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NEW ATTEMPTS USING COMPUTED TOMOGRAPHY IN DETERMINIG INDICATION OF GALLSTONE DISSOLUTION THERAPY

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ABSTRACT

Subjects for this study were 32 patients who had radiolucent stones in the gallbladder disclosed by conventional cholecystography. In all 12 patients with complete or partial dissolution of gallstones by gallstone dissolution therapy, the gallstone features on the CT scan were shown as an iso-density or a low-density in contrast to the bile, whereas, in 20 unresponsive patients, they were shown as shells of high-density in 9 out of 20 patients, and as a high-density in contrast to the bile in 7 out of 20 patients. If the gallstones contained 1.0 to 4.0% of calcium, the calcification could not be detected by conventional radiographic examinations, but could be clearly detected by CT examinations.

In the present study, we concluded that the patients with gallstones containing more than 1% of calcium were not suitable for dissolution therapy and that CT examinations were very useful for deciding about using dissolution therapy of the gallstones.

INTRODUCTION

More than 10 years have passed since 1972, when Danzinger et al.[1] and Bell et al.[2] reported on dissolution therapy of cholesterol stones in the gallbladder using chenodeoxycholic acid (CDCA). During this period, it was reported that ursodeoxycholic acid (UDCA), the epimer of CDCA, which has been used as a choleretic in Japan these past years, was also capable of dissolving cholesterol gallstones[3,4]. Because of this, both CDCA and UDCA are now widely used for dissolution therapy.[5-9]

The efficacy of dissolution therapy, however, was found to be only about 30 to 50 % in the previous reports. This indicates that over half of the patients in whom satisfactory results had been expected were eventually shown to be unsuited for dissolution

therapy. The previous criteria for using dissolution therapy were as follows: 1) a gallbladder in which stones are present is well shown by cholecystography, its shape being close to normal and its contraction good. 2) the gallstones, which are thought to be made up of cholesterol, are radiolucent without well-defined calcification. 3) the maximum diameter of the gallstones is preferably less than 15 mm.

Among the numerous factors which determined the efficacy of the gallstone dissolution therapy, in particular we noted a trace of calcification of the gallstones, and tried to investigate the relationship between the efficacy of dissolution therapy and the calcification of gallstones detected by computed tomography (CT) examinations ,which were more sensitive in contrast resolution than conventional radiographic examinations.

Materials and Methods

Subjects for the present study were 32 patients (15 men: ranging from 35 to 78 years of age; mean, 53.1 years of age; and 17 women: ranging from 33 to 65 years of age; mean, 50.4 years of age) who had radiolucent stones in the gallbladder disclosed by conventional cholecystography. The ranges and means of body weight were 45.0-77.5 kg and 64.3 kg in men and 46.0-71.0 kg and 55.9 kg in women, and those of the obesity index (body weight x 100/(body height-100) x 0.9) were 101-128 and 112.4 in men and 86-168 and 118.2 in women, respectively.

Drugs and Administration Period:

We treated these patients with three methods of bile acid administration: chenodeoxycholic acid alone, ursodeoxycholic acid alone and a combination of both bile acids. The amounts of daily administration were 400mg of CDCA, 450mg of UDCA, and CDCA 300mg plus UDCA 300mg in combination therapy, which were the usual doses in Japan. In case No. 10 in Table 1 and case No. 20 in Table 2, however, CDCA was given after a preceding administration of UDCA for several years. Periods of dissolution therapy were four months to 75 months (mean 21.8 months).

Computed Tomography:

Computed tomography(CT) examinations to investigate calcification were, in principle, carried out before dissolution therapy, but in a few cases, carried out two or three months after the initiation of dissolution therapy. The CT scanner primarily used was GE CT/T 8800 (General Electric Co. Ltd. USA), although a Delta 50 FS (Ohio Nuclear Co. Ltd. USA) was also occasionally used. The slice thickness in examinations was 10 mm on the GE CT/T 8800 and 13 mm on the Delta 50 FS.

Determination of Calcium Content in Gallstones:

Calcium content was measured using an atomic absorption spectrophotometer in 33 gallstone samples obtained from 27 patients who had undergone conventional radiogra-

phic examinations (plain X-ray and cholecystography), CT examinations and elective cholecystectomy. The methods of calcium measurement were as follows: after the gallstones obtained were dried by decompression and heating (−760 mmHg, 50°C), finally, the stones were ground with a pestle and mortar made of agate, and their weights were measured in a platinum melting pot. These samples were then ashed in muffle furnace at 500-550°C for seven hours. The samples considered to be bilirubin-rich were ashed at 600° C for twelve hours. The residue was dissolved in three milliliters of 1 N HCL at 70 -90°C, and the insoluble components were filtrated. The amounts of soluble components were increased to a volume of 50 ml with distilled water. Calcium content in this solution was estimated with an atomic absorption spectrophotometer (Hitachi type 180 -50 Japan) using an air-acetylene flame under the following conditions: air, 9.4 1/min.; acetylene, 2.6 1/min.; wave length, 442.7nm; and width of slit, 2.6mm.

Evaluation of Clinical Rediographic Examinations:

To compare the calcium content with the features of gallstones on a conventional radiogram and CT scan, the degree of calcification of gallstones in the above mentioned 27 cases was estimated by two radiologists who were not aware of the results of the cholecystogram, CT scan and calcium content of gallstones. If the diagnoses of the two observers were different, an agreement on the diagnoses was obtained by their discussion.

Experimental Study:

We made an experimental model for comparing the calcium content with the features of gallstones on CT scan. We used hepatic bile, instead of gallbladder bile, which was obtained from several patients with obstructive jaundice treated with percutaneous transhepatic biliary drainage. The hepatic bile was concentrated five times by a rotary evaporator. Test tubes made from polystyrene with 13 mm inner diameter and 15 mm outer diameter were placed in this concentrated hepatic bile, and each test tube was filled with solutions of calcium chloride at the calcium concentrations of 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0%. Subsequently, CT examinations of these test tubes were performed to determine the relationship between the amounts of calcium and the features of the calcium concentrations in the test tubes.

Statistical Analysis:

The data of the present study were subjected to statistical analysis using the Student' s unpaired t-test.

Results

We studied the backgrounds of 32 patients with radiolucent gallstones in the functioning gallbladder who underwent both conventional cholecystography and CT examinations, and divided them into two groups: a completely or partially dissolved group (Table

1); and an unresponsive group (Table 2). In the former, 5 patients were male and 7 patients were female, while in the latter, 10 patients were male and 10 patients were female. The difference in the age between the two groups was not statistically significant (the former: mean age, 53.6 yr; range, 36-64 yr; the latter: mean age, 50.6 yr; range, 33-78 yr). The difference in the obesity index between the two groups was not statistically significant (the former: mean index, 119.8; range, 97-142; the latter: mean index, 112.9; range, 86-168). There was no statistical difference in the maximal diameter of gallstones nor in the sex of the two groups. Although the period of administration in the responsive group was longer than that in the unresponsive group, there was no statistical significance between them.

In all 12 patients with complete or partial dissolution of gallstones, gallstone features were shown on the CT scan as an iso-density or a low-density in contrast to the bile (Table 1), whereas, in 20 unresponsive patients, they were shown as shells of high-density in 9 out of 20 patients, and were shown as a high-density in contrast to the bile in 7 out of 20 patients (Table 2). There were only four patients whose features on the CT scan were iso-dense to the bile in the unresponsive group. These facts indicate that the patients in whom the calcification of the gallstones is highly recognizable on the CT scan are among those who have been diagnosed as having radiolucent gallstones by conventional radiographic examinations. In addition, dissolution therapy had no effect on all patients in whom calcification of the gallstones was recognized on the CT scan.

Table 1. The clinical analysis and findings on CT scan in responsive patients undergoing dissolution therapy

Case	Sex	Age	Gallstones No.	Gallstones Max.diam.	CT findings (against bile)	Administration Drugs	Administration Periods	Efficacy
1	F	54	10↑	7 mm	Iso-density	Combination	4 mon.	Complete dissolution
2	M	56	1	7	Iso-density	Combination	6	Complete dissolution
3	M	64	1	8	Iso-density	U D C A	10	Complete dissolution
4	M	55	10↑	9	Iso-density	U D C A	12	Complete dissolution
5	F	59	3	16	Iso-density	U D C A	19	Complete dissolution
6	M	49	1	13	Iso-density	U D C A	75	Complete dissolution
7	M	49	1	22	Iso-density	Combination	8	Partial dissolution
8	F	51	2	27	Iso-density	Combination	16	Partial dissolution
9	F	64	1	13	Iso-density	U D C A	30	Partial dissolution
10	F	46	10↑	31	Iso-density	U D C A →C D C A	41	Partial dissolution
11	F	60	6	20	Iso-density	U D C A	70	Partial dissolution
12	F	36	10	6	Low-density Air containing	Combination	16	Partial dissolution

All patients were diagnosed having radiolucent gallstones in the gallbladder by conventional radiographic examinations.

Table 2. The clinical analysis and findings on CT scan in unresponsive patients undergoing dissolution therapy

Case	Sex	Age	Gallstones Number	Gallstones Max.diam.	CT findings (against bile)	Administration Drugs	Administration Periods
1	F	51	4	16 mm	Shell of high-density	Combination	6 mon.
2	M	44	2	14	Shell of "	C D C A	11
3	M	47	1	18	Shell of "	C D C A	12
4	F	46	1	18	Shell of "	Combination	17
5	M	43	1	25	Shell of "	U D C A	18
6	M	78	1	15	Shell of "	C D C A	18
7	F	50	6	14	Shell of "	U D C A	19
8	F	57	10	20	Shell of "	C D C A	24
9	F	49	2	22	Shell of "	C D C A	26
10	F	48	1	12	High-density	Combination	6
11	F	65	10↑	3	High-density	U D C A	13
12	M	60	6	8	High-density	C D C A	13
13	M	58	2	27	High-density	Combination	15
14	M	46	1	10	High-density	Combination	19
15	F	53	10↑	12	High-density	U D C A	28
16	M	35	4	10	High-density	U D C A	39
17	M	51	10↑	3	Iso-density	U D C A	7
18	M	60	6	24	Iso-density	C D C A	23
19	F	37	10↑	4	Iso-density	U D C A	24
20	F	33	10↑	6	Iso-density	U D C A →C D C A	53

All patients were diagnosed having radiolucent gallstones in the gallbladder by conventional radiographic examinations.

However, even in the patients in whom a iso-density in contrast to the bile was shown, dissolution therapy was sometimes ineffective. This indicats that the calcification of the gallstones is not the only influential factor in dissolution therapy.

We report on the following cases:

Case 1: 35 year-old male (case No. 16 in Table 2). He was found to have four radiolucent gallstones in the gallbladder by conventional cholecystography. However, these gallstones were shown as a high-density in contrast to the bile on the CT scan. During dissolution therapy with 450 mg of UDCA per day, calcification of the outer layer of the gallstones became gradually clear even in conventional cholecystography and the efficacy of dissolution therapy could not be obtained. A surgical operation was performed 39 months after the initiation of dissolution therapy. The gallstones obtained by

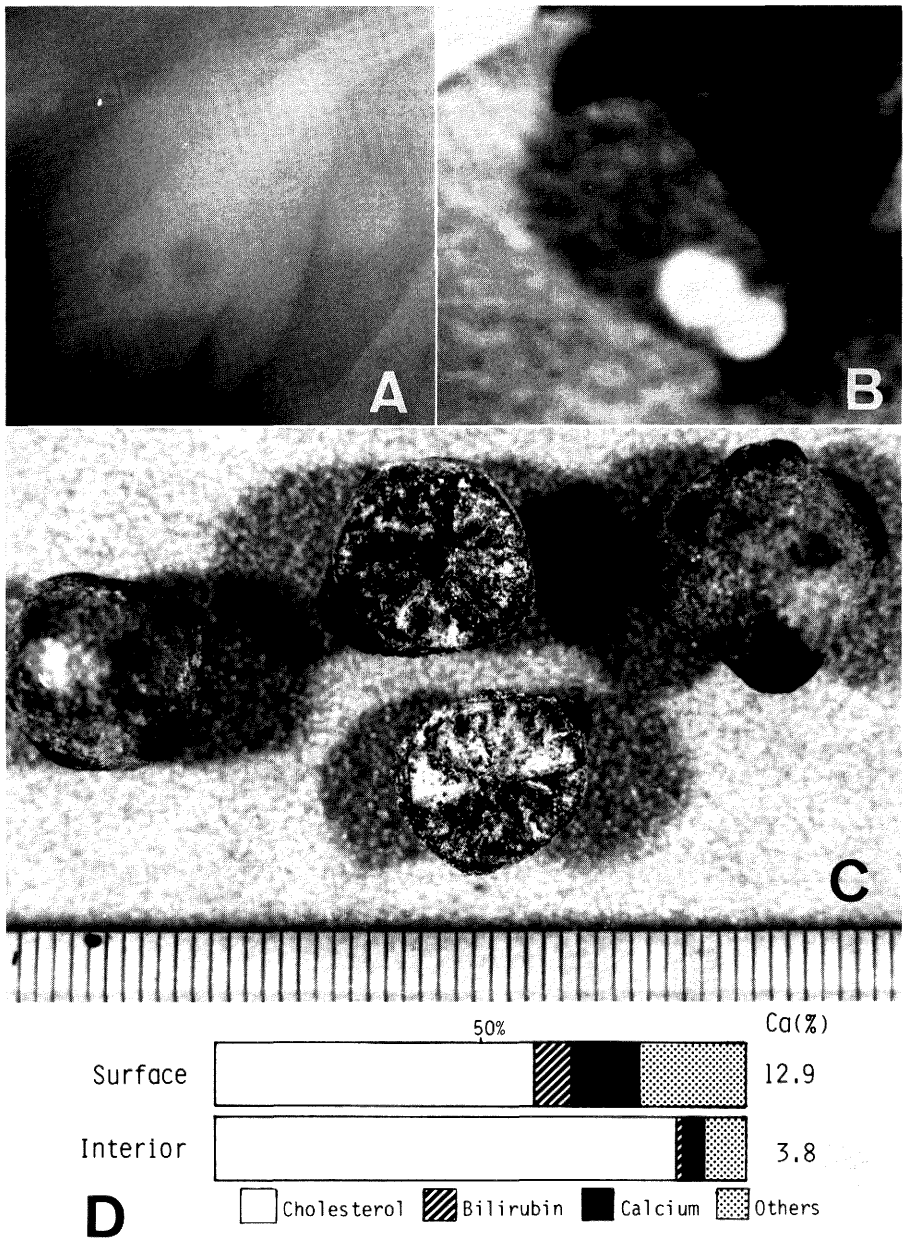


Fig. 1. 35 year-old male. (Case No. 16 in Table 2)
A: Cholecystography before dissolution therapy; four radiolucent gallstones existed in the gallbladder.
B: CT scan before dissolution therapy; gallstones were shown as a high-density in contrast to the bile.
C: Gallstones obtained by cholecystectomy after 39-month dissolution therapy.
D: Chemical composition of removed gallstones.

cholecystectomy contained 12.9% of calcium in the surface and 3.8% of calcium in the interior (Fig. 1).

Case 2: 49 year-old female (case No. 9 in Table 2). She was found to have two radiolucent gallstones in the gallbladder by conventional cholecystography, but on the CT scan, these gallstones were shown as shells of high-density. CT numbers were about 60 HU (Hounsfield's units) to 70 HU on the surface of the gallstones, while those of the bile around the gallstones were about 30 HU to 40 HU. Though she was given 400 mg of CDCA per day for 26 months, no dissolution tendency was shown (Fig. 2).

Case 3: 46 year-old female (case No. 10 in Table 1). She was found to have a large number of radiolucent gallstones of 31 mm in maximal diameter by conventional cholecystography, and on the CT scan, these gallstones were shown as an iso-density in contrast to the bile. After the administration of 450 mg of UDCA per day for 24 months, the gallstones were reduced in number to only one of 15 mm in diameter. Thereafter, though the dissolution therapy was continued for 41 months, there was no change in the residual stone. Finally, an operation was perfomed after the cessation of an additional ten months' administration of the drug. The gallstone obtained by cholecystectomy was 19 mm in diameter, slightly grown and composed of 59% cholesterol and 41% billrubin calcium (calcium: 0.83%) in the interior and more than 98% cholesterol in the surface (Fig. 3).

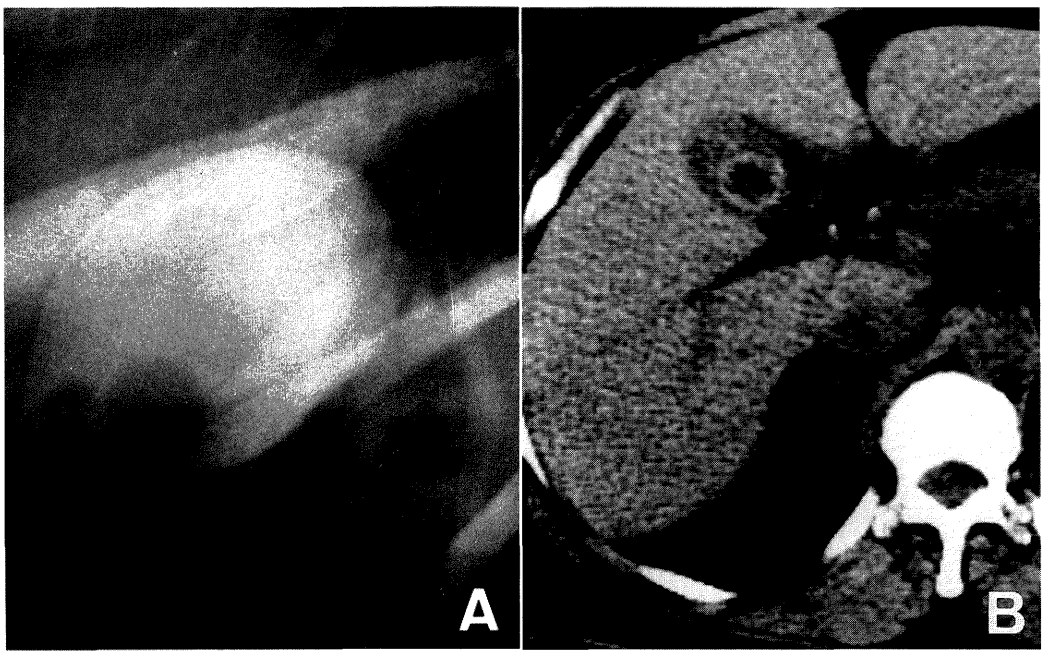
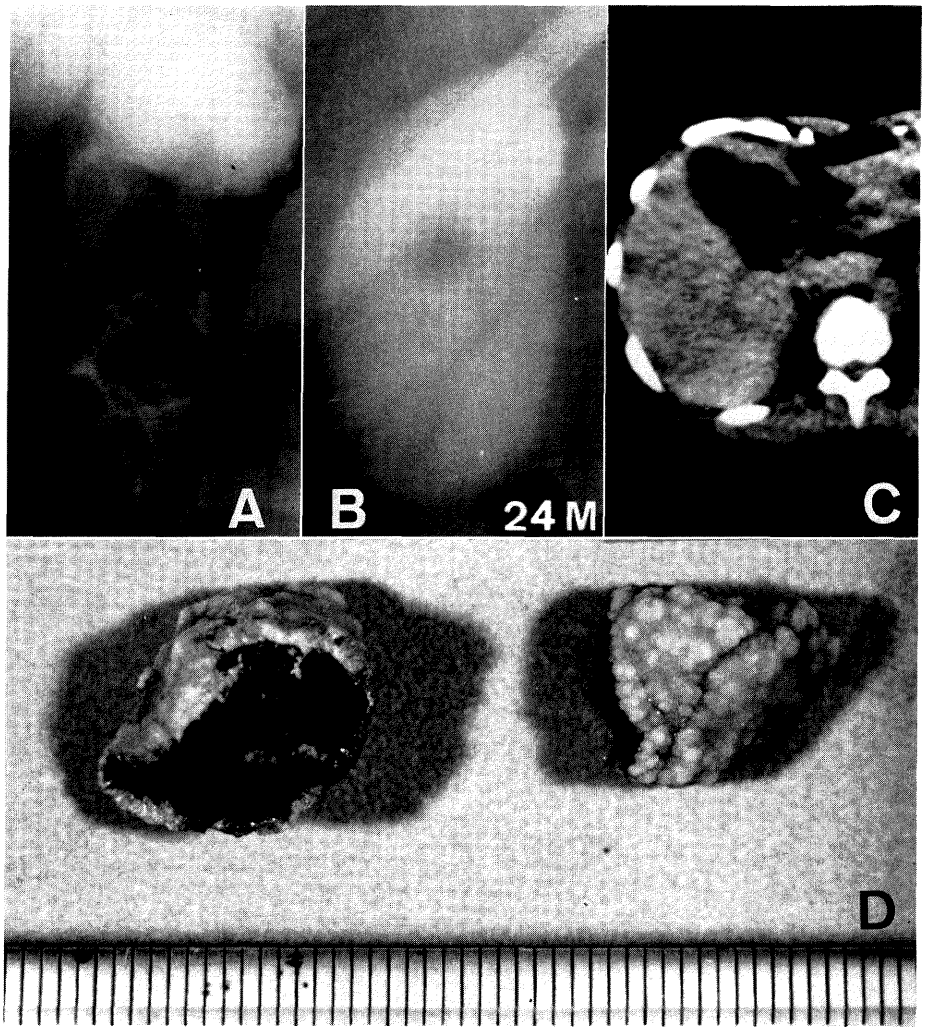


Fig. 2. 49 year-old female. (Case No. 9 in Table 2)
A: Cholecystography before dissolution therapy; two radiolucent gallstones existed in the gallbladder.
B: CT scan before dissolution therapy; gallstones were shown as shells of high-density.

We tried to compare the contents of calcium in the gallstones with the features on various radiographic examinations (Fig. 4). If the gallstones contained calcium below



1.0%, the calcification of the gallstones could be detected by neither conventional radiographic nor CT examinations, and if they contained 1.0 to 4.0% of calcium, the calcification could not be detected by conventional radiographic examinations, but could be clearly detected by CT examinations. Because of a small number of patients with radioopaque gallstones, in this study we could not determine the calcium concentration at which the calcification of the gallstones could be clearly detected by conventional radiographic examinations. Trotman et al.[10] have reported that calcium concentration of more than 4% usually result in radioopacity of gallstones on radiographic examinations. Furthermore, in our experimental study with CT (GE CT/T 8800) examinations using a hepatic bile concentrated five times and a solution containing various concentrations of calcium chloride, we found that a 1% calcium solution was indicated as an iso-density in contrast to the bile, and that in concentrations below 1%, the calcium solution was indicated as a low-density in contrast to the bile, and that in concentrations of more than 1%, it was indicated as a high-density in contrast to the bile (Fig. 5). Actually, when the calcium concentrations of the solutions were compared with their average CT numbers

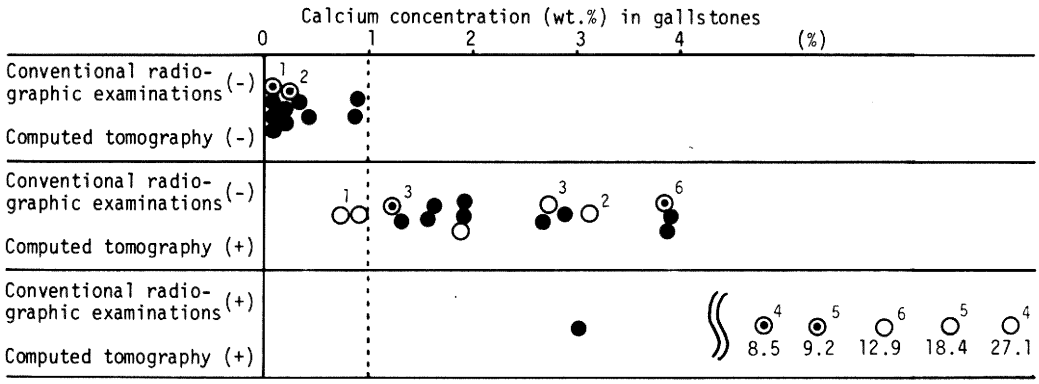


Fig. 4. Relationship between the content of calcium in the gallstones and features on various radiographic examinations. (−), radiolucent on conventional radiographic examinations or a low or iso-density in contrast to the bile on CT scan; (+), radioopaque on conventional radiographic examinations or a high -density or shell of high-density in contrast to the bile on CT scan; (●), calcium concentration in whole of gallstone; (⊙), in interior of gallstone; (○), in surface of gallstone. Number on the upper right of each circle indicates the same case. If the gallstones contained 1.0 to 4.0% of calcium, the calcification could be clearly detected by computed tomography in radiolucent gallstones disclosed by conventional radiographic examinations.

Fig. 3. 46 year-old female. (Case No. 10 in Table 1)
A: Cholecystography before dissolution therapy; a large number of radiolucent gallstones of 31 mm in maximal diameter existed in the gallbladder.
B: Cholecystography after 24-month dissolution therapy; the gallstone were reduced in number to one of 15mm diameter.
C: CT scan before dissolution therapy; gallstones were shown as an iso-density in contrast to the bile.
D: Gallstones obtained by cholecystectomy after 41-month dissolution therapy.
E: Chemical composition of obtained gallstones.

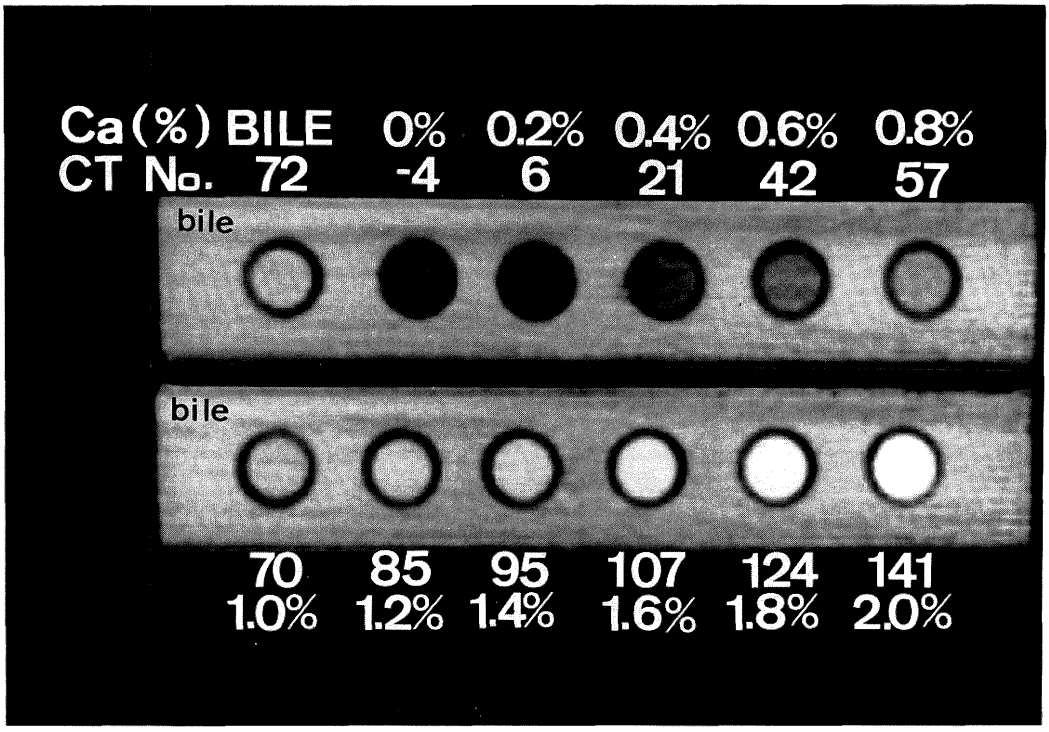


Fig. 5. Experimental study by CT (GE CT/T 8800) examinations using the hepatic bile concentrated five times and a solution containing various concentrations of calcium chloride in the test tube. If the calcium concentration in the solution was more than 1%, the solution was shown as a high-density in contrast to the bile.

of 9 voxels on the CT scan in each solution, there was very high correlation ($r=0.998$) between them (Fig. 6).

Discussion

Factors which determine the efficacy of gallstone dissolution therapy are calcification, size and number of the gallstones, function of the gallbladder, complications of diabetes mellitus, and obesity. In these factors, the calcification of the gallstones is usually examined by conventional radiographic examinations (plain X-ray and cholecystography) at present. We noted the relationship between the calcification of the gallstones and the efficacy of the gallstone dissolution therapy, and studied the calcification using a CT scan which was more highly sensitive than conventional radiographic examinations in its contrast resolution. Bateson et al.[11,12] and Raedsch et al.[13] reported that even a trace of calcification prevented the gallstones from dissolving, while Whiting et al.[14] speculated that a layer of calcium salts, probably calcium carbonate in most cases, might form a barrier between the cholesterol in the stone and the bile in the gallbladder. Bell et al.[15] reported that in 25 patients with radiolucent gallstones, the gallstones in 5

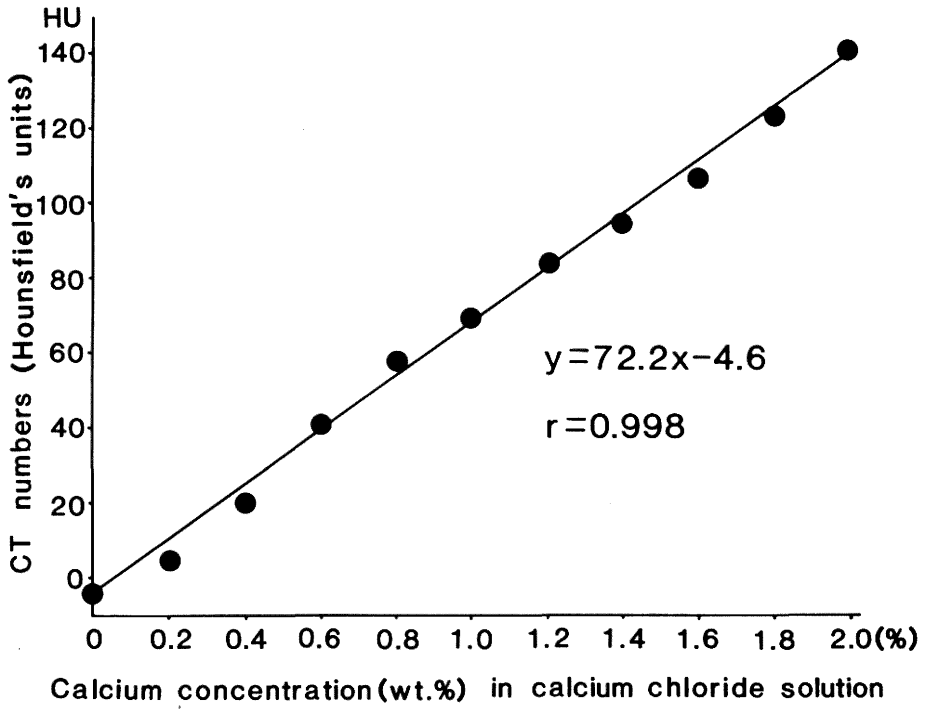


Fig. 6. Correlation between average CT numbers and calcium concentration (wt.%) in calcium chloride solution in the experimental study shown in Figure 5. There is very high correlation (r=0.998) between them.

patients contained less than 70% cholesterol, therefore, the radiolucent gallstones might not necessarily be equal to cholesterol-rich stones.

In this study, we investigated the relationship between the features on CT scan and the efficacy of dissolution therapy. In 12 out of 32 patients, dissolution therapy was effective, and in all of these twelve patients, the calcification of the gallstones could not be detected on the CT scan. On the other hand, in 20 out of 32 patients, dissolution therapy was not effective, and in 16 out of these twenty patients, the calcification of the gallstones could be detected on the CT scan in spite of radiolucent stones shown by conventional radiographic examinations. These facts indicate that the use of CT examinations for deciding about using dissolution therapy can double the rate of efficacy, from 37.5% (12/32) to 75.0% (12/16) (Table 1 and 2). However, in some of the cases unresponsive to dissolution therapy, the density of the gallstones were identical to the bile. This fact indicates that the gallstones with little calcium are not always cholesterol-rich. The relationship between calcium content in the gallstones and the features on the CT scan is shown in Fig. 4. If the gallstones contain more than 1% of calcium, the calcification of gallstones can be detected by CT examinations in spite of the lack of visualization by conventional radiographic examinations. The results mentioned above

were also supported by our experimental study using calcium chloride solution of various concentrations and five-time-concentrated hepatic bile; CT numbers of calcium chloride solution increased in proportion to calcium content in the solution, and if calcium content in the solution was over 1%, CT numbers of the solution were higher than those of the bile, and had a high-density in contrast to the bile on the CT scan (Fig. 5). Considering the findings in Fig. 5 and the relationship described above between the features on the CT scan and the efficacy of the dissolution therapy, we conclude that the patients with gallstones containing more than 1% of calcium are not suitable for dissolution therapy. Contrary to our observations, there is a report that a CT scan was negative in 4 out of 6 patients in whom the concentrations of calcium in the gallstones ranged from 10 to 100%, and that a CT scan is not sensitive enough to select the patients with gallstones for dissolution therapy[16]. However, this opinion was reported five years ago, and it was also speculated that newer CT scan techniques might increase the sensitivity to detect calcium in the gallstones.

In the present study, we have concluded that CT examinations are very useful for deciding about using dissolution therapy of the gallstones, and they might prevent us from making useless efforts in dissolution therapy.

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