

RAPID COMMUNICATION

Scintigraphic evaluation of gallbladder motor functions in *H pylori* positive and negative patients in the stomach with dyspepsia

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CONCLUSION: Our study showed that ^{14}C -UBT is highly reliable method to detect the presence of *H pylori*. The presence of *H pylori* infection does not directly affect the GB function.

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Key words: *H pylori*; Dyspepsia; Cholescintigraphy; Gallbladder; ^{14}C -urea breath test

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Abstract

AIM: To evaluate the relationship between gallbladder (GB) motor function and *H pylori* infection in the stomach.

METHODS: All cases (86) underwent the ^{14}C urea breath test (UBT). ^{14}C -UBT was found as positive in 58 and negative in 28 dyspeptic patients. ^{14}C -UBT was accepted as a gold standard test. Clo test and histopathologic examination were compared with the results of ^{14}C -UBT in cases who tolerated upper gastrointestinal endoscopy procedure. Cholescintigraphy with $^{99\text{m}}\text{Tc}$ -mebrofenin was used to determine the parameters of GB motor function (GB filling and emptying time, half of the emptying time, ejection fraction at 30th and 60th min) in all patients.

RESULTS: We found the sensitivity and specificity as 88% and 86% for Clo test and as 89% and 80% for histologic evaluation, respectively. The parameters of GB function were not significantly different in *H pylori* positive and negative patients. The GB emptying was normal in both groups. Minimum GB filling time was 30 min in 34 of 86 cases (39.5%), filling was not observed in 2 cases. The GB ultrasonography (USG) results were normal for all cases and bile composition abnormality was not determined.

INTRODUCTION

The *H pylori* infection is one of the most common chronic infections in humans^[1,2]. The *H pylori* colonizing on the surface of the upper gastrointestinal mucosa is an interesting cause of active chronic gastritis and duodenitis or even gastric cancer worldwide^[2-7]. The presence of *H pylori* infection could predispose to various disorders^[8-14]. Dental disease might be associated with a higher recurrence of *H pylori* infection^[9]. Some investigators have recently demonstrated the evidences that *H pylori* infection induced atherosclerosis and that *H pylori*-anti-heat-shock protein antibodies have been related to the prevalence of diseases such as coronary artery disease or cerebral infarction, resulted from atherosclerosis^[10,11]. The *H pylori* may play a role in the pathogenesis of slow coronary flow *via* the elevation of homocysteine, and/or a possible disturbance in its metabolism^[12].

The *H pylori* is present in about 67%-100% of duodenal ulcer patients and 13%-61% of normal population^[13]. The *H pylori* infection can be diagnosed by invasive techniques requiring endoscopy and biopsy (eg, histological examination and culture) and by noninvasive techniques such as serology, urea breath test or detection of *H pylori*

antigen in stool specimen^[1,16]. Urea breath tests (UBT) are based on the principle that urease activity is present in the stomachs of individuals infected with *H pylori*. The UBT is considered as the gold standard in the diagnosis of *H pylori* among the noninvasive tests^[16-19].

Gallbladder (GB) diseases are related more to an emptying abnormality than to resting volume changes^[20]. Cholescintigraphy using ^{99m}Tc-hepatobiliary iminodiacetic acid (HIDA) is a scintigraphic technique for measuring GB emptying. Cholescintigraphy is used to show both morphological and physiological changes in GB. Since physiological changes usually precede morphological alterations by several weeks or months, there is a great potential for early diagnosis by scintigraphy, before irreversible functional changes take place. The main advantage of cholescintigraphy is that the technique is noninvasive, quantitative, reproducible and has a low interobserver error^[20-24]. Dynamic biliary scintigraphy can measure biliary motor functions noninvasively and quantitatively in *H pylori* positive and negative patients with dyspepsia^[22]. Few reports have been published on the relationship between gallbladder emptying in patients with *H pylori* positive and negative idiopathic dyspepsia^[22,26]. Studies performed on this topic have not shown that dyspepsia could be related to gallbladder function.

The association between GB emptying and gastric emptying in dyspeptic patients has been investigated with several techniques such as real time ultrasonography, scintigraphy for gastric emptying, hepatobiliary scintigraphy and the emptying time was found similar for both of them^[25,26]. There is no literature available to confirm the effects of *H pylori* on the GB and gastrointestinal motor functions and regarding the relationship between these functional disorders and dyspeptic symptoms.

The objective in our study was scintigraphic evaluation of GB motor functions in *H pylori* positive and negative patients affected by dyspepsia.

MATERIALS AND METHODS

Patients and data collection

The study included 86 patients (44 male, 42 female) with symptoms of dyspepsia. These patients had no other complaints or systemic diseases and were not on any medications. The permission of the study was given by local ethic committee.

The *H pylori* was determined in each patient with ¹⁴C-UBT (Isotopes Co. Ltd. institute, Noster Sys. AB, HELIPROBE) as a gold standard as it is noninvasive, easy to perform and cheap diagnostic method for *H pylori*. Before the ¹⁴C-UBT, the subject fasted for at least 6 hours. *H pylori* positive 58 patients (23 female, 35 male; mean age 41 years) as study group and *H pylori* negative 28 subject (19 female, 9 male; mean age 45 years) as control group were studied. Written informed consent was obtained for each patient. The subjects were given ¹⁴C-urea capsule orally with 20 mL water. After 15-30 min, the subject exhaled into the BreathCard. The average breathing time was approximately 1-2 min. The Heliprobe BreathCard was put into slot of the Heliprobe Analyzer and after pressing start button, the

analyzer was measured within 4 min. The analysis is based on the number of emitted β -particles and is presented as decay per min (DPM) together with the test result < 50 DPM (0, negative), 50-199 DPM (1, equivocal), and \geq 200 DPM (2, positive). Within one week, the urease test (Clo test) and histopathologic examination were compared with the results of ¹⁴C-UBT in cases who tolerated upper gastrointestinal endoscopy procedure. Upper gastrointestinal endoscopy (Olympus GIF 1T 30) with biopsies from antrum and corpus was performed in total of 74 cases (52 patients and 22 control subjects) after history and physical examination were obtained. Twelve cases (6 patients and 6 control subjects) could not tolerate endoscopic examination.

After ¹⁴C-UBT, every patient was defined by using cholescintigraphy with ^{99m}Tc-mebrofenin to determine the parameters of GB motor function.

Dynamic Cholescintigraphy

After 6-8 h of fasting, all patients were injected intravenously 5 mCi of ^{99m}Tc Mebrofenin (NYCOMED AMERSHAM SORIN S.r.l., BRIDATEC) while lying supine underneath a gamma camera fitted with a 140-keV low energy, all purpose, parallel-hole (LEAP) collimator. The gamma camera (GE- Milenium Acq, entegra) was connected to a computer, which enabled simultaneous data acquisition in a 128 \times 128 matrix. Dynamic acquisition was started at time 0 min with simultaneous administration of a bolus injection of ^{99m}Tc Mebrofenin and was obtained (15 s/frame) for 5 min. After this acquisition, gallbladder filling was observed for approximately 30-60 min and at max. filling time, orally a standard fatty meal (100 g milky chocolate) instead of CCK (sincalide, kinevac) was ingested in the sitting position to stimulate gallbladder emptying. This has provided a physiological stimulation of GB contraction and prevented the false positive results. During the following 15 min, dynamic acquisition was started while lying supine with 30 s/frame and acquisition continued for 60-90 min thorough GB emptying (Figures 1 and 2).

All of the summed dynamic images (before and after oral stimulation of GB emptying) were evaluated with the raw data and cine projections from the computer.

We calculated the following parameters to describe GB emptying: (1) The filling time of gallbladder (GBFT): Time (min) for maximum counts per min during the interval between the filling period of gallbladder and meal ingestion; (2) Gallbladder Ejection Fraction (GBEF) at 30 min and 60 min; (3) Gallbladder half emptying time (GB $t_{1/2}$): This parameter was calculated automatically from the time-activity curve on the computer (GE Entegra).

To determine interobserver variation, GBEF (for 30 min and 60 min) was calculated independently by two separate observers (experienced and inexperienced nuclear medicine physicians) at separate times.

Statistical analysis

Data were analyzed with the SPSS 10.0 program. Statistical analysis was performed by using student's *t* test and *P* < 0.05 was considered as statistically significant. The data was presented as mean \pm SE or as mean \pm SD.

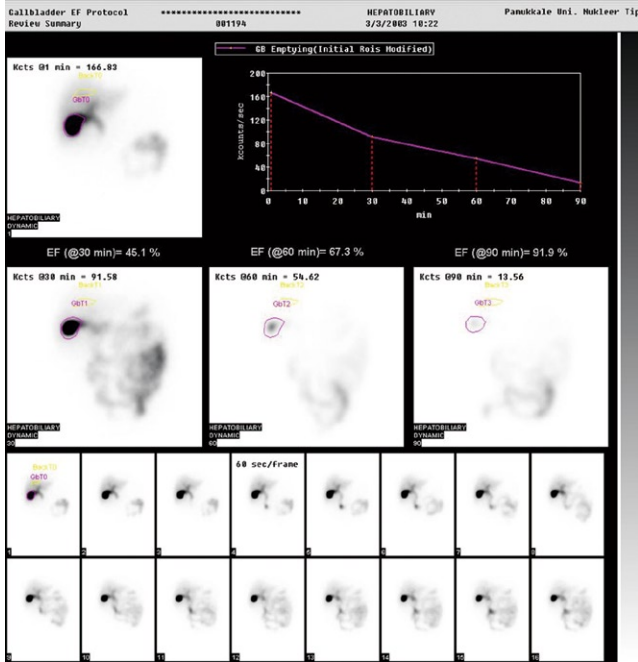


Figure 1 The image of a normal ^{99m}Tc-mebrofenin cholescintigraphy. Emptying of the whole gallbladder content takes almost 90 min.

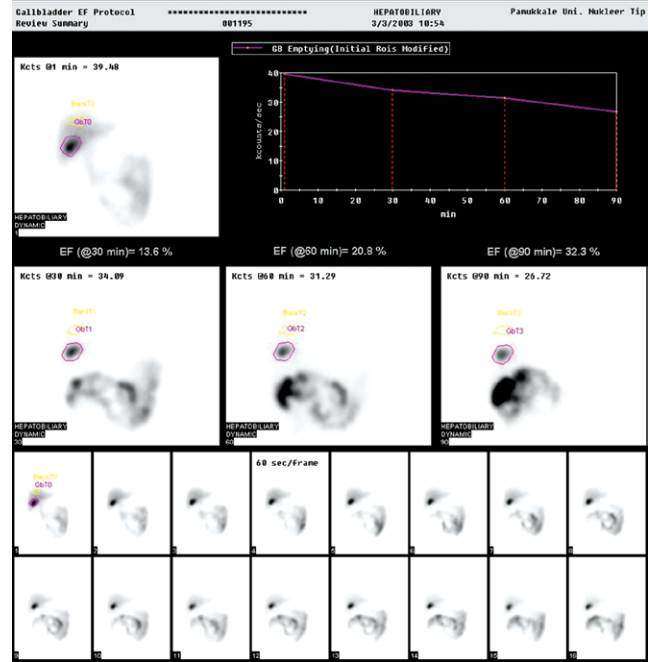


Figure 2 Emptying of the gallbladder content was slower and did not complete during the study in case with impaired GB functions.

Table 1 Gallbladder motor function parameters in *H pylori* positive and negative patients (mean ± SE)

¹⁴ C-UBT	GBFT (min)	GB t1/2 (min)	GBEF ₃₀ (A) %	GBEF ₆₀ (A) %	GBEF ₃₀ (B) %	GBEF ₆₀ (B) %
Positive (n = 58)	53.71 ± 3.49	44.15 ± 4.38 (n = 27)	36.58 ± 5.82 (n = 36)	52.88 ± 5.38 (n = 33)	35.55 ± 4.07 (n = 40)	53.86 ± 5.06 (n = 36)
Negative (n = 8)	61.21 ± 4.50	51.08 ± 4.43 (n = 12)	24.35 ± 3.80 (n = 20)	47.11 ± 5.88 (n = 19)	26.38 ± 3.53 (n = 21)	47.55 ± 4.57 (n = 20)

GBFT: Gallbladder filling time; GB t1/2: Gallbladder half emptying time; GBEF₃₀: Gallbladder ejection fraction at 30 min; GBEF₆₀: Gallbladder ejection fraction at 60 min; A: Experienced observer; B: Inexperienced observer.

RESULTS

¹⁴C-UBT was found as positive in 58 dyspeptic patients (35 male, 23 female, mean age of 41 years) and negative in 28 patients (9 male, 19 female, mean age of 45 years). In 74 cases, the sensitivity and specificity were determined as 88%-86% for Clo test and as 89%-80% for histologic evaluation respectively.

The parameters of GB function were not significantly different in *H pylori* positive and negative patients ($P > 0.05$) (Table 1). The GBFT of ¹⁴C-UBT positive patients (53.71 ± 3.49 min) did not differ significantly from that of ¹⁴C-UBT negative patients (61.21 ± 4.50 min) ($P > 0.05$). Minimum value of GBFT was 30 min and gallbladder filled at 30 min in 34 (39.5%) of the 86 cases. Two subjects who are one subject from *H pylori* positive group and the other one from negative group did not show gallbladder filling until the end of the acquisition. In 27 of 58 ¹⁴C-UBT positive patients (46.55%) and in 12 of 28 ¹⁴C-UBT negative patients (42.85%), GB emptying was observed (Figure 1). The GB t1/2 was 44.15 ± 4.38 min and 51.08 ± 4.43 min for ¹⁴C-UBT positive and negative patients, respectively and no significant difference was found between the two groups ($P > 0.05$). Mean GBEF values at 30 min (GBEF₃₀) and at 60 min (GBEF₆₀) obtained by the experienced observer (A) in ¹⁴C-UBT positive patients

Table 2 Correlation values of GBEF₃₀ and GBEF₆₀ between two observers in ¹⁴C-UBT positive and negative patients

	A	B	r value
¹⁴ C-UBT Positive			
GBEF ₃₀	36.58 ± 5.82	35.55 ± 4.07	0.78
GBEF ₆₀	52.88 ± 5.38	53.86 ± 5.06	0.94
¹⁴ C-UBT Negative			
GBEF ₃₀	24.35 ± 3.80	26.38 ± 3.53	0.88
GBEF ₆₀	47.11 ± 5.88	47.55 ± 4.57	0.88

GBEF₃₀: Gallbladder ejection fraction at 30 min; GBEF₆₀: Gallbladder ejection fraction at 60 min; A: Experienced observer; B: Inexperienced observer; r value: Correlation coefficient.

were $36.58\% \pm 5.82\%$ and $52.88\% \pm 5.38\%$, respectively. In ¹⁴C-UBT negative patients GBEF₃₀ was $24.35\% \pm 3.80\%$ and GBEF₆₀ was $47.11\% \pm 5.88\%$. Mean GBEF values at 30 min and at 60 min obtained by the inexperienced observer (B) in ¹⁴C-UBT positive patients were $35.55\% \pm 4.07\%$ and $53.86\% \pm 5.06\%$, and in ¹⁴C-UBT negative patients were GBEF₃₀ $26.38\% \pm 3.53\%$ and GBEF₆₀ $47.55\% \pm 4.57\%$, respectively. GBEF values did not differ significantly ($P > 0.05$). A highly significant positive correlation of corresponding values was found between the two observers (Table 2).

DISCUSSION

There is no previously published study regarding the direct relationship between the gallbladder motor functions and *H pylori* infection in dyspeptic patients. In the previous studies, the relationship between gastric and gallbladder emptying functions were reported. But, no definitive physiological data of the gallbladder kinetic parameters has been published yet^[20,25-29]. Marzio *et al.*^[25,26] showed that gastric emptying is strictly correlated with gallbladder emptying and refilling. It has been reported that impairment of gallbladder dynamic functions might be due to inflammation resulting from *H pylori* infection. In our dyspeptic patients, high incidence of *H pylori* infection (67%) and delayed GBFT support the hypothesis that this bacteria can cause dyspepsia^[27,15,16]. On the other hand, since *H pylori* was found as negative in 33% of our dyspepsia patients, it seemed unlikely that *H pylori* was the unique factor for dyspepsia. Abnormal bile composition may be responsible even if GB USG is normal. Further studies in patients with dyspepsia would be helpful in clarifying this issue.

In our study, each subject was studied with a standardized fatty meal releasing endogenous CCK as a stimulant for GB emptying. Krishnamurthy *et al.*^[30,31] reported that the GBFT and the GB latent period before the beginning of emptying were much longer, and GBEF values at 60 min were significantly lower obtained with fatty meal ingestion than with CCK injection. It probably resulted from the time taken for release of endogenous CCK. They suggested that acquisition has to last for at least 60 min. Dependent on these results, we acquired GB kinetic images up to 90 min and our results supported the reports of Krishnamurthy *et al.*^[30,31]. In all of our cases, GBFT and GB t1/2 time were increased while the mean GBEF value at 60 min was decreased. Interestingly, that GB functions impaired more prominently in *H pylori* negative patients was observed, however no statistically significant difference was detected between the two groups for each observer (Tables 1 and 2).

In conclusion, cholescintigraphy using ^{99m}Tc-Mebrofenin and a fatty meal ingestion is a well established and reliable noninvasive method for estimating gallbladder motor functions. Since we did not find any significant difference in gallbladder kinetic parameters between *H pylori* positive and negative patients with dyspepsia, *H pylori* did not seem to cause the abnormal gallbladder function (filling or emptying). Up to date, direct relationship between *H pylori* infection and gallbladder motor functions has not been reported. For that reason, we are not able to compare our results directly with any other published data, and further studies on this topic may help to clarify our findings.

COMMENTS

Background

The *H pylori* is an interesting cause of active chronic gastritis and duodenitis or even cancer worldwide. The presence of *H pylori* could also predispose to various disorders such as dental disease, atherosclerosis, coronary artery disease, slow coronary flow and cerebral infarction. Few reports have been published on the relationship between gallbladder emptying in patients with *H pylori* positive and negative idiopathic dyspepsia. Our aim was scintigraphic evaluation of gallbladder motor functions in *H pylori* positive and negative patients affected by dyspepsia.

Research frontiers

Higher incidence of *H pylori* infection in dyspeptic patients supports the idea that it can cause to the development of dyspepsia. In the previous studies on dyspeptic patients showed that a group of dyspeptic patients had a reduced gallbladder response to a liquid meal. However, no definitive data of the gallbladder kinetic parameters has been published in the previous studies.

Innovations and breakthroughs

¹⁴C-UBT is reliable noninvasive method for the diagnosis of *H pylori* infection. Up to date, direct relationship between *H pylori* infection and gallbladder motor functions has not been studied. We showed for the first time that the gallbladder motor functions such as filling time, ejection fraction and emptying time values were not affected from *H pylori* infection.

Applications

Our study was designed to analyse the scintigraphic gallbladder motor function parameters in *H pylori* positive and negative patients based on dyspeptic symptoms, ¹⁴C-UBT and upper gastrointestinal endoscopy procedure. The *H pylori* did not appear to cause the impairment in gallbladder function.

Terminology

¹⁴C-UBT: Urea breath test using ¹⁴C capsule is based on the principle that urease activity is present in the stomachs of individuals affected with *H pylori*; GBEF: Gallbladder ejection fraction parameter describes gallbladder emptying function; ^{99m}Tc-Mebrofenin: It is a radiopharmaceutical agent for hepatobiliary scintigraphy.

Peer review

This is a report designed to analyse the gallbladder motor function parameters in *H pylori* positive and negative patients with dyspepsia. This clinical study was well designed.

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