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Gastric emptying in patients with chronic liver diseases

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There have been a number of reports of gastric emptying in cirrhosis, all with unconfirmed results. Moreover, the mechanism for delayed emptying in cirrhotic patients is unclear. We evaluated gastric emptying in patients with chronic hepatitis and cirrhosis by means of gastric emptying scintigraphy. ***Methods:*** The subjects were 18 normal controls and 75 patients with chronic viral hepatitis (50 patients had chronic hepatitis and 25 patients had cirrhosis). Tc-99m diethyltriamine pentaacetic acid labeled solid meals were used to evaluate gastric emptying; the half-time (T 1/2) of which was calculated. Digestive symptom scores were determined at the time of gastric emptying tests. ***Results:*** Fourteen (28%) of 50 patients with chronic hepatitis and 16 (64%) of 25 patients with cirrhosis had delayed gastric emptying. T 1/2 in patients with cirrhosis was significantly higher than that in normal controls and patients with chronic hepatitis ($p = 0.0001$ and 0.0003, respectively). The difference between T 1/2 in patients with chronic hepatitis and that in normal controls was not significant. On regression analysis, two indices—the serum albumin level and platelet count—were found to be significantly related to delayed gastric emptying. ***Conclusions:*** Gastric emptying was more delayed in cirrhotic patients than in those with chronic hepatitis and normal controls. Delayed gastric emptying may be related to liver function and portal hypertension.

Key words: gastric emptying, liver cirrhosis, chronic hepatitis, Tc-99m DTPA

INTRODUCTION

DELAYED GASTRIC EMPTYING may be one cause of gastrointestinal symptoms such as anorexia, dyspepsia and abdominal distention, of which cirrhotic patients often complain.[1] There have been a number of studies of gastric emptying in cirrhosis of the liver, all with unconfirmed results.[2–5] Chesta et al.[2] evaluated the gastric emptying in cirrhotic patients and noted a slight but non-significant delay in gastric emptying. Wegener et al.[3] reported that the presence of cirrhosis had not influenced on gastric emptying in patients with chronic alcoholism. Isobe et al.[4] and Galati et al.[5] found a high prevalence of delayed gastric emptying in cirrhotic patients, but the mechanism of delayed emptying in such patients is unclear.

Radionuclide gastric emptying study is a non-invasive, simple method for obtaining quantitative information on gastric emptying.[6–9] In this study, we investigated the gastric emptying time in patients with chronic hepatitis or liver cirrhosis by gastric emptying scintigraphy, and evaluated the correlation between abnormal gastric emptying and clinical manifestations.

MATERIALS AND METHODS

Patients

We studied 18 healthy subjects (mean age 49.1 ± 13.4 years), and 75 patients with liver diseases (50 with chronic hepatitis and 25 with cirrhosis) who were admitted to our hospital. All patients had underlying infection with hepatitis B or C virus. Cirrhosis and chronic hepatitis were diagnosed by examination of specimens obtained by

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Table 1 Baseline clinical data and characteristics of patients

	Chronic hepatitis	Liver cirrhosis	p-value
Number	50	25	
Age (yr)	51.7 ± 11.5	57.6 ± 13.3	0.086
Male/Female	31/19	15/10	NS
HBV/HCV	6/44	5/20	NS
Digestive symptom score	1.10 ± 1.21	1.88 ± 2.60	0.532
Blood glucose level (g/dl)	95 ± 19	105 ± 39	0.585
AST (U/l)	67 ± 28	145 ± 150	< 0.0001
ALT (U/l)	106 ± 58	138 ± 94	0.137
Total bilirubin (mg/dl)	0.9 ± 0.3	1.1 ± 0.6	0.461
Serum albumin (g/dl)	4.0 ± 0.3	3.5 ± 0.4	< 0.0001
Prothrombin time (%)	124 ± 26	94 ± 26	< 0.0001
Platelet count (/mm^3)	18.7 ± 4.1	9.8 ± 3.0	< 0.0001

HBV, hepatitis B virus; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase

laparoscopy or by needle biopsy performed under ultrasonic guidance. All patients lacked endoscopic abnormalities that might explain their digestive symptoms. None had alcoholic liver disease or a history of gastric surgery. Splenomegaly was classified in 4 grades (spleen index) by ultrasonographic images (0 = no splenomegaly, 1 = mild splenomegaly, 2 = moderate splenomegaly, and 4 marked splenomegaly). This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Osaka City University Medical School. Informed consent was obtained from all subjects. The laboratory data and characteristics of the patients are shown in Table 1.

Gastric Emptying Study

The test meal consisted of a 200 g pancake (51.6 g carbohydrate, 8.1 g protein, 5.7 g fat, 291 kcal) containing 37 MBq of Tc-99m diethyltriamine pentaacetic acid. The pancake was ingested with 100 m*l* of water within 2 minutes by all subjects. Immediately after the test meal, the subjects were placed in the standing position, and a gamma camera (VERTEX-PLUS; ADAC Corp., CA, USA) recorded the radioactivity over the upper abdomen. Gastric emptying data were acquired with one minute anterior images of the stomach at 30-minute intervals for a total of 120 minutes. Between standing image acquisitions, the subjects were allowed to sit. Data were corrected for radionuclide decay; the region encompassing the stomach was selected on the gamma camera images, and the radioactivity of this region was plotted. The half-time of gastric emptying (T 1/2), the time at which 50% of the peak radioactivity had left the stomach, was calculated by computer analysis (PEGASYS; ADAC Corp., CA, USA). The images and time-activity curve are shown in Figure 1.

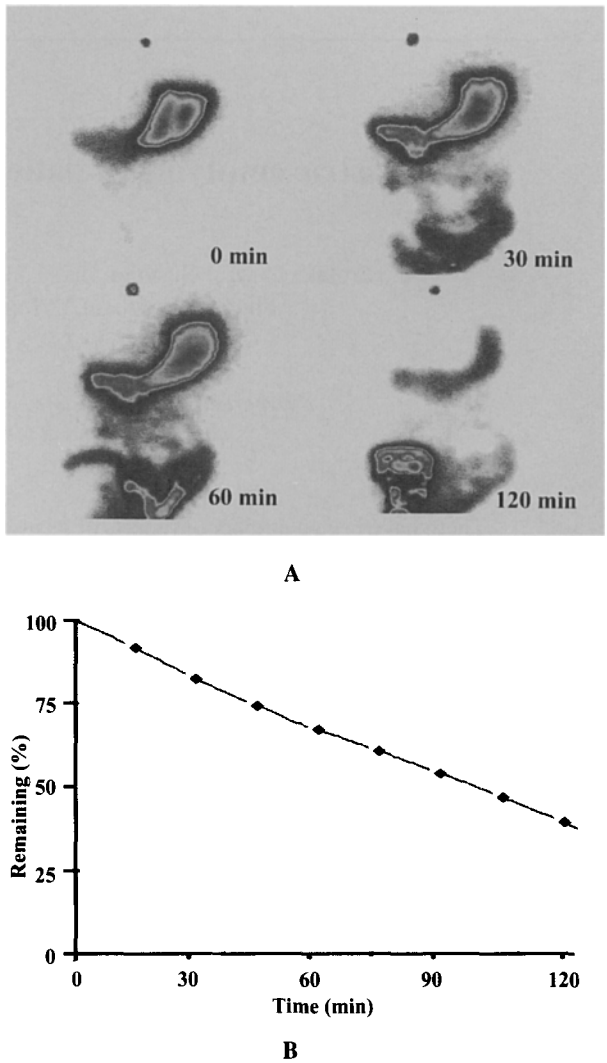

Fig. 1 Images of gastric emptying scintigraphy (A), and time-activity curve (B).

Assessment of Digestive Symptoms

Digestive symptoms were assessed at the time of gastric emptying tests by a modified version of the method described by Gatto et al.[10] Anorexia, nausea, vomiting, abdominal distention, belching, heartburn and epigastric pain were scored as follows: 0 = not present, 1 = mild (symptom could be ignored if the patient did not think about it), 2 = moderate (symptom could not be ignored, but did not affect daily activities), and 3 = severe (symptom affected daily activities). The digestive symptom score was calculated as the sum of these scores.

Statistical Analysis

Results are expressed as means with standard deviation (SD). T 1/2 and the digestive symptom score for chronic liver diseases were analyzed by the Mann-Whitney U test. Correlations between T 1/2 and digestive symptom scores or liver function tests were analyzed by Spearman's rank correlation test. Regression analysis was used for multi-

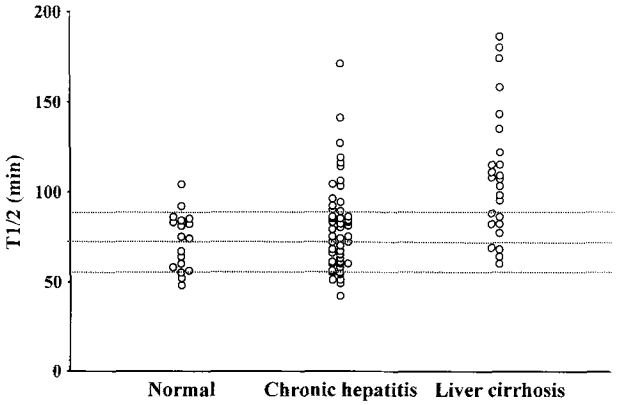

Fig. 2 T 1/2 in normal controls, patients with chronic hepatitis or cirrhosis of the liver. Dotted line shows the mean ± SD in normal controls.

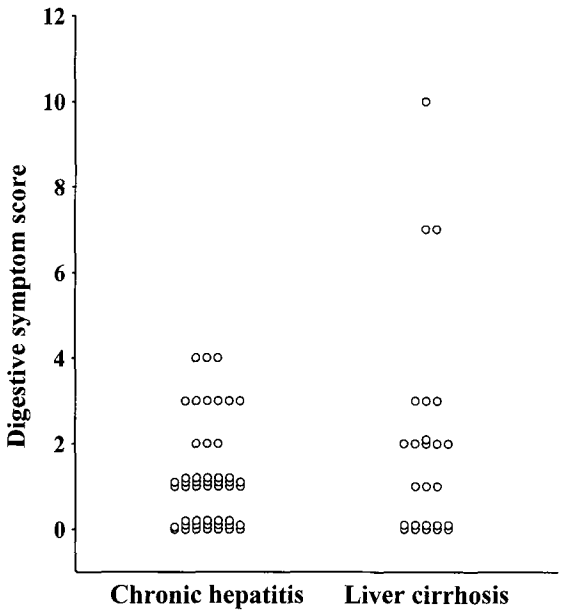

Fig. 3 Digestive symptom score in patients with chronic hepatitis or cirrhosis of the liver.

variate analysis of delayed gastric emptying. Differences with probability values less than 0.05 were considered significant, and those with probability values less than 0.1 were considered to indicate a tendency toward significance.

RESULTS

Gastric emptying and digestive symptom score in chronic liver disease

T 1/2 in normal controls, patients with chronic hepatitis, and cirrhosis are shown in Figure 2. Fourteen (28%) of 50 patients with chronic hepatitis and sixteen (64%) of 25 patients with cirrhosis had delayed gastric emptying (higher than mean T 1/2 plus SD in normal controls). The mean T 1/2 was 73 ± 15 min in normal controls, 80 ± 24 min in patients with chronic hepatitis, and 110 ± 36 min in

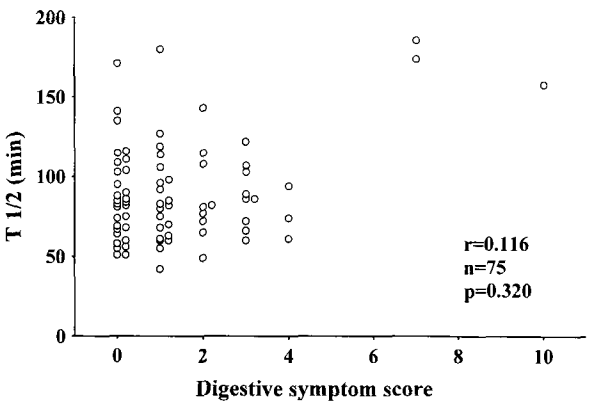

Fig. 4 Correlation between T 1/2 and digestive symptom score.

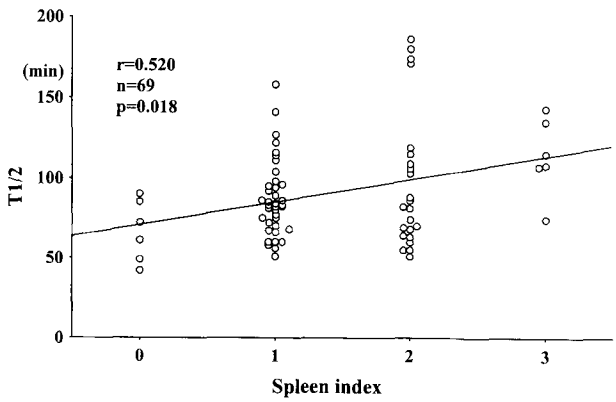

Fig. 5 Correlation between T 1/2 and spleen index.

patients with cirrhosis of the liver. The difference between T 1/2 in patients with chronic hepatitis and that in normal controls was not significant (p = 0.239). T 1/2 in patients with cirrhosis was significantly higher than that in normal controls and that in patients with chronic hepatitis (p = 0.0001 and 0.0003, respectively). The mean T 1/2 was 126 ± 33 min in cirrhotic patients with varices (n = 8) and 103 ± 36 min in patients without (n = 17); this difference exhibited a tendency toward significance (p = 0.085).

Digestive symptom scores in patients with chronic hepatitis or cirrhosis are shown in Figure 3. The mean digestive symptom score was 1.10 ± 1.21 in patients with chronic hepatitis, and 1.88 ± 2.60 in patients with cirrhosis of the liver; the difference was not significant (p = 0.532).

Correlation between T 1/2 and digestive symptom score or liver function tests

The correlation between T 1/2 and digestive symptom scores was not significant (r = 0.116, p = 0.320; Fig. 4). The correlation between T 1/2 and the blood glucose level was not significant (r = 0.125, p = 0.286). The correlation between T 1/2 and the spleen index was significant (r = 0.520, n = 69, p = 0.018; Fig. 5). The correlations were significant between T 1/2 and the serum albumin level (r = –0.335, n = 75, p = 0.003; Fig. 6) and platelet count

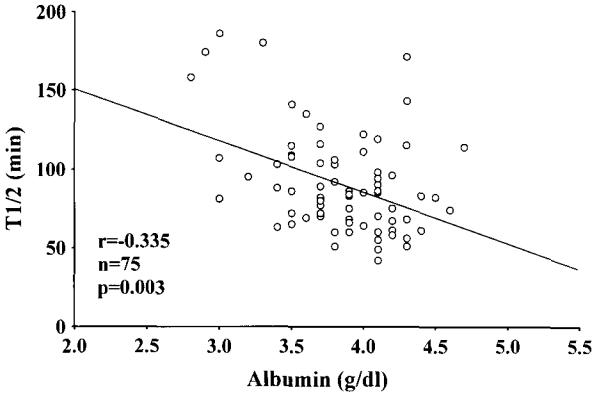

Fig. 6 Correlation between T 1/2 and serum albumin level.

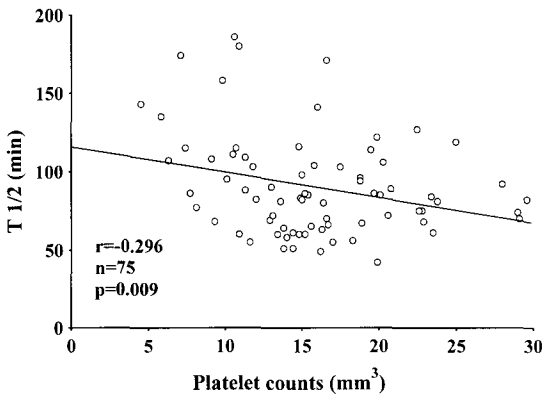

Fig. 7 Correlation between T 1/2 and platelet count.

Table 2 Results of regression analysis

Variable	Coefficient (β)	Standard error	Wald chi-square	P value	Risk ratio	95% CI
Blood glucose	0.112	0.120	0.93	0.356	1.02	0.88 to 1.41
ALT	0.009	0.116	0.08	0.931	1.01	0.79 to 1.28
Total bilirubin	0.013	0.121	0.11	0.813	1.01	0.80 to 1.28
Serum albumin	−0.249	0.119	2.09	0.041	1.28	1.02 to 1.62
Platelet count	−0.270	0.128	2.11	0.038	1.31	1.02 to 1.68

ALT, alanine aminotransferase

($r = -0.296$, $n = 75$, $p = 0.009$; Fig. 7). The correlations were significant between T 1/2 and the serum albumin level ($r = -0.396$, $n = 25$, $p = 0.048$) and platelet count ($r = -0.424$, $n = 25$, $p = 0.034$) in patients with cirrhosis, but the correlation were not significant between T 1/2 and the serum albumin level ($r = -0.147$, $n = 50$, $p = 0.308$) and platelet count ($r = -0.196$, $n = 50$, $p = 0.173$) in patients with chronic hepatitis. The correlations were not significant between T 1/2 and prothrombin time ($r = -0.180$, $n = 75$, $p = 0.122$), total bilirubin level ($r = 0.043$, $n = 75$, $p = 0.714$), and alanine aminotransferase activity ($r = 0.122$, $n = 75$, $p = 0.298$).

On regression analysis (Table 2), two indices—the serum albumin level and platelet counts—were found to be significantly related to delayed gastric emptying.

DISCUSSION

Scintigraphic techniques are regarded as the most reliable means of measuring gastric emptying. Gastric scintigraphy is simple, non-invasive, well accepted by patients, and widely used both clinically and experimentally.[6] Moreover, this method is highly reproducible[7] and useful for determining temporal changes in the same patient. But comparison of the results of scintigraphic studies from independent centers is difficult because of methodological differences[8] (choice of meal and radiolabel; method used for data acquisition; data analysis and interpretation). We used a method that is widely recognized in Japan,[9] and some clinical applications have been reported using it.[11]

The relationship between gastric emptying time and gastrointestinal symptoms is controversial. Horowitz et al.[12] reported that a delay in gastric emptying indicated gastroduodenal motor abnormality in patients with diabetes and was not a direct cause of symptoms. Isobe et al.[4] found a significant correlation between gastrointestinal symptoms and gastric emptying in cirrhotic patients, suggesting that delay in gastric emptying may contribute to gastrointestinal symptoms in cirrhosis. In our study, no significant correlation was found between digestive symptoms and gastric emptying in patients with chronic liver disease.

Wegener et al.[3] reported that the presence of cirrhosis had not affected gastric emptying in patients with chronic alcoholism. They compared chronic alcoholics with cirrhosis to those without it, but not with normal controls. This may have been responsible in part for the differences between their study and ours in conclusions. The reason for this seems to be that chronic alcoholism is frequently associated with autonomic impairment despite the presence of cirrhosis, but Isobe et al.[4] found high prevalence of delayed gastric emptying in patients with cirrhosis with hepatitis viral infection. In our study, delayed gastric emptying was found in 16 (64%) of 25 patients with cirrhosis, but in only 14 (28%) of 50 patients with chronic hepatitis. Moreover, gastric emptying may be delayed in older patients. But no significant difference was seen

between the age of patients with chronic hepatitis and cirrhosis. No report concerning gastric emptying in patients with chronic hepatitis and aging have been available.

Abnormal gastric motor function may have major effects on the management of diabetic patients, by causing upper gastrointestinal symptoms and impaired oral drug absorption and contributing to poor control of the blood glucose concentration.[12] The blood glucose level is often high in patients with cirrhosis,[13] and gastric emptying is delayed in patients with diabetes mellitus.[14] Nevertheless, our patients did not have a significant correlation between blood glucose level and gastric emptying time; the reason for this may be that few (only 4 of 75 patients) of our patients had diabetes mellitus.

Galati et al.[5] reported that the effect of chronic liver disease on gastric emptying appeared to be unrelated to the severity of underlying liver dysfunction, as measured by serum levels of albumin, total bilirubin, and prothrombin time, but their subjects had various diseases such as alcohol-related liver disease, chronic viral hepatitis, primary sclerosing cholangitis and primary biliary cirrhosis. On the other hand, Isobe et al.[4] reported significant correlations between gastric emptying and various liver function tests, and suggested that liver function is responsible for delay of gastric emptying in cirrhotic patients. All of their subjects had hepatitis B or C virus infection. In our study, significant correlations were found between gastric emptying time and serum albumin and the platelet count in cirrhotic patients.

The pathophysiology of abnormal gastric emptying remains unclear. In the past, gastrointestinal symptoms in patients with cirrhosis have been attributed to compression and displacement of the stomach and small intestine by ascites and splenomegaly.[1] Galati et al.[5] investigated gastric emptying in patients with chronic liver diseases and portal hypertension, and found that although splenomegaly of modest degree was present in all patients, none had clinically detectable ascites. They found it difficult to believe that mechanical "compression" of the stomach was related to delayed gastric emptying. Moreover, mucosal edema, secondary to hypoalbuminemia and portal hypertension, may be one of the causes of delayed gastric emptying. In an animal study, gastric mucosal edema has been found to be associated with accelerated emptying in a rat model of portal hypertension.[15] This finding shows that mucosal edema also appears to be an unlikely explanation of delayed gastric emptying.

In our study, the platelet count was related to delayed gastric emptying on regression analysis, and gastric emptying time in patients with varices was longer than that in patients without. The platelet count was related to hypersplenism complicated by portal hypertension, and varices often appeared in patients with portal hypertension. Moreover, gastric emptying time was significantly longer in patients with cirrhosis than in normal controls, but was not longer in patients with chronic hepatitis than that in normal controls. The reason for this may be that the changes in portal hemodynamics in chronic liver disease were not steady and portal hypertension occurred after cirrhosis had developed.[16]

We believe that delayed gastric emptying in patients with cirrhosis may have multiple several causes. Further studies are needed to clarify the effects of various clinical manifestations of cirrhosis of the liver on gastric emptying.

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