Relation of abnormal gallbladder arterioles to gallbladder emptying in patients with gallstone and diabetes mellitus

Xiong Ding, Jian-Ping Gong, Chang-You Lu, Chang-An Liu, Yu-Jun Shi and Gen-Wu Gao

Chongqing, China

BACKGROUND: **Diabetes mellitus is thought to be related to gallstone formation in emptying the gallbladder. Diabetes mellitus may lead to many changes in microarterioles and micronerves; the aim of this study was to investigate the abnormality of arterioles in the gallbladder and its relation to gallbladder hypomotility in patients with gallstone and diabetes mellitus.**

METHODS: **Thirty patients with simple gallstones and 30 patients with gallstones and diabetes mellitus were analyzed, and their gallbladder emptying function was measured with B ultrasound before operation. After operation, the arterioles of the gallbladder rinsed with periodic acid-schiff (PAS) reagent in photos were used for analysis of the tublar area and stereo system with the Beihang CM-2000B biological and medical photo system.**

RESULTS: **In patients with gallstones and diabetes mellitus, the gallbladder emptying function was significantly impaired, the area ratio of the arteriole wall to whole arterioles in cross section was significantly higher than that in patients with simple gallstones (0.81 ± 0.09 vs. 0.58 ± 0.15, $P < 0.01$), and the average sound density was also higher (0.41 ± 0.07 vs. 0.30 ± 0.12, $P < 0.01$) in patients with gallstones and diabetes mellitus than in those with simple gallstones. The size of arterioles (diameter) was not significantly related to the area ratio ($P > 0.05$).**

CONCLUSION: **In patients with diabetes mellitus, the sedimentation of PAS positive material in the wall of arterioles leads to the stenosis of arterioles. It is probably contributive to hypomotility of the gallbladder.**

(***Hepatobiliary Pancreat Dis Int 2004*; *3*: *275-278*)

KEY WORDS: **gallstone; diabetes mellitus; arterioles; gallbladder motility**

Introduction

Gallstones associated with diabetes mellitus are common in China with an incidence of cholelithiasis of 10% in a population detected by B ultrasound, of whom 50% are gallstone patients. The incidence of cholelithiasis is three-fold that of diabetes mellitus in a population.[1] Gallstone formation is related to many cases, in which the impaired emptying function owing to hypomotility of the gallbladder is considered an important factor for the development of gallstone.[2-4] Because of hypomotility and lowered emptying function, the incidence of gallstone is higher in patients with diabetes mellitus than in other population. Untill now, the study of relation between diabetes mellitus and gallstone was mainly dependent on the volume of the gallbladder detected by ultrasound.[5,6] But the mechanism of the high incidence especially in the microstructure and molecular level remains unknown. The aim of this study was to recognize the cause or mechanism of gallbladder hypomotility in patients with diabetes mellitus from the view-point of the change of arterioles.

Methods

Patients

Thirty patients with gallstones served as controls. They were 13 men and 17 women, aged on average 41.2 years (range 32-69 years). Other 30 patients with gallstones associated with diabetes mellitus were included in the study group. They were 14 men and 16 women, aged on average 39.8 years (range 35-67 years). In all patients, hyperlipoidemia and hypertension were ruled out.

Test of gallbladder emptying function

B ultrasound was employed to measure the maximal or average length (L), width (W) and diameter (D) of the gallbladder twice in fasting and 2 hours after eating respectively. Dodds' method[7] was used to calculate the volume of the gallbladder: $V = \pi/6 \times L \times W \times D$. The fasting volume of the gallbladder was V_0, and the 2-

Author Affiliations: Department of Hepatobiliary Surgery, Second Clinical College, Chongqing University of Medical Science, Chongqing 400010, China (Ding X, Gong JP, Lu CY, Liu CA, Shi YJ and Gao GW)

Corresponding Author: Xiong Ding, MD, Department of Hepatobiliary Surgery, Second Clinical College, Chongqing University of Medical Science, Chongqing 400010, China (Tel: 86-23-63784175; Fax: 86-23-63711527; Email: dingpanda@163.com)

hour volume after eating was V_2. The ejection volume of bile juice was calculated with $EV=V_0-V_2$. The index of gallbladder emptying 2 hours after eating was: $GBEF_2$ (%)=$(1-V_2/V_0)\times100\%$.

Analysis of arterioles in the gallbladder wall

Sections of gallbladders in two groups were analyzed pathologically and rinsed by periodic acid-schiff (PAS) reagent. Photos were taken in constant-fold with an optic microscope, and input into a computer. Thirty photos were selected for analysis of the tublar area and stereo system with the Beihang CM-2000B biological and medical photo system in the two groups respectively. The area ratio of the arteriole wall to the whole area in each cross section and the average sound density of the arteriole wall were obtained.

Statistical analysis

Quantitative variables were expressed as mean±standard deviation. The computer software SAS8.0 was used in the analysis of variance and linear regression.

Results

Function of gallbladder emptying

Compared with the control group, V_0[(59.3±0.6) ml^3 vs. (37.9±5.4) ml^3] and V_2[(44.7±6.6) ml^3 vs. (14.3±4.9) ml^3] increased significantly ($P<0.01$), whereas EV[(14.5±7.1) ml^3 vs. (23.4±9.3) ml^3] and $GBEF_2$(%) [(24.9±12.7) vs. (61.5±8.5)] decreased significantly ($P<0.01$) in the study group (Table 1).

Changes of thickness in the arteriole wall

In the control group, the wall and cavity of arterioles changed insignificantly (Fig. 1); but their thickness of wall was increased and their cavity narrowed both significantly in the study group (Fig. 2). The tuberlar cavity was analyzed in the two groups (Table 2 and Fig. 3). The area ratio of arteriole wall to the whole arterioles in each cross section (0.81±0.09) in the study group was higher than that in the control group (0.58±0.15) ($P<0.01$). Analysis of the area ratio and the size of arterioles (diameter) with linear regression showed no significant difference ($P>0.05$).

Table 1. The variables of gallbladder emptying function (mean±SD)

Variables	Control group	Study group
V_0(ml^3)	37.9±5.4	59.3±0.6 *
V_2(ml^3)	14.3±4.9	44.7±6.6 *
EV (ml^3)	23.4±9.3	14.5±7.1 *
$GBEF_2$(%)	61.5±8.5	24.9±12.7 *

*: compared with the control group, $P<0.01$.

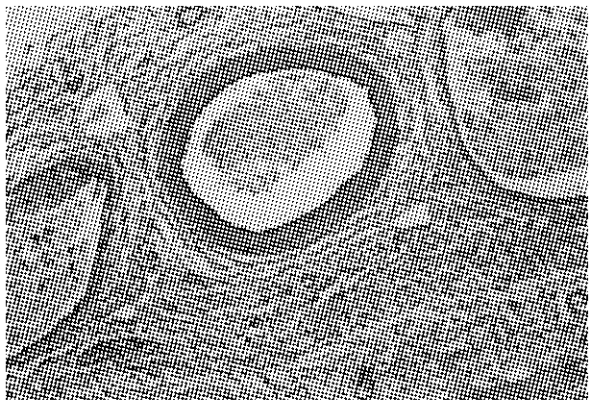

Fig. 1. The cavity and wall of arterioles were not significantly changed in patients with simple gallstones (PAS, original magnification×100).

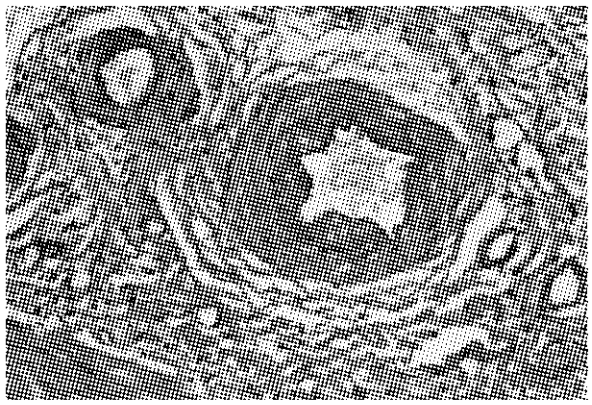

Fig. 2. The thickness of arteriole wall was higher and the cavity narrowed in patients with gallstones associated with diabetes mellitus (PAS, original magnification×100).

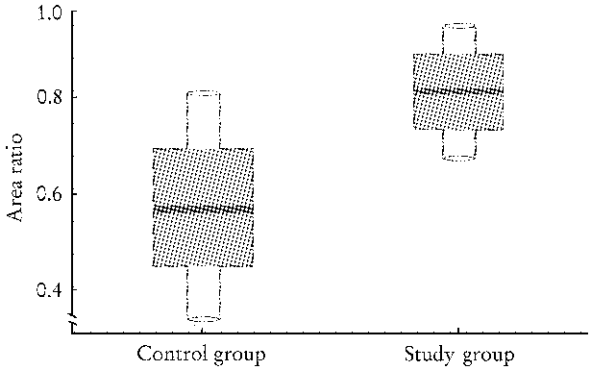

Fig. 3. The area ratio of arteriole wall to whole arterioles in each cross section.

Changes of average sound density in the arteriole wall

Table 2. The analysis of the tublar area and stereo system in the two groups (mean±SD)

Group	The area ratio of wall to the whole arterioles in each cross section	Size of arterioles (μm)	Average sound density
Control	0.58±0.15	37.44±15.87#	0.30±0.12
Study	0.81±0.09*	37.39±20.69##	0.41±0.07**

*: compared with control group, F=52.57, P<0.001; **: compared with control group, F=33.19, P<0.001; compared with the area ratio in the same group; #: F=1.15, P>0.05; ##: F=3.04, P>0.05.

Thirty photos rinsed with PAS reagent were selected from the two groups respectively. The average sound density in the study group (0.41±0.07) was higher than in the control group (0.30±0.12) (P<0.01, Table 2).

Discussion

Impaired gallbladder emptying function has been observed in the formation of gallstone and the hypomotility of the gallbladder has been regarded as the main cause of impaired gallbladder emptying.[8-10] Because of the stasis of bile juice, the bilirubin concentration is inevitably higher when gallbladder emptying is lowered, thus resulting in hypersaturation of cholesterol, and deposition of micropellet and bacteria development in the bile duct, which contribute to the formation of gallstone.[11] In the study of gallbladder wall in vitro, Carey[12] found the common hypomotility in patients with gallstone, which was consistent with the increased gallbladder volume in fasting and residual conditions of gallstone patients.

Many evidence has proved the correlation between diabetes mellitus, dependence of insulin, abnormal metabolism of fat, and gallstone formation.[13-17] The correlation is evident between the degree of gallbladder hypomotility and the duration of diabetes mellitus;[3] it is more serious in patients with abnormality of the automatic nervous system.[18] Cisapride is a prokinetic drug for diseases of the gastrointestinal tract and can lower evidently the volume of the gallbladder in patients with diabetes mellitus and shorten the time of gallbladder emptying.[19] Moreover, the research into gallbladder motility with γ sonography has found that the contractility of the gallbladder decreases significantly, and more significantly in patients with abnormality of arterioles and the automatic nervous system. The degree of the disease is consistent with the abnormality of motility.[20,21] In our research, the gallbladder volume after fasting and two hours after eating was larger in patients with gallstones associated diabetes mellitus than in those with simple gallstones, in addition to the lowered ejection of bile. These findings proved that the contractility of the gallbladder lowered more evidently.

The mechanism of lowered gallbladder contractility has not been elucidated in patients with diabetes mellitus, and their cholesterol sedimentation in the gallbladder probably originates from the hypomotility of the gallbladder or bile stasis.[22] In patient with diabetes mellitus, abnormal metabolism of fat can lead to hypercholesterolemia and changes of microarterioles and the automatic nervous system. In our study, the thickness of arteriole wall and the average sound density after rinsing with PAS reagent increased evidently, proving that the change of microarterioles is mainly due to the sedimentation of PAS positive material in the wall of arterioles, resulting in narrowed cavity, lowered blood supply, and impaired nutrition, which contribute to gallbladder hypomotility.

Acknowledgment

We are indebted to Ying Ma, Zhi Leng, Guang-Zhi Tan from the Department of Pathology, Second Clinical College, Chongqing University of Medical Science, Chongqing and Ge Xu, Xiao-Gang Liao, Zi-Guo Luo from Basic Medical College, Chongqing University of Medical Science, Chongqing, China for their invaluable help.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References

1 Chapman BA, Wilson IR, Frampton CM, Chisholm RJ, Stewart NR, Eagar GM, et al. Prevalence of gallbladder disease in diabetes mellitus. Dig Dis Sci 1996;41:2222-2228.
2 Pagliarulo M, Fornari F, Fraquelli M, Zoli M, Giangregorio F, Grigolon A, et al. Gallstone disease and related risk factors in a large cohort of diabetic patients. Dig Liver Dis 2004;36:130-134.
3 Fraquelli M, Pagliarulo M, Colucci A, Paggi S, Conte D. Gallbladder motility in obesity, diabetes mellitus and coeliac disease. Dig Liver Dis 2003;35:S12-16.
4 Chen CY, Lu CL, Lee PC, Wang SS, Chang FY, Lee SD. The risk factors for gallstone disease among senior citizens: an Oriental study. Hepatogastroenterology 1999;46:1607-1612.
5 Arslanoglu I, Unal F, Sagin F, Isguven P, Isik K. Real-time sonography for screening of gallbladder dysfunction in children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2001;14:61-69.
6 Portincasa P, Colecchia A, Di Ciaula A, Larocca A, Muraca M, Palasciano G, et al. Standards for diagnosis of gastrointestinal motility disorders. Section: ultrasonography. A position statement from the Gruppo Italiano di Studio Motilita Apparato Digerente. Dig Liver Dis 2000;32:160-172.
7 Dodds WJ, Groh WJ, Darweesh RM, Lawson TL, Kishk SM, Kern MK. Sonographic measurement of gallbladder volu-

me. Am J Roentgenol 1985;145:1009-1011.
8 Acalovschi M, Dumitrascu DL, Nicoara CD. Gallbladder contractility in liver cirrhosis: comparative study in patients with and without gallbladder stones. Dig Dis Sci 2004;49:17-24.
9 Sato N, Miyasaka K, Suzuki S, Kanai S, Ohta M, Kawanami T, et al. Lack of cholecystokinin-A receptor enhanced gallstone formation: a study in CCK-A receptor gene knockout mice. Dig Dis Sci 2003;48:1944-1947.
10 Shuai J, Zhang S, Han T, Jiang Y, Lei R, Chen S. Correlation between gene expression of CCK-A receptor and gallbladder emptying in gallstone patients. Zhonghua Wai Ke Za Zhi 1999;37:292-294.
11 Lu Y, Xiang TH, Shi JS, Zhang BY. Bile anaerobic bacteria detection and antibiotic susceptibility in patients with gallstone. Hepatobiliary Pancreat Dis Int 2003;2:431-434.
12 Carey MC. Pathogenesis of gallstones. Am J Surg 1993;165:410-449.
13 Stone BG, Gavaler JS, Belle SH, Shreiner DP, Peleman RR, Sarva RP, et al. Impairment of gallbladder emptying in diabetes mellitus. Gastroenterology 1988;95:170-176.
14 Tran KQ, Goldblatt MI, Swartz-Basile DA, Svatek C, Nakeeb A, Pitt HA. Diabetes and hyperlipidemia correlate with gallbladder contractility in leptin-related murine obesity. J Gastrointest Surg 2003;7:857-862.
15 Misciagna G, Guerra V, Di Leo A, Correale M, Trevisan M. Insulin and gall stones: a population case control study in southern Italy. GUT 2000;47:144-147.
16 Ruhl CE, Everhart JE. Association of diabetes, serum insulin, and C-peptide with gallbladder disease. Hepatology 2000;31:299-303.
17 Sasazuki S, Kono S, Todoroki I, Honjo S, Sakurai Y, Wakabayashi K, et al. Impaired glucose tolerance, diabetes mellitus, and gallstone disease: an extended study of male self-defense officials in Japan. Eur J Epidemiol 1999;15:245-251.
18 Gaur C, Mathur A, Agarwal A, Verma K, Jain R, Swaroop A. Diabetic autonomic neuropathy causing gallbladder dysfunction. J Assoc Physicians India 2000;48:603-605.
19 Gursoy M, Guvener N, Isiklar I, Tutal E, Ozin B, Boyacioglu S. The effect of cisapride on gallbladder contractility in type II diabetic patients. Hepatogastroenterology 2001;48:1262-1265.
20 Hahm JS, Park JY, Park KG, Ahn YH, Lee MH, Park KN. Gallbladder motility in diabetes mellitus using real time ultrasonography. Am J Gastroenterol 1996;91:2391-2394.
21 Varkonyi TT, Lengyel C, Madacsy L, Velosy B, Kempler P, Fazekas T, et al. Gallbladder hypomotility in diabetic polyneuropathy. Clin Auton Res 2001;11:377-381.
22 Kayacetin E, Kisakol G, Kaya A, Akpinar Z. Real-time sonography for screening of gallbladder motility in diabetic patients: relation to automatic and peripheral neuropathy. Neuroendocrinol Letters 2003;24:73-76.

Received January 31, 2004
Accepted after revision March 24, 2004