



Autonomic neuropathy and gallbladder motility in patients with liver cirrhosis

LIVER/BILIARY

Kemal Kul, Ender Serin, Tolga Yakar, Arif Mansur Coşar, Birol Özer

Department of Gastroenterology, Başkent University Adana Research and Training Hospital, Adana, Turkey

ABSTRACT

Background/Aims: Impaired gallbladder motility has been suggested as a contributor to increased incidence of gallstones in patients with liver cirrhosis. The purpose of this study was to determine gallbladder function and its relation with autonomic neuropathy in liver cirrhosis.

Materials and Methods: Gallbladder function was measured using ultrasonography in 48 patients with liver cirrhosis and in 31 controls. Autonomic neuropathy tests were applied in patients with liver cirrhosis. Patients with liver cirrhosis were analyzed in subgroups according to the severity of disease using the Child-Pugh classification.

Results: Fasting gallbladder volume was 16.2 mL (range: 2.1 mL-71.9 mL) in patients and 17.6 mL (range: 4.9 mL-76.6 mL) in controls. There were no differences in fasting gallbladder volume among the study groups ($p>0.05$). Gallbladder ejection fraction was significantly higher in patients compared with controls (84% vs. 65%) ($p<0.001$). No correlation was found between gallbladder ejection fraction and autonomic neuropathy ($p>0.05$).

Conclusion: Our results indicate that liver cirrhosis does not impair gallbladder emptying, and that there is no association between gallbladder motility and autonomic neuropathy. Further investigations are required to explain increased gallbladder motility in liver cirrhosis.

Keywords: Liver cirrhosis, gallbladder emptying, autonomic neuropathy

INTRODUCTION

Patients with cirrhosis of the liver have a higher incidence and prevalence of cholelithiasis compared with the general population (1-3). Some studies have proposed changes in gallbladder motility as a causative factor in the pathogenesis of cholelithiasis (4). There are conflicting results among studies about gallbladder motility in patients with cirrhosis. The reason why patients with cirrhosis have some disorder with regard to gallbladder motility may depend on either humoral or neurological alterations. The humoral control of gallbladder function is mainly coordinated by meal-induced cholecystokinin (CCK), which stimulates gallbladder contraction. Neural control is more complex and involves sympathetic, parasympathetic, and enteric nervous systems.

Patients with cirrhosis, especially those in a decompensated state, usually have autonomic dysfunction (AD), which can affect gallbladder function. A recent

study suggested that autonomic neuropathy (AN) contributes to the formation of gallstones in patients with advanced cirrhosis (4). Acceleration, delay, or no significant change in gastric emptying in patients with cirrhosis was reported by a number of studies (5-9). AD seems to affect biliary motility directly through the neural pathway and/or indirectly through the probable effect of alteration in gastric emptying on CCK secretion.

We designed the present study to determine whether there is any abnormality of gallbladder emptying in patients with liver cirrhosis and the effect of autonomic dysfunction on this probable disorder.

MATERIALS AND METHODS

Patients and controls

The study subjects were 48 patients with liver cirrhosis and 31 healthy controls. The diagnosis of cirrhosis

Address for Correspondence: Ender Serin, Department of Gastroenterology, Başkent University Adana Research and Training Hospital, Adana, Turkey

E-mail: eserin67@yahoo.com

Received: November 01, 2012

Accepted: May 10, 2013

© Copyright 2015 by The Turkish Society of Gastroenterology • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2015.4469

was made on the basis of patterns of clinical, laboratory, and/or histological findings. For this purpose, endoscopic and/or ultrasonographic signs of portal hypertension and/or the finding of an irregular liver margin on ultrasonography (US) were used. Exclusion criteria were diabetes mellitus, ischemic heart diseases, cholelithiasis, a history of cholecystectomy, gastric or intestinal surgery, and drugs that can be associated with AN. The patients were grouped according to the Child-Pugh classification.

Tests for autonomic functions

The autonomic functions were assessed using five standard cardiovascular tests and interpreted according to the study of Ewing and Clarke (10). Briefly, Valsalva ratio (heart rate response during Valsalva maneuver), heart rate variability during deep breathing, and immediate heart rate response to standing were determined for the evaluation of parasympathetic system. The sympathetic system was evaluated by systolic blood pressure fall on standing and rise in systolic blood pressure over baseline to sustained handgrip. The results of cardiovascular tests were identified as normal, borderline, or abnormal, as previously described in the literature. Patients were categorized into four groups reflecting the degree of autonomic involvement:

- 1) Normal: All the tests were normal;
- 2) Early involvement: One abnormal heart rate test or two borderline abnormal heart rate tests;
- 3) Definite involvement: Two or more heart rate tests were abnormal;
- 4) Combined involvement: Two or more heart rate tests were abnormal and one or both blood pressure tests were abnormal.

US for gallbladder motility

The ultrasonographic examination (Philips HDI 5000 with 3.25–5-MHz transducer) was performed after one night of fasting and ensuring that no drugs known to affect gallbladder function were taken. A single operator determined the gallbladder volumes using the US software after the input of longitudinal, anterior-posterior, and lateral-lateral diameters. The premenopausal women were evaluated during the first phase of their menstrual cycles because of the variability of gallbladder motility observed during the menstrual cycle. All patients who had gallbladder pathology such as cholecystitis; cholelithiasis; and debris, polyp, or cholesterol crystals in the gallbladder were excluded. In fasting conditions, after measuring the dimensions of the gallbladder (width, height, and depth), patients received 100 g of a standard chocolate (58% carbohydrate, 35% fat, and 4.5% protein, totally 2.2×10^3 kJ) orally. After this, postprandial measurements were performed at 2 and 3 h. In this manner, the calculations of the fasting volume, postprandial residual volume, and ejection fraction were performed. Volume calculations were performed using the ellipsoid formula $V = Q/6$ (width \times height \times depth). The maximum residual volume was considered the lowest postprandial volume of the gallbladder.

Table 1. Demographic and clinical characteristics of the study population

	Controls	Patients
No.	31	48
Child-Pugh A		23
Child-Pugh B		15
Child-Pugh C		10
Sex (F/M)	22/9	30/18
Age (years)	43	56
Etiology of cirrhosis		
Hepatitis B		20
Hepatitis C		22
Alcohol		2
Unknown		4

The formula used for the measurement of gallbladder ejection fraction was as follows: fasting volume - maximum residual volume/fasting volume $\times 100$ (11).

Statistical analysis

Continuous variables were expressed as the median \pm range and were compared using the Mann-Whitney U test. The values of patient groups based on the Child-Pugh classification were compared using ANOVA. The statistical significance was set at the $p < 0.05$ level. All analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., IL, USA) for Windows, version 11.0.

This study was approved by the Ethics Committee of Başkent University Faculty of Medicine and informed consent was obtained from all patients and controls.

RESULTS

Some of the demographic and clinical characteristics of study population are summarized in Table 1. The median age of patients was 56 years, with a range of 33–85 years. There were 30 men and 18 women. The etiologies of cirrhosis were hepatitis B in 20 patients (41.6%), hepatitis C in 22 (45.8%), and alcohol in 2 (4.1%).

Fasting gallbladder volumes of patients and controls were similar ($p > 0.05$), whereas ejection fraction of gallbladder was higher in patients compared with controls ($p < 0.001$). There was no statistically significant difference among the ejection fractions of the Child-Pugh groups, but the difference compared with controls was significant for Child A or B patients ($p = 0.006$ and $p = 0.001$, respectively) (Table 2).

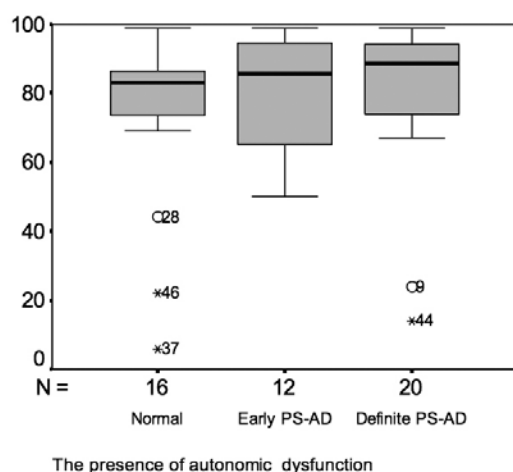
We determined autonomic dysfunction in 32 patients, 12 of whom had early parasympathetic involvement and the remaining showed definite parasympathetic involvement. The distribution of the types of AD according to the Child-Pugh

Table 2. Median gallbladder volumes in the fasting and postprandial states and values of ejection fraction (EF)

	Gallbladder volume, mL (range)			EF (%)
	Fasting	2 h after test meal	3 h after test meal	
All patients with cirrhosis	16.2 (2.1-71.9)	4.2 (0.1-92.8)	4.4 (0.1-98.5)	84 (6-99)
Child-Pugh A	24.4 (8.6-71.9)	5.4 (0.1-33.6)	5.9 (0.4-21.0)	83 (6-99)
Child-Pugh B	14.0 (4.7-60.6)	2.8 (0.1-21.4)	1.2 (0.1-42.9)	93 (51-99)
Child-Pugh C	12.9 (2.1-5.6)	6.6 (0.1-92.8)	6.2 (0.1-98.5)	83 (14-99)
Controls	17.6 (4.9-76.6)	7.7 (0.1-45.1)	7.1 (0.4-33.2)	65 (5-99)

Table 3. The distribution of the types of autonomic dysfunction according to Child-Pugh stages

	Child-Pugh A N: 23 No. (%)	Child-Pugh B N: 15 No. (%)	Child-Pugh C N: 10 No. (%)	Entire group N: 48 No. (%)
Types of autonomic dysfunction				
Normal	11 (48)	3 (20)	2 (20)	16 (33)
Early parasympathetic involvement	4 (17)	6 (40)	3 (30)	13 (27)
Definite parasympathetic involvement	8 (35)	5 (33)	3 (30)	16 (33)
Combined dysfunction		1 (7)	2 (20)	3 (7)

**Figure 1.** The comparison of gallbladder ejection fractions among cirrhotic patients with or without parasympathetic autonomic dysfunction (PS-AD).

classification is summarized in Table 3 and there was no significant difference among the Child-Pugh groups. Patients with AD had similar gallbladder ejection fraction compared with those without AD ($p>0.05$) (Figure 1).

DISCUSSION

Patients with liver cirrhosis frequently have extrahepatic manifestations due to cirrhosis or alterations secondary to liver pathology. The frequency of gallbladder dysfunction and cholelithiasis has been suggested to be increased in patients with cirrhosis (1-4). One of the suggested mechanisms underlying cholelithiasis is gallbladder dysfunction (4).

Sonography is increasingly used for the estimation of gastric emptying and is accepted as the "gold standard" for the study

of gallbladder motility. In the present study, patients with cirrhosis showed similar fasting gallbladder volume compared with controls. There are studies showing fasting gallbladder volumes either similar between patients with cirrhosis and normal subjects (11) or higher, especially in patients with cirrhosis Child C, compared with healthy controls (12-14).

Some studies have suggested that cirrhosis impairs the gallbladder emptying on the basis of the findings of gallbladder ejection fraction by either US or cholescintigraphic measurements. The results of the studies by Li et al. (12) and Pompili et al. (14) have revealed similar ejection fraction values between patients with cirrhosis and control subjects. However, in the present study, we found higher values of ejection fraction in patients compared with healthy controls, and EF did not show a significant difference among the Child-Pugh groups. Sari et al. (15) have found greater gallbladder contractility in patients with cirrhotic ascites than in those with malignant ascites. Acalovschi et al. (13) and Kao et al. (16) have reported impairment of gallbladder emptying in liver cirrhosis. The results of each study are slightly different in terms of values among the Child groups. Kao et al. have demonstrated a gradual decrease in EF with the severity of cirrhosis, whereas Acalovschi et al. have reported similar EF values among Child-Pugh groups. One possible explanation of the discrepancy between our study and the others is the spectrum of etiology of cirrhosis in the study groups. We had fewer patients with alcoholic cirrhosis compared with the others. There has been some evidence about the possible effects of ethanol on gallbladder function regarding both secretion and motility (17,18). However, cholelithiasis was shown to be more frequent in patients with cirrhosis with previous alcohol abuse compared with nonalcoholics (19). Another factor underlying the difference between

results of the other studies may be the presence of gallstones. In some studies reporting low EFs of gallbladder in patients with cirrhosis, patients with cholelithiasis were included in the study. Decreased postprandial fractional emptying in patients with gallstones has been demonstrated in previous studies (20,21).

Gallbladder emptying in response to feeding is mainly controlled by gastric emptying with subsequent CCK release (22). Depending on several studies that have reported different rates of gastric emptying in patients with cirrhosis, CCK release can be earlier or later than normal (23,24). However, patients with cirrhosis have shown increased plasma levels of basal and postprandial CCK (14). These may explain higher EF values of patients with cirrhosis in the present study compared with controls. High levels of CCK can be responsible for the increased gallbladder motility observed in our Child-Pugh A-B patients. The time of postprandial measurement of gallbladder EF was not homogeneous among studies. Because CCK release can be delayed in patients with cirrhosis, studies using the early evaluation of gallbladder motility can show lower values compared with those using later measurements. We should not ignore the possible effect of test meal content and structure on the different results of EF in various studies.

The complex neurohormonal control of biliary motility involves the sympathetic, parasympathetic, and enteric nervous systems (25). In this study, we proposed a relation between autonomic neuronal dysfunction and gallbladder motility in patients with cirrhosis. We found that the frequency of autonomic neuropathy was 67% in patients with cirrhosis, comparable to that in previous studies (26,27). Autonomic neuropathy is common in patients with cirrhosis and comparable in alcoholics and nonalcoholics. The increase in severity accompanies an increase in the extent of liver damage. This suggests that liver damage contributes to neurological deficit (27). There was no significant difference in autonomic neuropathy among the Child-Pugh groups in the present study. To the best of our knowledge, there have been no previous studies on the relation between autonomic neuropathy and gallbladder motility in patients with cirrhosis. Chawla et al. (4) have found the prevalence of gallstones to be significantly higher in patients with autonomic neuropathy compared with those with normal autonomic functions who have Child C cirrhosis. They have suggested that autonomic neuropathy contributes to the formation of gallstones in patients with advanced cirrhosis. We could not find a difference in the ejection fractions of gallbladder between patients with and without autonomic neuropathy. According to our study, we suggest that autonomic neuropathy and gallstone disease in patients with cirrhosis is not a cause-effect relationship but instead a coincidence.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Başkent University Faculty of Medicine.

Informed Consent: Written informed consent was obtained from all patients and controls.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - K.K., E.S.; Design - K.K., E.S.; Supervision - E.S., A.M.C., B.Ö.; Resource - K.K., E.S., T.Y., A.M.C., B.Ö.; Materials - K.K., T.Y., A.M.C.; Data Collection &/or Processing - K.K., T.Y., A.M.C., Analysis &/or Interpretation - K.K., E.S., T.Y., A.M.C., B.Ö.; Literature Search - K.K., E.S., T.Y., A.M.C., B.Ö.; Writing - K.K., E.S., A.M.C.; Critical Reviews - E.S., A.M.C., B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Acalovschi M, Badea R, Dumitroscu D, Varga C. Prevalence of gallstones in liver cirrhosis: A sonographic survey. *Am J Gastroenterol* 1988; 83: 954-6.
2. Coste D, Barisoni D, Mandelli C, et al. Cholelithiasis in cirrhosis: analysis of 5000 cases. *Am J Gastroenterol* 1991; 86: 1629-32.
3. Fornari F, Imberti D, Squillaste MM, et al. Incidence of gallstones in a population of patients with cirrhosis. *J Hepatol* 1994; 20: 797-801. [\[CrossRef\]](#)
4. Chawla A, Puthumana L, Thuluvath PJ. Autonomic dysfunction and cholelithiasis in patients with cirrhosis. *Dig Dis Sci* 2001; 46: 495-8. [\[CrossRef\]](#)
5. Verne GN, Soldevia-Pico C, Robinson ME, Spicer KM, Reubes A. Autonomic dysfunction and gastroparesis in cirrhosis. *J Clin Gastroenterol* 2004; 38: 72-6. [\[CrossRef\]](#)
6. Gümürdülü Y, Yapar Z, Canatarioğlu A, et al. Gastric emptying time and the effect of cisapride in cirrhotic patients with autonomic neuropathy. *J Clin Gastroenterol* 2003; 36: 175-8. [\[CrossRef\]](#)
7. Ishizu H, Shimai S, Kawamura E, et al. Gastric emptying in patients with chronic liver diseases. *Ann Nucl Med* 2002; 16: 177-82. [\[CrossRef\]](#)
8. Reilly JA, Forst CF, Quigley EMM, Rikkers LF. Gastric emptying of liquids and solids in the portal hypertensive rat. *Dig Dis Sci* 1990; 35: 781-6. [\[CrossRef\]](#)
9. Balan KK, Grime SJ, Sutton R, Critchley M, Jenkins SA. Do alterations in the rate of gastric emptying contribute to the pathogenesis of portal hypertensive gastropathy? *Gut* 1994; (Suppl 2): S13.
10. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *BMJ* 1982; 285: 916-9. [\[CrossRef\]](#)
11. Doods WJ, Groh WJ, Darweesh RMA, Lawson TL, Kishk SM, Kern MK. Sonographic measurement of gallbladder volume. *Radiology* 1985; 145: 1009-11. [\[CrossRef\]](#)
12. Li CP, Hwang SJ, Lee FY, et al. Evaluation of gallbladder motility in patients with liver disease. Relationship to gallstone formation. *Dig Dis Sci* 2000; 45: 1109-14. [\[CrossRef\]](#)
13. Acalovschi M, Dumitrascu DL, Csakany I. Gastric and gallbladder emptying of a mixed meal are not coordinated in liver cirrhosis. A simultaneous sonographic study. *Gut* 1997; 40: 412-7. [\[CrossRef\]](#)
14. Pompili M, Rapaccini GL, Caturelli E, et al. Gallbladder emptying, plasma levels of estradiol and progesterone, and cholecystokinin secretion in liver cirrhosis. *Dig Dis Sci* 1995; 40: 428-34. [\[CrossRef\]](#)
15. Sarı R, Yıldırım B, Sevinc A, Bahceci B, Hilmioglu F. Gallbladder contractility in patients with cirrhotic versus malignant ascites. *J Clin Ultrasound* 2002; 30: 477-80. [\[CrossRef\]](#)
16. Kao CH, Hsieh JF, Tsai SC, Ho YJ, Chen SD. Evidence of impaired gallbladder function in patients with liver cirrhosis by quantita-

- tive radionuclide cholescintigraphy. *Am J Gastroenterol* 2000; 95: 1301-4. [\[CrossRef\]](#)
17. Masui H, Wakabayashi I, Hatake K, Yoshimoto S, Sakamoto K. Effects of ethanol on contractile response of gall bladder isolated from guinea pig. *Eur J Pharmacol* 1993; 248: 103-10.
18. Kurtin WE, Schwesinger WH, Stewart RM. Effect of dietary ethanol on gallbladder absorption and cholesterol gallstone formation in the prairie dog. *Am J Surg* 1991; 161: 470-4. [\[CrossRef\]](#)
19. Benvegna L, Noventa F, Chmello L, Fattovich G, Alberti A. Prevalence and incidence of cholecystolithiasis in cirrhosis and relation to the etiology of liver disease. *Digestion* 1997; 58: 293-8. [\[CrossRef\]](#)
20. Kishk SM, Darweesh RM, Dodds WJ, et al. Sonographic evaluation of resting gallbladder volume and postprandial emptying in patients with gallstones. *AJR Am J Roentgenol* 1987; 148: 875-9. [\[CrossRef\]](#)
21. Pomeranz IS, Shaffer EA. Abnormal gallbladder emptying in a subgroup of patients with gallstones. *Gastroenterology* 1985; 88: 987-91.
22. Baxter JN, Grime SJ, Critchley M, Shields R. Relationship between gastric emptying of solids and gallbladder emptying in normal subjects. *Gut* 1985; 26: 342-51. [\[CrossRef\]](#)
23. Tsai SC, Kao CH, Huang CK, Wang SJ, Chen GH. Abnormal gastric emptying in patients with liver cirrhosis. *Kaohsiung J Med Sci* 1996; 12: 285-9.
24. Balan KK, Grime S, Sutton R, Critchley M, Jenkins SA. Abnormalities of gastric emptying in portal hypertension. *Am J Gastroenterol* 1996; 91: 530-4.
25. Elta GH. Motility and dysmotility of the biliary tract and sphincter of Oddi. In: Feldman M, Friedman LS, Sleisenger MH, ed. *Sleisenger and Fordtran's gastrointestinal and liver disease*. 7th ed. Philadelphia: Saunders; 2002.p.1043-8.
26. Hendriksen MT, Thuluvath PJ, Triper DR. Natural history of autonomic neuropathy in chronic liver disease. *Lancet* 1992; 13: 1462-4. [\[CrossRef\]](#)
27. Bajaj BR, Agarwal MP, Kristina Ram B. Autonomic neuropathy in patients with hepatic cirrhosis. *Postgrad Med J* 2003; 79: 408-11. [\[CrossRef\]](#)