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

Olga Taşkaya Yaylalı, Mustafa Yılmaz, Fatma Suna Kıraç, Serkan Değirmencioğlu, Metin Akbulut

INTRODUCTION

The H pylori infection is one of the most common chronic infections in humans[8,9]. 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[10,11]. The presence of H pylori infection could predispose to various disorders[12,13]. Dental disease might be associated with a higher recurrence of H pylori infection[14]. 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[15]. 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[16].

The H pylori is present in about 67%-100% of duodenal ulcer patients and 13%-61% of normal population[17]. 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\textsuperscript{[1,14]}. Urea breath tests (UBT) are based on the principle that urease activity is present in the stomachs of individuals infected with \textit{H pylori}. The UBT is considered as the gold standard in the diagnosis of \textit{H pylori} among the noninvasive tests\textsuperscript{[16-19]}

Gallbladder (GB) diseases are related more to an emptying abnormality than to resting volume changes\textsuperscript{[20]}. Cholescintigraphy using \textit{\textsuperscript{99m}Tc-}hepato-biliary 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\textsuperscript{[20-23]}. Dynamic biliary scintigraphy can measure biliary motor functions noninvasively and quantitatively in \textit{H pylori} positive and negative patients with dyspepsia\textsuperscript{[22]}. Few reports have been published on the relationship between gallbladder emptying in patients with \textit{H pylori} positive and negative idiopathic dyspepsia\textsuperscript{[22,23]}. 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\textsuperscript{[23,24]}. There is no literature available to confirm the effects of \textit{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 \textit{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 \textit{H pylori} was determined in each patient with \textit{\textsuperscript{14}C-}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 \textit{H pylori}. Before the \textit{\textsuperscript{14}C-}UBT, the subject fasted for at least 6 hours. \textit{H pylori} positive 58 patients (23 female, 35 male; mean age 41 years) as study group and \textit{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 \textit{\textsuperscript{14}C-}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 $\beta$-particles and is presented as decay per min (DPM) together with the test result < $\leq$ 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 \textit{\textsuperscript{14}C-}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 \textit{\textsuperscript{14}C-}UBT, every patient was defined by using cholescintigraphy with \textit{\textsuperscript{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 \textit{\textsuperscript{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 \textit{\textsuperscript{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 $A/2$): 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 ± SE or as mean ± SD.
RESULTS

$^{14}$C-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 $^{14}$C-UBT positive patients (53.71 ± 3.49 min) did not differ significantly from that of $^{14}$C-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 (Figure 1). The GB $t_{1/2}$ was 44.15 ± 4.38 min and 51.08 ± 4.43 min for $^{14}$C-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 (GBEF$_{30}$) and at 60 min (GBEF$_{60}$) obtained by the experienced observer (A) in $^{14}$C-UBT positive patients were 36.58% ± 5.82% and 52.88% ± 5.38%, respectively. In $^{14}$C-UBT negative patients GBEF$_{30}$ was 24.35% ± 3.80% and GBEF$_{60}$ was 47.11% ± 5.88%. Mean GBEF values at 30 min and at 60 min obtained by the inexperienced observer (B) in $^{14}$C-UBT positive patients were 36.58% ± 5.82% and 52.88% ± 5.38%, respectively. In $^{14}$C-UBT negative patients GBEF$_{30}$ was 24.35% ± 3.80% and GBEF$_{60}$ was 47.11% ± 5.88%. Mean GBEF values at 30 min and at 60 min obtained by the inexperienced observer (B) in $^{14}$C-UBT positive patients were 36.58% ± 5.82% and 52.88% ± 5.38%, respectively. In $^{14}$C-UBT negative patients GBEF$_{30}$ was 24.35% ± 3.80% and GBEF$_{60}$ was 47.11% ± 5.88%. Mean GBEF values at 30 min and at 60 min obtained by the inexperienced observer (B) in $^{14}$C-UBT positive patients were 36.58% ± 5.82% and 52.88% ± 5.38%, respectively. In $^{14}$C-UBT negative patients GBEF$_{30}$ was 24.35% ± 3.80% and GBEF$_{60}$ was 47.11% ± 5.88%. Mean GBEF values at 30 min and at 60 min obtained by the inexperienced observer (B) in $^{14}$C-UBT positive patients were 36.58% ± 5.82% and 52.88% ± 5.38%, respectively. In $^{14}$C-UBT negative patients GBEF$_{30}$ was 24.35% ± 3.80% and GBEF$_{60}$ was 47.11% ± 5.88%.

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

| Parameters | $^{14}$C-UBT Positive (n = 58) | $^{14}$C-UBT Negative (n = 8) |
|------------|-----------------------------|-------------------------------|
| GBFT (min) | 53.71 ± 3.49                | 61.21 ± 4.50                 |
| $t_{1/2}$ (min) | 44.15 ± 4.38 (n = 27) | 51.08 ± 4.43 (n = 12) |
| GBEF$_{30}$ (A) % | 36.58 ± 5.82 (n = 36) | 24.35 ± 3.80 (n = 20) |
| GBEF$_{60}$ (A) % | 52.88 ± 5.38 (n = 33) | 47.11 ± 5.88 (n = 19) |
| GBEF$_{30}$ (B) % | 35.55 ± 4.07 (n = 40) | 26.38 ± 3.53 (n = 21) |
| GBEF$_{60}$ (B) % | 53.86 ± 5.06 (n = 36) | 47.55 ± 4.57 (n = 20) |

GBFT: Gallbladder filling time; $t_{1/2}$: Gallbladder half emptying time; GBEF$_{30}$: Gallbladder ejection fraction at 30 min; GBEF$_{60}$: Gallbladder ejection fraction at 60 min; A: Experienced observer; B: Inexperienced observer.

Table 2  Correlation values of GBEF$_{30}$ and GBEF$_{60}$ between two observers in $^{14}$C-UBT positive and negative patients

| Parameters | 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 |

GBEF$_{30}$: Gallbladder ejection fraction at 30 min; GBEF$_{60}$: Gallbladder ejection fraction at 60 min; A: Experienced observer; B: Inexperienced observer; $r$ value: Correlation coefficient.
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. Marzio et al. reported 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. 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. 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. Depending on these results, we acquired GB kinetic images up to 90 min and our results supported the reports of Krishnamurthy et al. In all of our cases, GBFT and GB t½ 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 99mTc-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 be able to compare our results directly with any other published data, and further studies on this topic may help to clarify our findings.

REFERENCES

1 Blaser MJ. Helicobacter pylori: its role in disease. Clin Infect Dis 1992; 15: 386-391
2 Nai GA, Parizi AC, Barbosa RL. Association between Helicobacter pylori concentration and the combining frequency of histopathological findings in gastric biopsies specimens. Arq Gastroenterol 2007; 44: 240-243
3 The EUROGAST Study Group. An international association between Helicobacter pylori infection and gastric cancer. Lancet 1993; 341: 1359-1362
4 Wolodarek D, Pakszys W, Barlik M. Helicobacter pylori—does it only cause gastroduodenal disease? Pol Merkur Lekarski 2001; 11: 456-459
5 Moss SF, Malfertheiner P. Helicobacter and gastric malignancies. Helicobacter 2007; 12 Suppl 1: 23-30
6 Rokkas T, Simsek I, Ladas S. Helicobacter pylori infection and non-malignant diseases. Helicobacter 2007; 12 Suppl 1: 20-22
7 Gisbert JP, Gonzalez L, de Pedro A, Valbuena M, Prieto B, Llorca I, Briz R, Khorraram S, Garcia-Gravalos R, Pajares JM. Helicobacter pylori and bleeding duodenal ulcer: prevalence of the infection and role of non-steroidal anti-inflammatory drugs. Scand J Gastroenterol 2001; 36: 717-724
8 Bernardini G, Braconi D, Lusini P, Santucci A. Helicobacter pylori: immunoproteomics related to different pathologies. Expert Rev Proteomics 2007; 4: 679-689
9 Sheu BS, Cheng HC, Yang YJ, Yang HB, Wu JY. The presence of dental disease can be a risk factor for recurrent Helicobacter pylori infection after eradication therapy: a 3-year follow-up. Endoscopy 2007; 39: 942-947
10 Ayada K, Yokota K, Kobayashi K, Shoenfeld Y, Matsuura E, Oguma K. Chronic infections and atherosclerosis. Ann N Y Acad Sci 2007; 1108: 594-602
11 Jin SW, Her SH, Lee JM, Yoon HJ, Moon SJ, Kim PJ, Baek SH, Seung KB, Kim JH, Kang SB, Kim JH, Kim KY. The association between current Helicobacter pylori infection and coronary artery disease. Korean J Intern Med 2007; 22: 152-156
12 Evrengül H, Tanriverdi H, Kuru O, Enli Y, Yuksel D, Kilic A, Kaftan A, Kirac S, Kilic M. Elevated homocysteine levels

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

13C-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. 13C-UBT and upper gastrointestinal endoscopy procedure. The H pylori did not appear to cause the impairment in gallbladder function.

Terminology

13C-UBT: Urea breath test using 13C 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. 99mTc-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.
in patients with slow coronary flow: relationship with Helicobacter pylori infection. Helicobacter 2007; 12: 298-305
13 Yiannopoulou KG, Efthymiou A, Karydakis K, Arhimandritis A, Bovaretos N, Tzivras M. Helicobacter pylori infection as an environmental risk factor for migraine without aura. J Headache Pain 2007; Epub ahead of print
14 Gasbarrini A, De Luca A, Fiore G, Franceschi F, Ogetti V V, Torre E, Di Campli C, Candelli M, Pola R, Serricchio M, Tondi P, Gasbarrini G, Pola P, Giacovazzo M. Primary Headache and Helicobacter Pylori. Int J Angiol 1998; 7: 310-312
15 Graham DY. Helicobacter pylori: its epidemiology and its role in duodenal ulcer disease. J Gastroenterol Hepatol 1991; 6: 105-113
16 Logan RP, Polson RJ, Misiewicz JJ, Rao G, Karim NQ, Newell D, Johnson P, Wadsworth J, Walker MM, Baron JH. Simplified single sample 13Carbon urea breath test for Helicobacter pylori: comparison with histology, culture, and ELISA serology. Gut 1991; 32: 1461-1464
17 Boivin C. 13C-urea versus 14C-urea breath test--which is the safer? Nucl Med Commun 1999; 20: 978
18 Shackett P. Breath Test for H. Pylori: PYtest C-14 Urea Breath Test (UBT). In: Nuclear Medicine Technology, Procedure and Quick Reference. 1st ed. Philadelphia: Lippincott Williams &Wilkins, 2000: 46-50
19 Vakil N, Vaira D. Non-invasive tests for the diagnosis of H. pylori infection. Rev Gastroenterol Disord 2004; 4: 1-6
20 Krishnamurthy S, Krishnamurthy GT. Gallbladder ejection fraction: a decade of progress and future promise. J Nucl Med 1992; 33: 542-544
21 Krishnamurthy GT, Bobba VR, McConnell D, Turner F, Mesgarzadeh M, Kingston E. Quantitative biliary dynamics: introduction of a new noninvasive scintigraphic technique. J Nucl Med 1983; 24: 217-223
22 Jazrawi RP. Review article: measurement of gall-bladder motor function in health and disease. Aliment Pharmacol Ther 2000; 14 Suppl 2: 27-31
23 Shaffer EA. Review article: control of gall-bladder motor function. Aliment Pharmacol Ther 2000; 14 Suppl 2: 2-8
24 Ryan J, Cooper M, Loberg M, Harvey E, Sikorski S. Technetium-99m-labeled n-(2,6-dimethylphenylcarbamoylmethyl) iminodiacetic acid (tc-99m HIDA): a new radiopharmaceutical for hepatobiliary imaging studies. J Nucl Med 1977; 18: 997-1004
25 Marzio L, Di Felice F, Taico MG, Imbimbo B, Lapenna D, Cucurullo F. Gallbladder hypokinesia and normal gastric emptying of liquids in patients with dyspeptic symptoms. A double-blind placebo-controlled clinical trial with cisapride. Dig Dis Sci 1992; 37: 262-267
26 Marzio L, Falcucci M, Ciccaglione AF, Malatesta MG, Lapenna D, Ballone E, Antonelli C, Grossi L. Relationship between gastric and gallbladder emptying and refilling in normal subjects and patients with H. pylori-positive and -negative idiopathic dyspepsia and correlation with symptoms. Dig Dis Sci 1996; 41: 26-31
27 Dodds WJ, Groh WJ, Darwesh RM, Lawson TL, Kishk SM, Kern MK. Sonographic measurement of gallbladder volume. AJR Am J Roentgenol 1985; 145: 1009-1011
28 Xynos E, Pechlivanides G, Zoras OJ, Chrysos E, Tzovaras G, Fountos A, Vassilakis JS. Reproducibility of gallbladder emptying scintigraphic studies. J Nucl Med 1994; 35: 835-839
29 Toftdahl DB, Hojgaard L, Winkler K. Dynamic cholescintigraphy: induction and description of gallbladder emptying. J Nucl Med 1996; 37: 261-266
30 Krishnamurthy GT, Krishnamurthy S. Diseases of the gallbladder. In: Nuclear Hepatology. 3rd ed. Berlin Heidelberg: Springer-Verlag, 2000; 199-210
31 Krishnamurthy GT, Brown PH. Comparison of fatty meal and intravenous cholecystokinin infusion for gallbladder ejection fraction. J Nucl Med 2002; 43: 1603-1610

S-Editor Zhong XY I-Editor Alpini GD E-Editor Ma WH