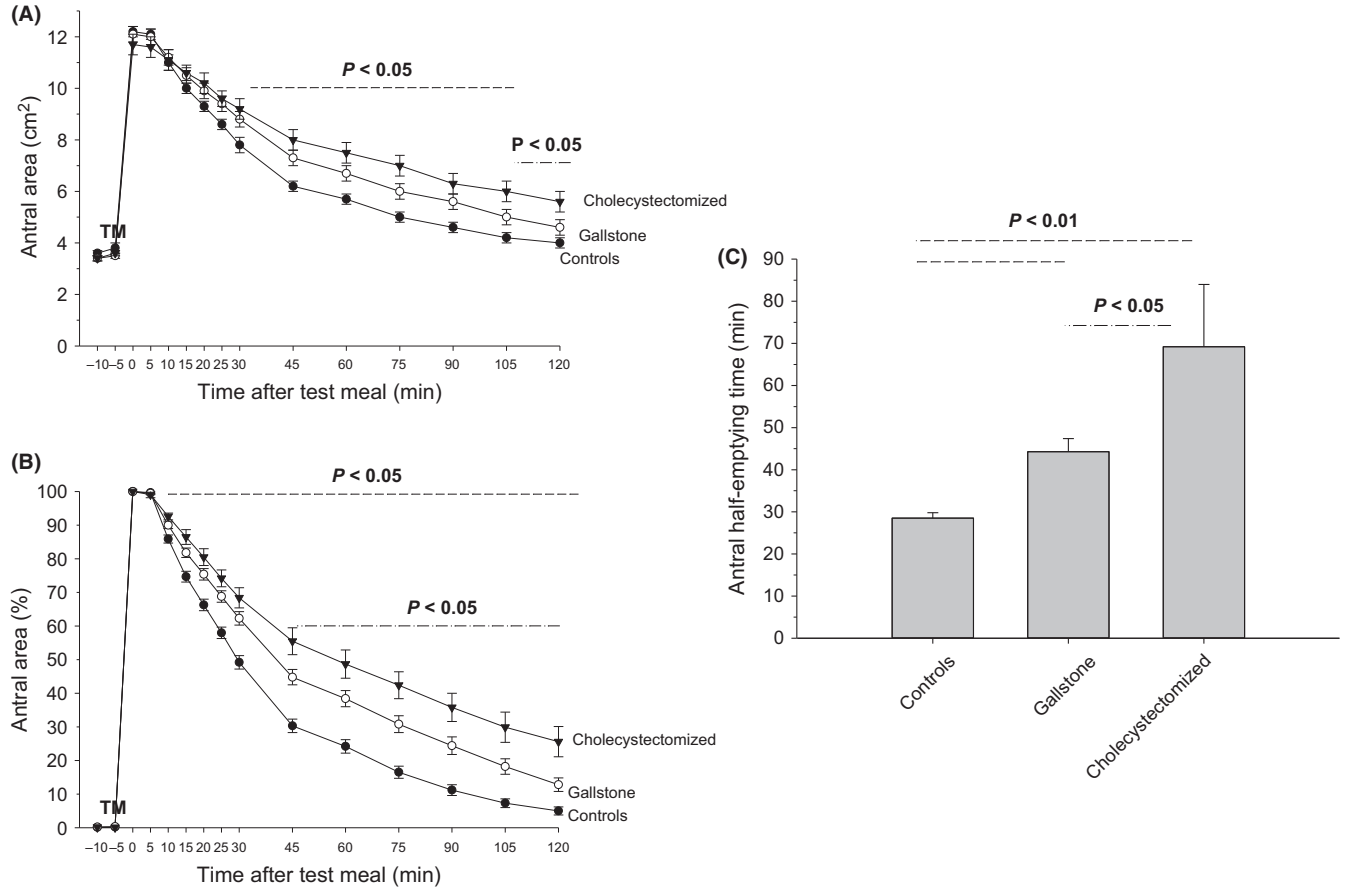

FIGURE 2 Gastric emptying studies. Time-dependent changes of fasting and postprandial antral areas and half-emptying time in 46 gallstone patients, 24 cholecystectomized patients and 65 control healthy subjects. Symbols indicate means, and vertical lines are standard errors. TM = test meal administered. A, Absolute values in cm^2 with significant difference ($P < 0.05$) between gallstone patients, cholecystectomized patients and controls (----) from 25 to 105 min, and between gallstone patients and cholecystectomized patients (-.-.-) between 105 and 120 min; B, Percentage of maximal antral area with significant difference ($P < 0.05$) between gallstone patients, cholecystectomized patients and controls (----) between 10 and 120 min, and between gallstone patients and cholecystectomized patients (-.-.-) between 45 and 120 min; C, Half-emptying time in min. Significant differences $P < 0.01$ vs controls (---) and $P < 0.05$ vs gallstone patients (-.-.-)

on the Oddi sphincter. Sphincter denervation might explain such findings.[46] From the above-mentioned results, it is clear that further prospective studies are necessary to enrol a larger number of gallstone patients and examined at different time points before and after gallbladder removal.

All gallstone patients had a small gallstone burden (<30% of fasting volume), a condition unable to affect the gallbladder kinetics directly by obstructing the cystic duct and impeding gallbladder emptying.[16,17] Major acute and chronic inflammatory changes of the gallbladder wall were absent, as confirmed by a thin gallbladder wall. All gallstone and cholecystectomized patients had suffered from typical colicky pain without known complications of gallbladder disease (ie acute cholecystitis, empyema, biliary pancreatitis, etc).[37,38] However, we found that gallstone patients displayed increased fasting, postprandial volumes and delayed gallbladder emptying, as compared with controls, suggesting the presence of sluggish gallbladder function and ongoing gallbladder stasis.[16] Growth of cholesterol gallstones depends on at least five primary pathogenic defects and involves *LITH* genes and genetic factors, hepatic hypersecretion of cholesterol accumulating in a supersaturated gallbladder bile, rapid phase precipitation of solid cholesterol crystals in bile and gallbladder stasis. This type of visceral stasis is a clear predisposing factor towards accumulation of concentrated supersaturated bile and hypersecretion of mucin gel from the gallbladder epithelium during the immune-mediated gallbladder inflammation. Additional factors involve intestinal cholesterol absorption, defective intestinal motility and changes of the gut microbiota.[47,48] The presence of a hypomotile gallbladder, both in the fasting state[49,50] and in response to neurohormonal postprandial stimuli,[16,51,52] plays an important role. Gallbladder hypomotility, in fact, is one of the major pathogenic factors contributing to the accumulation of excess biliary cholesterol in the gallbladder lumen,[47,52] as well as precipitation of solid cholesterol crystals, a key step in the further growth of gallstones.[48] This study assessed

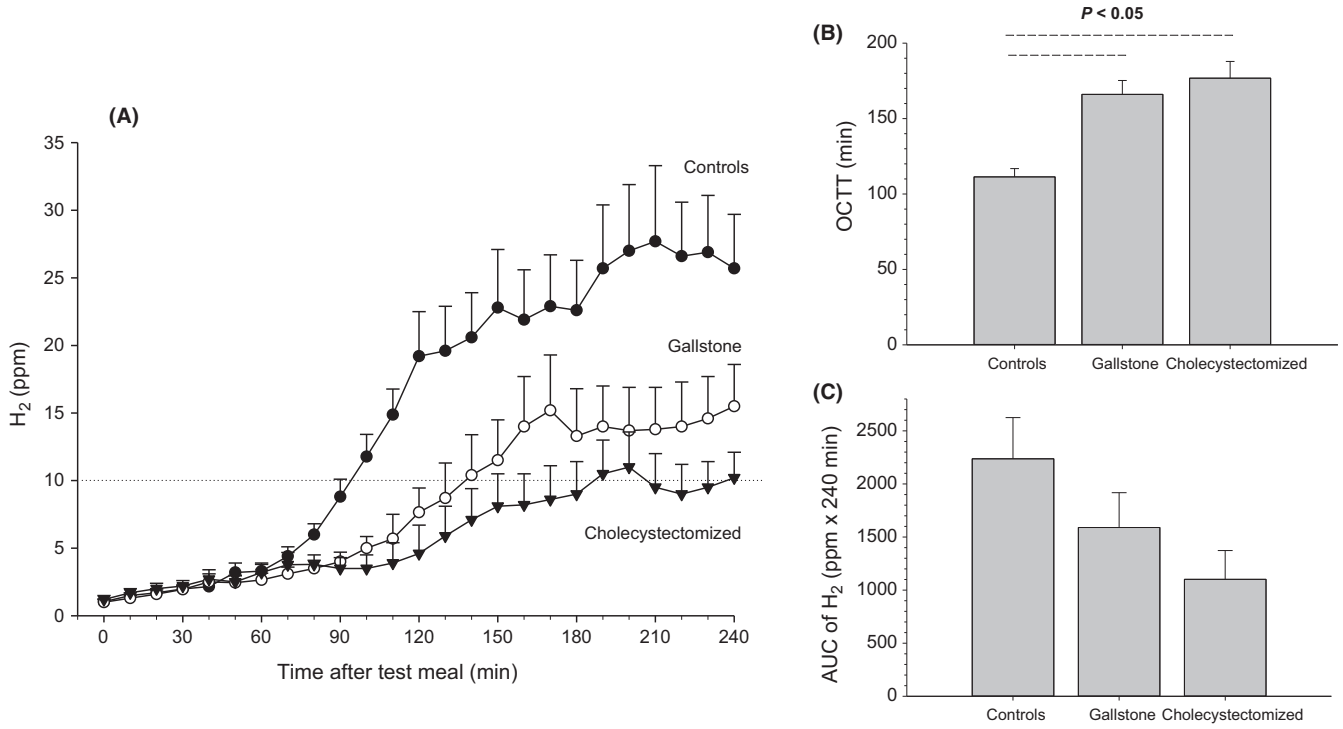

FIGURE 3 Intestinal transit. A, Time-dependent curves of H2 levels (ppm) in exhaled air in 46 gallstone patients, 24 cholecystectomized patients and 65 control healthy subjects. Symbols indicate means, and vertical lines are standard errors. The horizontal dotted line indicates the cut-off level to document a significant increase in H_2 production (10 ppm); B, Orocecal transit time (OCTT). Significant differences $P < 0.05$ vs controls (---); C, Area under curve (AUC) of H_2 levels in exhaled air (ppm × 240 min)

gallbladder motility in patients with cholesterol gallstones, but a type of intermediate motility defect also exists in patients with pigment stones.[53,54]

Gallbladder kinetics depends on about 60 to 80% of its reduction on vagal cholecystokinin-mediated mechanisms, which lead to expulsion and increased intraluminal concentrations of bile acids (BA).[55] BA recirculation increases following cholecystectomy, and this mechanism may contribute to the increased risk for metabolic syndrome observed after gallbladder removal.[55] The missing gallbladder function may also explain why several components of metabolic syndrome, such as glucose or lipids homeostasis, are present after a cholecystectomy, mainly due to abnormal metabolic signalling on gene expression, BA/farnesoid X receptor (FXR) and BA/G-coupled bile acid receptor-1 (GPBAR-1) and fibroblast growth factor 19 (FGF19) axis.[56]

Our results confirm that both gallstone and cholecystectomized patients have a more general impairment of gastrointestinal motility, which also involves the small intestine. Here, we find that OCTT is delayed in response to the test meal containing lactulose, a substrate which becomes fermentable at the level of the cecum, where gut microbiota displays the highest density.[57]

A previous observation reported a significantly delayed OCTT in gallstone patients, an increased prevalence of small intestinal bacterial overgrowth (SIBO), high levels of serum BA and a positive correlation between OCTT and serum BA levels in patients with both gallstones and SIBO.[58] Remarkably, another study found prolonged large intestinal transit and increased levels of biliary deoxycholate in a subgroup of gallstone patients.[59]

This study also shows a trend towards a progressive decrease of fermentation of lactulose, from controls to gallstone and cholecystectomized patients. Although the difference among average AUC values of H_2 in expired air did not reach the statistical significance, this trend suggests a reduced overall fermentation capacity of gut microbiota in patients with gallstone disease (with or without "in situ" gallbladder), as compared to healthy subjects. This hypothesis could be confirmed, at least in part, by previous observations describing relevant qualitative differences in gut microbiota between healthy subjects, gallstone patients and cholecystectomized subjects.[60–62] Further studies are certainly required in order to better explore this possibility.

Delay of intestinal transit, associated with gallbladder hypomotility, should be seen in the context of a wide "intestinal disease",[63] since a greater proportion of hepatic bile leads to dihydroxylation, partly mediated by the gut microbiota with a consequent increase of the deoxycholate, strongly hydrophobic and cytotoxic BA. The reuptake in the enterohepatic circle of deoxycholate is able to influence

the phenomena of crystallization and nucleation of biliary cholesterol with greater lithogenic effects.[64,65]

Overall, the results of the present study suggest that patients developing cholesterol cholelithiasis suffer from a type of "pan-enteric" motility defect.[63] Abnormalities may involve the oesophagus,[66] the stomach,[66] the small intestine and the colon as well.[67–70] The link between cholesterol cholelithiasis and obesity[28,29] and/or diabetes,[71] as components of the metabolic syndrome, might further deteriorate the overall profile of gastrointestinal motility.[52] Apparently, the motility defect persists (or worsens as in the case of gastric emptying) after a cholecystectomy.

Further studies should involve a larger number of subjects with gallstones of any type and size, in order to avoid possible biases. In this context, studies should focus on existing links between multiple gastrointestinal motility defects, pathogenic pathways of gallstones, and persisting (or worsening) of symptoms and defects after gallbladder removal.

5 | CONCLUSION

This study shows that gallstone patients with the gallbladder "in situ" or after cholecystectomy display symptoms of dyspepsia. Symptoms are associated with multiple gastrointestinal motility defects involving increased fasting and residual gallbladder volume, along with delayed gastric and small intestine transit. After a cholecystectomy, gastric emptying worsens.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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