

# Long-Term Ursodeoxycholic Acid Therapy Is Associated With Reduced Risk of Biliary Pain and Acute Cholecystitis in Patients With Gallbladder Stones: A Cohort Analysis

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Whether ursodeoxycholic acid (UDCA) therapy alters the long-term clinical course of gallstones (GS) without stone dissolution remains unknown. We aimed to clarify the relationship between long-term UDCA therapy and risks of biliary pain or acute cholecystitis in GS patients. We also aimed to identify factors affecting the natural course, and to explore a simple patient selection criteria for UDCA therapy. A cohort of 527 uncomplicated GS patients with or without UDCA (600 mg/d) followed for up to 18 years was analyzed. Patients who had frequent attacks or were complicated with cholecystitis were converted to cholecystectomy. History and UDCA therapy were identified on Cox analysis as 2 factors affecting the long-term clinical course. In patients without therapy, history was the only predictor of biliary pain among various patient or stone characteristics; biliary pain was rare in asymptomatic patients, while frequent in symptomatic patients ( $P < .001$ ). UDCA therapy was associated with reduced risk for biliary pain in both symptomatic (62% vs. 92% in untreated patients at 10 years;  $P < .001$ ; relative risk, 0.19; 95% CI, 0.10-0.34) and asymptomatic patients (6% vs. 12% in untreated patients at 10 years;  $P = .037$ ; relative risk, 0.19; 95% CI, 0.04-0.91). Risk for the conversion was also reduced in UDCA-treated symptomatic patients (26% vs. 88% in untreated patients at 10 years,  $P < .001$ ; relative risk, 0.08; 95% CI, 0.03-0.22). These effects were independent of stone dissolution. Three factors were identified on Cox analysis as affecting GS dissolution: radiolucency, small size ( $< 10$  mm) of stones, and visualized gallbladder (GB) on cholecystogram. A selection criteria based on these appears to exhibit high sensitivity (74%) and specificity (95%) for dissolution. UDCA therapy might be considered in symptomatic patients fulfilling these criteria, and also in

patients who have significant surgical risk, because the long-term therapy is clearly associated with reduced risk of biliary pain and acute cholecystitis. (HEPATOLOGY 1999;30:6-13.)

The natural course of gallstone (GS) disease is critically important in making decisions about its treatment.<sup>1-4</sup> The development of biliary pain (biliary colic) and further complication of acute cholecystitis are the primary problems. Historical series have yielded controversial results on the risk factors.<sup>5-7</sup> More recent studies have suggested significance of history of biliary pain,<sup>8-12</sup> but some claimed other risk factors (i.e., gender, characteristics of GS) for the development of symptoms.<sup>9,13,14</sup> No long-term prospective study, which systematically examines the risk factors for the GS attack by multiple regression analysis, is available.

Bile acid therapy (BAT) using chenodeoxycholic acid<sup>15-17</sup> or ursodeoxycholic acid (UDCA)<sup>18-30</sup> has been widely performed as safe nonsurgical therapy of GS. In addition, several studies have suggested that BAT may inhibit GS-related symptoms,<sup>21-23,31,32</sup> independent of GS dissolution. These reports have been received with some skepticism because of the variable effort to differentiate symptoms consistent with biliary colic or acute cholecystitis from other nonspecific symptoms.<sup>25</sup> On the other hand, the National Cooperative Gallstone Study<sup>16</sup> and another study<sup>17</sup> have demonstrated that chenodeoxycholic acid does decrease the nonspecific symptoms, but not the rates of biliary pain or conversion to surgery. The duration in these studies was short, and the indication criteria for conversion to surgery was not clear. Therefore, whether BAT can alter the long-term clinical course (development of biliary pain and complication) in GS patients still remains unknown.<sup>22,25</sup>

Furthermore, since the introduction of highly effective laparoscopic cholecystectomy, more strict indication of BAT has been proposed,<sup>1-3</sup> because of the low successful dissolution rates (30%-40%) with the high recurrence rates. Multiple characteristics of GS and gallbladder (GB) on either plain x-ray,<sup>33-35</sup> oral cholecystography (OCG),<sup>33,34</sup> ultrasound (US),<sup>35-37</sup> computer-assisted tomography (CAT)<sup>38,39</sup> or GB function,<sup>40</sup> have been *independently* compared with the primary outcome of BAT. These examinations, however, have not been *simultaneously* tested on multivariate analysis.

In the present cohort study, we had the following 3 aims: first, to identify factors affecting the natural course of GS, second, to clarify whether UDCA therapy is associated with altered clinical course of GS; and third, to explore a simple yet sufficient selection criteria for UDCA therapy, in the era of laparoscopic cholecystectomy.

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Abbreviations: GS, gallstone; BAT, bile acid therapy; UDCA, ursodeoxycholic acid; GB, gallbladder; OCG, oral cholecystography; US, ultrasonography; CAT, computer-assisted tomography.

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## PATIENTS AND METHODS

**Patients and Study Design.** A total of 527 consecutive patients with uncomplicated cholecystolithiasis who were diagnosed in the Tsukuba University Hospital between January 1976 to December 1994 were studied. The entry criteria included: 1) US (3.75-MHz convex-array transducer, SAL-100, SSA-240, Toshiba, Tokyo, Japan) diagnosis of cholecystolithiasis, 2) absence of severe symptoms or features (fever  $>37.5^{\circ}\text{C}$ , leukocytosis, elevated biliary enzymes or US findings) suggestive of complications such as acute cholecystitis, choledocholithiasis, or GB cancer, and 3) no history of any drug therapy (including UDCA) during the previous 6 months. These entry criteria resulted in a cohort of uncomplicated GS patients. The entry date was defined as the date of US diagnosis.

Biliary pain or biliary colic was clinically defined according to previously adopted criteria.<sup>8,11,13</sup> Briefly, the patients were asked whether they had experienced any episode of intense upper abdominal pain. If the answer was yes, whether the pain was GS-origin (biliary colic) was assessed by at least 2 expert gastroenterologists, from the location (epigastric or right hypochondriac), the episodicity (sudden onset without warning), the duration (a plateau lasting more than 20 minutes before gradual resolution), and the severity (severe enough for the patient to remember) of the pain. Symptoms not fulfilling these criteria were regarded as nonspecific. Patients who presented with a history of at least 1 episode of biliary pain before entering the study were designated as symptomatic GS, while those with no history of biliary pain or with history of only nonspecific symptoms were designated as asymptomatic GS patients.<sup>8,11,13</sup>

The characteristics of all patients (gender, age, previous experience of biliary pain, UDCA administration), GS (number and maximum diameter on US, radiolucency on plain x-ray), and GB (visualization of the GB on OCG) were recorded. When the GS almost or completely filled the GB, they were categorized into a large-stone group, because their size could not be precisely measured in such cases.

**UDCA Therapy and Follow-up Procedure.** Basic information regarding the UDCA therapy was given to all enrolled patients. These included poor successful dissolution rate by short-term administration (20%-30% in 2-years), and possible, but unproven, beneficial effects on the development of biliary pain. The decision of whether to receive the long-term UDCA therapy was based solely on the patient's preference; those who agreed received oral administration of 600 mg (200 mg 3 times) of UDCA per day. Those who refused had the same follow-up as the UDCA-treated patients. The baseline characteristics were similar in the 2 groups.

All patients were followed up regularly at the Tsukuba University Hospital. The development of any abdominal pain was asked about and recorded when they visited the hospital every 1 or 2 months, or alternatively, this was performed by regular telephone interview. In addition, the patients were asked to come in when they experienced typical biliary pain. The US examination and the testing of complete blood counts and serum hepatobiliary enzymes were performed every 6 months, or alternatively, at shorter intervals if the biliary pain emerged. The number and the size of GS as well as the development of complications, such as acute cholecystitis (leukocytosis, elevated enzymes, and typical US findings), choledocholithiasis, or biliary malignancy were assessed based on these examinations. When the GS disappeared in patients receiving UDCA therapy, US was re-examined 1 month later by another gastroenterologist to confirm the complete GS dissolution. The development of the above complications, or frequent (more than twice) biliary colic, constituted the clinical indication of cholecystectomy, and those who met this criteria were referred to surgeons. Other patients who preferred cholecystectomy without complications or frequent attacks also received elective cholecystectomy, but they were regarded as withdrawn.

**End-point.** The end-points for the present study were: 1) development of biliary pain, 2) clinically indicated cholecystectomy (chole-

cystitis, choledocholithiasis, or frequent biliary pain), and 3) complete GS dissolution. The observation period was calculated from the date of entry until the end-point or the end of the observation period, which was updated on December 31, 1995.

**Statistical Analysis.** Differences between proportions and means were assessed by the  $\chi^2$  test with Yates correction and Student's *t* test. Cox proportional hazard regression model<sup>41</sup> was used to analyze potential risk factors for the development of biliary colic or cholecystectomy (age, gender, UDCA therapy, number, maximum size, and radiolucency of GS, visualization of GB on OCG), and to analyze factors affecting the dissolution of GS (age, gender, UDCA therapy, number, maximum size, and radiolucency of GS, visualization of GB on OCG). Life-table analysis was performed according to the method of Kaplan and Meier.<sup>42</sup> The difference in curves was tested using the log rank test.  $P < .05$  was regarded as statistically significant.

## RESULTS

Five hundred twenty-seven Japanese GS patients fulfilling the inclusion criteria were followed for  $66.4 \pm 45.3$  months (maximum, 214 months). Among these, 181 patients received UDCA therapy (74 symptomatic and 107 asymptomatic), while 346 patients were followed up with no therapy (112 symptomatic and 234 asymptomatic). No significant difference in the baseline characteristics of patients, GS, and GB was observed between the UDCA group and the no-therapy group (Table 1). The observation period of the symptomatic no-therapy group ( $26.7 \pm 18.7$  months) was significantly ( $P < .01$ ) shorter than those of the symptomatic UDCA group ( $70.5 \pm 47.8$  months), the asymptomatic no-

TABLE 1. Characteristics of GS Patients

	Number (%)		P
	No Treatment (n = 346)	UDCA (n = 181)	
Patient characteristics			
Gender			.90
Male	143 (41)	73 (40)	
Female	203 (59)	108 (60)	
Age (yr)			.06
<40	81 (23)	49 (27)	
$40 \leq <60$	144 (42)	87 (48)	
$\geq 60$	121 (35)	45 (25)	
mean $\pm$ SD	54.3 $\pm$ 12.8	53.4 $\pm$ 13.0	.49
Previous experience of biliary colic			
Yes	112 (32)	74 (41)	.07
No	234 (68)	107 (59)	
GS characteristics			
Number			.09
1	153 (44)	62 (34)	
2-9	106 (31)	64 (35)	
$\geq 10$	87 (25)	55 (31)	
Size			.42
Small*	166 (46)	78 (43)	
Large†	186 (54)	103 (57)	
Radiolucency			
Yes	288 (83)	152 (84)	.93
No	58 (17)	29 (16)	
Gallbladder characteristics visualized on OCG			
Yes	287 (83)	142 (78)	.25
No	59 (17)	39 (22)	

\*Stone diameter  $<10$  mm and not filling GB.

†Stone diameter  $\geq 10$  mm or GB is filled with GS.

therapy group ( $81.7 \pm 51.8$  months), and the asymptomatic UDCA group ( $68.9 \pm 45.3$  months), because of the highest incidence of cholecystitis and subsequent cholecystectomy in this group. None of the patients developed biliary malignancy. Two hundred twenty-nine patients were withdrawn from the study when they received other therapy such as elective (not clinically indicated) cholecystectomy ( $n = 73$ ), extracorporeal shockwave lithotripsy ( $n = 34$ ), other medications or abdominal surgery unrelated to biliary tract disease ( $n = 75$ ), lost to follow-up ( $n = 25$ ), discontinuation of the UDCA therapy ( $n = 12$ , side effects or patients' loss of interest). Forty-one of these withdrawals occurred during the first 12 months of follow-up.

We first analyzed the use of UDCA and other potential confounding factors for the occurrence of biliary pain and the conversion to cholecystectomy on the Cox proportional hazard model. Two factors were identified as significantly affecting the occurrence of biliary pain: the previous experience of GS attack (asymptomatic or symptomatic) and the UDCA administration (UDCA or no-therapy) (Table 2). These two factors were also identified as significant factors affecting the probability of cholecystectomy (Table 3).

**The Natural Course of GS.** We next analyzed 346 patients followed up without UDCA on the Cox hazard model. History of biliary pain (symptomatic or asymptomatic) was identified as the only factor affecting both the risk of biliary pain and of clinically indicated cholecystectomy. Biliary pain was eventually developed in 35 (31%) of the 112 symptomatic patients, whereas it emerged in only 20 (8%) of the 234 asymptomatic patients. The GB was surgically removed in 24 symptomatic patients (21%), while in only 2 asymptomatic patients (0.8%). As shown in Fig. 1, the risk of biliary pain

TABLE 2. Analysis of Factors Affecting the Incidence of Biliary Colic in GS Patients by Cox Proportional Hazard Model

	Hazard Ratio	95% CI	P
Gender			
Female	1.18	0.73-1.88	.496
Male	1		
Age (yr)			
<40	0.72	0.39-1.34	.719
$40 \leq <60$	0.67	0.37-1.18	.666
$\geq 60$	1		
Previous experience of biliary colic			
No	0.029	0.02-0.06	<.001
Yes	1		
UDCA administration			
Yes	0.267	0.15-0.46	<.001
No	1		
GS number			
1	1.29	0.73-2.30	.381
2-9	0.59	0.31-1.08	.534
$\geq 10$	1		
GS size (mm)			
Small*	0.85	0.51-1.41	.852
Large†	1		
GS radiolucent			
Yes	1.25	0.67-2.33	.481
No	1		
GB visualized on OCG			
Yes	1.25	0.67-2.33	.945
No	1		

\*Stone diameter <10 mm and not filling GB.

†Stone diameter  $\geq 10$  mm or GB is filled with GS.

TABLE 3. Analysis of Factors Affecting the Incidence of Clinically Indicated Cholecystectomy in GS Patients by Cox Proportional Hazard Model

	Hazard Ratio	95% CI	P
Gender			
Female	0.86	0.91-1.40	.380
Male	1		
Age (yr)			
<40	0.39	0.13-1.23	.109
$40 \leq <60$	0.58	0.23-1.48	.255
$\geq 60$	1		
Previous experience of biliary colic			
Yes	0.01	0.001-0.02	<.001
No	1		
UDCA administration			
No	0.240	0.04-0.10	<.001
Yes	1		
GS number			
1	0.73	0.27-2.02	.550
2-9	0.99	0.41-2.38	.173
$\geq 10$	1		
GS size (mm)			
Small*	0.99	0.41-2.39	.982
Large†	1		
GS radiolucent			
Yes	1.23	0.41-3.63	.712
No	1		
GB visualized on OCG			
Yes	1.02	0.45-2.33	.963
No	1		

\*Stone diameter <10 mm and not filling GB.

†Stone diameter  $\geq 10$  mm or GB is filled with GS.

was significantly higher in the symptomatic group (line A) than in the asymptomatic group (line C;  $P < .001$  by log rank test); the 2-, 5-, and 10-year cumulative probabilities were 58%, 84%, and 92%, respectively, in the former group, whereas these rates were 2%, 5%, and 12%, respectively, in the latter group. As shown in Fig. 2, the risk of cholecystectomy was significantly higher in the symptomatic group (line A) than in the asymptomatic group (line C;  $P < .001$  by log rank test); the 2-, 5-, and 10-year cumulative probabilities of cholecystectomy were 41%, 78%, and 88%, respectively, in the former group, whereas these rates were 0%, 0%, and 2%, respectively, in the latter group. The relative risk of biliary pain and conversion to cholecystectomy in the asymptomatic group versus the symptomatic group was 0.19 (CI, 0.10-0.34;  $P < .001$ ) and 0.04 (CI, 0.01-0.10;  $P < .001$ ), respectively.

**UDCA Therapy and Risk of Biliary Pain and Cholecystectomy.** We then examined the risk of biliary pain and conversion to cholecystectomy in relation to the UDCA therapy and found a significant association. As shown in Fig. 1, in the symptomatic patients with UDCA therapy, the cumulative probability of biliary pain (14%, 33%, and 62%, at 2, 5, and 10 years, respectively) (line B) was significantly lower compared with the symptomatic no-therapy group (line A;  $P < .001$  by log rank test). Moreover, as shown in Fig. 2, the cumulative probability of cholecystectomy in the symptomatic UDCA group (5%, 11%, and 26%, at 2, 5, and 10 years, respectively) (line B) was significantly lower compared with the no-therapy group (line A;  $P < .001$  by log rank test). The relative risks in the symptomatic UDCA group compared with the no-therapy group were calculated to be 0.19 (CI, 0.10-0.34;

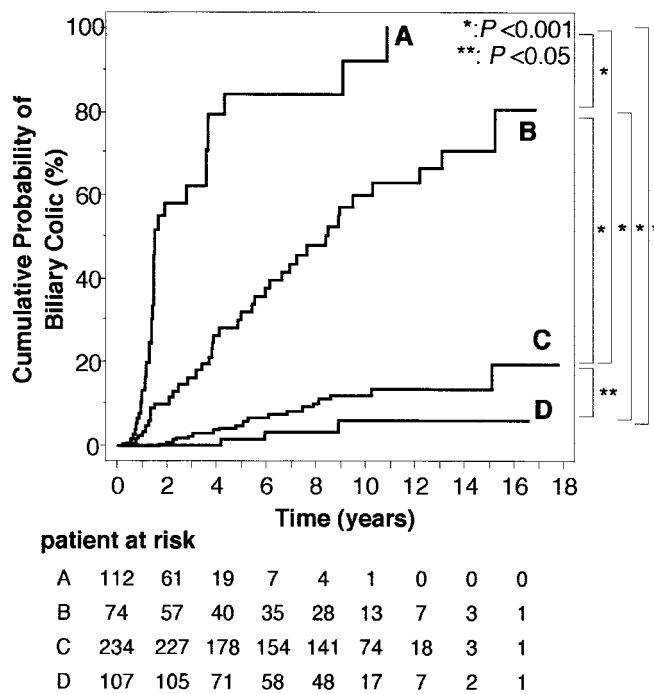


FIG. 1. Cumulative probability of biliary pain in GS patients. The probability of biliary pain was significantly higher in the symptomatic no-therapy group (line A) than in the asymptomatic no-therapy group (line C) ( $P < .001$ ). The probability of biliary pain in the symptomatic UDCA group (line B) was significantly lower than in the symptomatic no-therapy group (line A) ( $P < .001$  by log rank test). Also, the probability of biliary pain in the asymptomatic UDCA group (line D) was significantly lower than in the asymptomatic no-therapy group (line C) ( $P = .048$  by log rank test).

$P < .001$ ) for biliary pain and 0.08 (CI, 0.03-0.22;  $P < .001$ ) for cholecystectomy.

In the asymptomatic patients with UDCA therapy, cumulative probabilities of GS attack (2% and 8% at 5 and 10 years, respectively) (Fig. 1, line D) were significantly lower than in the asymptomatic no-therapy group (Fig. 1, line C) ( $P = .048$  by log rank test). The relative risk of GS attack in the asymptomatic UDCA group to the no-therapy group was 0.19 (CI, 0.04-0.91;  $P = .037$ ). The cumulative probabilities of cholecystectomy were low in asymptomatic GS patients regardless of taking UDCA or not, and no significant difference was observed between the asymptomatic UDCA group (Fig. 2, line D) and the asymptomatic no-therapy group (Fig. 2, line C).

All patients with successful GS dissolution by UDCA did not experience GS attack or surgery, but it seemed that many patients who did not achieve complete GS dissolution also remained pain-free and did not develop overt acute cholecystitis. The Cox analysis was re-examined after excluding those with complete GS dissolution. The relative risks for biliary pain compared with the no-therapy group were still significantly low both in the asymptomatic UDCA group (0.26; CI, 0.14-0.50;  $P < .001$ ) and in the symptomatic UDCA group (0.28; CI, 0.15-0.53;  $P < .001$ ). Also, the relative risks for conversion to surgery compared with the no-therapy group were still significantly low in the symptomatic UDCA group (0.09; CI, 0.03-0.24;  $P < .001$ ). Thus, the UDCA therapy was associated with reduced risks even without GS dissolution.

**Factors Affecting GS Dissolution by UDCA.** Complete GS dissolution was observed in 19 (18 were dissolved within 5

years and 1 thereafter) of the 120 UDCA patients who received regular US examination. Factors affecting complete dissolution of the GS were assessed by a Cox proportional hazard regression analysis. This analysis selected the following 3 conditions as significantly influencing the dissolution of GS in an independent manner: radiolucency on plain x-ray (hazard ratio: 13.05; CI, 1.59-107.0;  $P = .017$ ), opacification of GB on OCG (hazard ratio, 11.09; CI, 1.41-87.41;  $P = .022$ ), and small stone (diameter less than 10 mm and not filling GB) in US (hazard ratio, 13.15; CI, 3.35-51.65;  $P < .001$ ) (Table 4).

The cumulative dissolution rates for patients who fulfill all of these 3 conditions ( $n = 19$ ) displayed satisfactory cumulative dissolution rates (32%, 57%, and 75%, respectively, at 1, 2, and 5 years), whereas those who do not showed very low dissolution rates (0%, 4%, and 8%, respectively, at 1, 2, and 5 years;  $P < .001$ ). Therefore, it was considered that these 3 conditions constitute a reasonable primary selection criteria for UDCA therapy. The sensitivity, specificity, and overall accuracy of the primary selection criteria for the GS dissolution were 74%, 95%, and 92%, respectively.

DISCUSSION

**Association of UDCA Therapy With Reduced Risk of Biliary Pain and Complication.** The main new findings in the present study regard the relationship between the long-term use of UDCA and the clinical course of uncomplicated GS patients. On the multivariate analysis with other potential confounding fac-

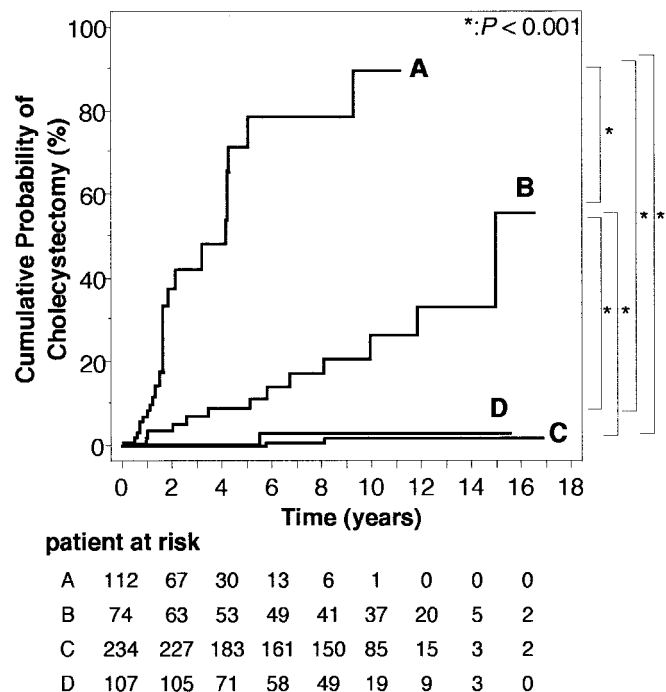


FIG. 2. Cumulative probability of clinically indicated cholecystectomy. The probability of clinically indicated (frequent attacks or clinical evidence of acute cholecystitis) cholecystectomy was significantly ( $P < .001$ ) higher in the symptomatic no-therapy group (line A) than in the asymptomatic no-therapy group (line D). The probability of cholecystectomy was significantly ( $P < .001$ ) lower in the symptomatic UDCA group (line B), compared with the symptomatic no-therapy group (line A). The probability of cholecystectomy was low in asymptomatic GS patients regardless of taking UDCA or not, and no significant difference was observed between the UDCA group (line D) and the no-therapy group (line C).

TABLE 4. Factors Affecting Dissolution With UDCA Therapy Analyzed by a Cox Proportional Hazard Model

	Hazard Ratio	95% CI	P
Gender			
Female	2.93	0.91-9.31	.072
Male	1		
Age (yr)			
<40	2.03	0.40-10.21	.389
40 ≤ <60	0.52	0.09-2.86	.452
≥60	1		
Previous experience of biliary colic			
Yes	0.43	0.11-9.09	.219
No	1		
GS number			
1	0.78	0.22-2.78	.707
2-9	0.39	0.06-2.50	.319
≥10	1		
GS radiolucent			
Yes	13.05	1.59-107.0	.017
No	1		
GS size (mm)			
Small*	13.15	3.35-51.65	<.001
Large†	1		
GB visualized on OCG			
Yes	11.09	1.41-87.41	.022
No	1		

\*Stone diameter <10 mm and not filling GB.

†Stone diameter ≥10 mm or GB is filled with GS.

tors, the use of UDCA was found to be associated with reduced risk for the development of biliary pain and acute cholecystitis; the association seems to be significant both statistically ( $P < .001$ ) and clinically (relative risk <0.3), regardless of whether or not complete GS dissolution is achieved. We are not aware of previous reports studying the relationship between any drug use and the long-term clinical course of GS, but such an observational (pharmacoepidemiological) approach emerged as a realistic way to examine long-term effects of various drugs; for instance, the chemopreventive effect of aspirin on certain gastrointestinal cancers has been established primarily by several case-control and cohort series.<sup>43,44</sup>

The UDCA group and the control (no-therapy) group were well matched in terms of various patient characteristics at enrollment (Table 1). The UDCA group exhibited significantly lower incidence of biliary pain than the no-therapy group. Furthermore, the UDCA-treated symptomatic GS patients experienced a lower conversion rate to cholecystectomy than the no-therapy group. This reflects that a single episode of biliary pain is neither followed by frequent attacks nor development of cholecystitis that necessitates surgical intervention in many UDCA-treated patients. In the case of asymptomatic GS, few patients required surgery, and probably because of this, no statistical difference in the conversion rate was observed between those with and without UDCA therapy. Altogether, these data documented that long-term UDCA therapy is associated with reduced risk of GS attack and subsequent complication of acute cholecystitis, especially in symptomatic patients, independent of complete stone dissolution.

The limitations of our study relate to potential bias and restraints set by nonrandomized study. First, ascertainment bias must be assessed; pain or complications are more likely

to be found during frequent visits to the clinic when patients receive greatest medical attention. This does not seem to be an issue here, because our UDCA group had lower incidence of pain and cholecystitis, despite more frequent visits to our clinic, than the no-therapy group. Also, we did not treat our symptomatic patients with other drugs, such as nonsteroidal anti-inflammatory drugs that inhibit the development of complication.<sup>45</sup> Furthermore, classification bias as well as placebo effects are also not likely to be involved, because we used strict criteria for the diagnosis of biliary pain and cholecystitis, excluding borderline or mild signs and symptoms. Finally, selection bias, the possibility that the patients who are not likely to develop pain and complications somehow have chosen the UDCA therapy must be considered, which is common in observational studies. Against this bias is the higher proportion of the history, a known confounder, in the UDCA group (Table 1) and independence of the UDCA therapy from the history in the Cox analysis. Other potential confounders, such as age, sex, and duration of follow-up, were also adjusted for by the Cox analysis. However, there is always a potential problem with confounders not recognized by us.

To confirm our new findings, we have planned a randomized trial, but we could not enroll a sufficient number of patients, because many had their preference and refused to accept randomization. Sondena et al.<sup>46</sup> recently encountered similar problems in their failed randomized trial aimed at comparing the outcome of surgery or observation in symptomatic GS. Plaisier et al.<sup>47</sup> also reported that patients' preference did not allow them to complete a randomized trial for extracorporeal shockwave lithotripsy or cholecystectomy in GS patients. Carefully designed randomized trials that also consider patients' preference may fill this gap between randomization and patients' preference,<sup>48</sup> but even those trials do not seem to be feasible because of long duration, large sample size, and great cost.<sup>44</sup> At the least, sufficient observational data must be accumulated first. Therefore, further observational (case-control or cohort) studies of larger size seem to be preferable to confirm our observation.

How UDCA administration reduces the emergence of biliary pain without complete GS dissolution is of particular interest. Biliary pain is generally believed to occur as a result of mechanical obstruction of cystic duct or common bile duct by GS, microlith, or sludge.<sup>1</sup> GB biles from cholesterol GS patients almost always contain cholesterol crystals or microlith,<sup>49</sup> and it has been shown that these crystals are causally related to the occurrence of acute pancreatitis with or without GS.<sup>50</sup> We recently observed that cholesterol crystals are more frequently detected in duodenal biles from symptomatic than those from asymptomatic GS patients, and that these incidences dramatically decrease in patients receiving UDCA therapy (Abei M, unpublished observation, May 1998). From these, we consider that dissolution of cholesterol microlith or crystals is the most likely mechanism for the low biliary pain incidence in UDCA-treated patients. The suppressive effect of UDCA on GB contractility probably plays an additional role.<sup>51,52</sup> Furthermore, anti-inflammatory effects (inhibiting arachidonic acid-cascade and eicosanoid production<sup>53</sup>) or immunomodulatory action<sup>54,55</sup> of UDCA probably have contributed to the decreased rate of conversion to surgery as a result of cholecystitis.

**The Natural Course of GS Patients.** Our study also identified history of biliary pain as another factor significantly affecting

the clinical course of uncomplicated GS. Patients who have experienced biliary colic (symptomatic GS) are likely to repeat such episodes, while the majority of those who presented without such experience (asymptomatic GS) will remain free of pain. This confirms previous studies without multivariate analysis.<sup>5-12</sup> Furthermore, the history was found to be the *only* significant risk factor for biliary pain in the patients without UDCA therapy (natural course). No other characteristics of patients or GS were found to be of value in predicting the risk for biliary pain. Some previous studies noted gender as another risk factor, with women having more frequent symptoms than men.<sup>6,12,14</sup> Although our patients also showed such tendency (Tables 2 and 3), more women initially presented as symptomatic GS than men, and probably because of this, gender was not found to be a significant independent factor when the history was included in the multivariate analysis (Tables 2 and 3). Multiple GS as opposed to solitary GS has been suggested as another risk factor in 1 study,<sup>9</sup> but not in another.<sup>56</sup> Our data did not confirm this. We also found that the conversion rate to cholecystectomy is much higher in symptomatic than in asymptomatic patients. These results support the NIH consensus development conference statement, which recommends treatments for symptomatic cases, but not for asymptomatic cases in general.<sup>57</sup>

Symptoms other than typical biliary pain, such as painless dyspepsia, were excluded from our study. Although some investigators included dyspepsia as GS-related,<sup>31,32</sup> this has been shown to be not more frequent in GS patients than in the general population, and its presence is not an indication for treatment.<sup>2,3,8,11,13</sup> Also, it has been pointed out that tendency of patients to report such atypical or nonspecific symptoms changes from time to time and is thus difficult to analyze scientifically.<sup>4</sup>

None of our patients developed biliary malignancy. According to large-scale prospective data by Maringhini et al.,<sup>58</sup> the risk of GB cancer in GS patients is threefold higher than in those without GS, but still remains as low as 0.1% per year in North America. The prevalence of biliary malignancies is reportedly higher in Japan than in Western countries, but this is probably related to the higher incidence of other premalignant conditions such as anomalous junction of the pancreatobiliary duct in Japan. Although the precise risk in Japanese GS patients awaits a larger prospective study, our data at least do not justify prophylactic cholecystectomy.

In the present study, we focused on clinical indices that can be obtained in general before making a decision about treatments and did not compare with composition of GS. About 15% to 20% of GB stones in Japan are pigment stones, according to GS composition data from our previous study as well as from other institutes. Differences in stone composition may affect the risks for biliary pain and/or cholecystitis, and also the efficacy of UDCA to alter those risks. These issues await further studies (cross-sectional or retrospective studies) comparing the stone composition and the history of patients.

**Primary Patient Selection for UDCA Therapy.** Based on a simple correlation with the GS dissolution rate, small size, radiolucency of GS, and reserved GB function have been listed as indication criteria for UDCA therapy.<sup>1-3,29</sup> Our Cox multivariate analysis has shown that these are the 3 independent factors that significantly affect the outcome of the

therapy, from which reasonable primary selection criteria for UDCA therapy can be formed.

Small GS (maximum size less than 10 mm) not filling the GB on US appears to be a requirement for the UDCA therapy. Size rather than number of stones is the primary determinant of the dissolution rate.<sup>19,20,24,27,29,30</sup> GS smaller than 5 mm shows a better dissolution rate than those exceeding 5 mm<sup>19,20,24</sup> and are superoptimal. If GS of 5 to 10 mm in size were excluded, however, the sensitivity of the selection criteria for successful dissolution decreases. Cox analysis supported that GS ranging from 5 to 10 mm in size are also optimal candidates, provided that they are radiolucent, not filling the GB, and the GB is visualized on OCG.

Radiolucency on x-ray (GS factors), which has been adopted in most previous reports, was found to be another requirement. Several reports have suggested additional use of more sensitive CAT.<sup>38,39</sup> These reports cannot be directly compared with ours, because they did not include data of plain x-ray, US, or OCG, while we did not perform pretreatment CAT examination in many patients. Our selection criteria not including CAT gave us high accuracy (92%) for predicting the outcome. We speculate that this is because a substantial number of mildly calcified GS, which would have been detected only by CAT, was excluded in our criteria because of concomitant nonvisualized GB on OCG or large GS size on US. Supporting this view is the fact that the acidification of bile by the GB mucosa (mediated by the Na<sup>+</sup>-H<sup>+</sup> exchanger) is specifically impaired in patients with calcified GS, suggesting that GS calcification is associated with impaired GB mucosal function.<sup>59,60</sup> It is also true that calcified cholesterol GS is often larger than 10 mm in size.

Well-visualized GB on OCG (GB factor) was found as the third essential condition. Although its frequency has declined after wide use of US, OCG is valuable in evaluating the cystic duct patency, the GB concentrating function, and the presence of GS calcification. If GS smaller than 10 mm, not filling the GB, were found on US in a patient with a history of typical attack, OCG should probably be performed next. Brakel et al.<sup>37</sup> claimed that OCG should be performed secondary to US, unless US demonstrates a contracted GB or stone impaction in cystic ducts that is predictive of nonvisualized GB on OCG. Others<sup>40</sup> have suggested that evaluation of GB motor function by US might have similar value as OCG in selecting patients for BAT. The role of testing GB contractility or CAT must be examined further, in view of the satisfactory predictive value of our simple primary selection criteria.

As stated by Strasberg and Clavien in their comprehensive review,<sup>3</sup> the indication of BAT must be considered, in addition to the primary effectiveness, with secondary effectiveness (recurrence of GS), cost-effectiveness, and lastly with the patient's preference. We agree that these issues must be addressed further. For instance, recurrence of GS occurs in 30% to 40% after primary successful BAT,<sup>61,62</sup> reducing the overall effectiveness, although recent studies have shown that recurrent stones are dissolvable by repeated BAT.<sup>63,64</sup> These issues should be informed to the patients who fulfill the primary selection criteria, and thereafter patients' preference also must be considered.

Our finding of reduced risk of biliary colic and cholecystitis in UDCA-treated patients obviously does not justify general use of UDCA for the purpose of preventing GS attack. However, a limited number of high-risk GS patients who cannot receive surgical treatments for certain other health

conditions would probably deserve such prophylactic use of UDCA. This approach may also be valuable in symptomatic patients who wish to preserve their functioning GB or several subgroups of asymptomatic GS (*i.e.*, elderly or diabetic patients<sup>65</sup>) who might develop serious complications before being symptomatic. The precise natural courses as well as the value of UDCA in such subgroups must be uncovered.<sup>3</sup>

In conclusion, this prospective cohort study with multivariate analysis supports that: 1) asymptomatic GS patients do not require any therapy, because most of them remain asymptomatic for years; and that 2) symptomatic patients with a) radiolucent, b) small multiple GS (<10 mm) not filling the GB on US, and c) a well-visualized GB on OCG are applicable for the UDCA therapy. Furthermore, the UDCA therapy might be considered in patients who have significant risks for surgical intervention, because it is associated with the reduced risk of recurrent GS attack and cholecystitis that require such intervention.

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