Multifactorial analysis of recurrence of cholecystolithiasis in Shanghai area

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Subject headings cholecystolithiasis/therapy; recurrence; follow-up studies

Abstract
AIM To explore the risk factors of gallbladder stone recurrence.
METHODS A multifactorial analysis was made for 1058 patients in Shanghai area whose gallbladder stones disappeared after different kinds of nonsurgical therapy, including oral litholytic therapy, extracorporeal shock wave lithotripsy and percutaneous choledocholithotomy. Serum level of insulin and total bile acid were determined in 122 patients.
RESULTS After 1-8.8 years of follow-up, the recurrence rate of gallbladder stone was 11.6%, 22.4%, 29.5%, 36.4%, 39.3% and 39.7% respectively within 1, 2, 3, 4, 5 and over 5 years. The risk factors for the recurrence are: primary multiple gallstones ($P<0.05$); family history of cholecystolithiasis ($P<0.05$); greasy food intake ($P<0.01$); low mean value of serum insulin ($P<0.01$); and high mean value of total bile acid ($P<0.01$).

CONCLUSION The recurrence of cholecystolithiasis is related to overintake of high fat and high cholesterol food, and might also be related to low level of serum insulin.

INTRODUCTION
With the clinical application of different kinds of nonsurgical therapy, such as oral dissolution of gallstone (ODG), extracorporeal shock wave lithotripsy (ESWL), percutaneous transhepatic gallbladder catheterization (PTGC) and contact dissolution, and percutaneous choledocholithotomy (PCCL), the recurrence and anti-recurrence of cholecystolithiasis come as a problem now. The clinical value of these methods mostly depends on the recurrence rate of this disease. Discover y of the risk factors of the recurrence of cholecystolithiasis, and interference procedures make it possible to lower the recurrence rate of gallstone. A multifactorial analysis of the recurrence of cholecystolithiasis in Shanghai area was carried out by the Shanghai Gallstone Research Coordination Group.

MATERIALS AND METHODS
Research subjects
A total of 1058 patients whose gallbladder stones had disappeared after different kinds of non-surgical therapy in Shanghai area entered this study, including 454 cases after ESWL, 594 cases after PCCL and 10 cases after ODG.

Collection of follow-up materials
Formulation of follow-up table Let patients mark the items in the table and put the database into computer. The table includes sex, age of gallstone inception, height, weight, diet hobby, symptoms and medical treatment, related diseases (such as diabetes mellitus, coronary heart disease, liver disease), family history of gallstone, size and number of gallstone, recurrence and recurrence time of cholecystolithiasis.

Examination of patients One hundred and twenty-two patients were randomly selected from gallstone patients. Stone recurrence was found in 48 patients and non recurrence in 74. Venous blood of 5ml was drawn before breakfast in the morning. After standing still for half an hour, serum was sealed after centrifugation. Serum insulin level was determined with Coat-Acount insulin kit, and serum total bile acid (TBA) level by Ausbile Auto kit at the same time. Ultrasound examination was performed to evaluate the condition of gallbladder (length, width, height, stones), the degree of the liver lipid infiltration and the condition of the common bile duct (CBD), about 1 hour after greasy food. Ultra-

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Received 1998-10-04
somography was repeated to reveal the width, length and height of the constricted gallbladder. With the formula $V = \frac{3.1416 \times L \times H \times W}{6}$, the volume of gallbladder when starve or after diet, and the contraction ratio of the gallbladder volume were calculated.

**Statistical method**

1. There were 792 pieces of subjective materials and 122 objective materials when database was set up.
2. The follow-up rate, recurrence rate and loss to follow-up rate of patients after ESWL, PCCL and ODG were calculated. 3. To find out the statistical difference between the recurrence and non-recurrence groups (Table 1). 4. To find out the statistical difference between the multiple and solitary stones groups (Table 2). 5. With the help from Epidemiology Teaching and Research group of Shanghai Medical University, the Epi-info Version 5.01a software was used to process the data.

| Table 1 Difference between recurrence and non-recurrence groups |
|------------------|-----------------|--------|---|
|                | Odds ratio | M-H Chi square | P value |
| Incipient stone | 1.52       | 6.43        | <0.05 |
| Sex proportion  | 0.91       | 0.31        | 0.58  |
| Diet hobby      | 0.66       | 6.02        | <0.05 |
| Related disease | 0.85       | 0.87        | 0.35  |
| Clinical symptom| 12.51      | 190.97      | <0.01 |
| Medical treatment| 1.70      | 9.03        | <0.01 |
| Family history  | 1.55       | 4.54        | <0.05 |
| Mean thickness of gallbladder wall | 1.95 | 2.75 | 0.10 |
| Adipose infiltration of liver | 1.01 | 0.00 | 0.98 |

| Table 2 Difference between multiple stones and solitary stone groups |
|------------------|-----------------|--------|---|
|                | Odds ratio | M-H Chi square | P value |
| Recurrence       | 1.52       | 6.43        | <0.05 |
| Sex proportion   | 1.08       | 0.21        | 0.65  |
| Diet hobby       | 1.26       | 2.10        | 0.15  |
| Related disease  | 0.95       | 0.09        | 0.76  |
| Medical treatment| 1.42       | 4.35        | <0.05 |
| Clinical value of serum insulin | 1.21 | 1.38 | 0.24 |
| Family history   | 1.08       | 0.13        | 0.72  |
| Mean thickness of gallbladder wall | 0.55 | 2.15 | 0.14 |
| Adipose infiltration of liver | 0.91 | 0.05 | 0.83 |

**RESULTS**

**Total follow-up rate and stone recurrence rate**

From January 1988 to October 1995, there were 1058 patients whose gallbladder stones had disappeared after different kinds of non-surgical therapy. Seven hundred and ninety-two patients were followed up for 1-8.8 years with a rate of 74.8%. The stone recurrence rate was 11.6%, 22.4%, 29.5%, 36.4%, 39.3% and 39.7% respectively within 1, 2, 3, 4, 5 and over 5 years. The total recurrence rate was 30.8%.

**Follow-up rate and recurrence rate after ESWL**

Among 454 patients treated with ESWL, 413 patients are followed up, with a rate of 91.0%. There were 285 cases with non-recurrence and 128 with recurrence (17 were treated surgically, the others received conservative treatment). Forty-one patients lost to follow-up. The recurrence rate of gallstone was 11.9%, 20.2%, 34.8%, 35.7%, 37.2% respectively within 1, 2, 4, 5 and over 5 years. The total recurrence rate was 31.0%.

**Follow-up and stone recurrence rate after PCCL**

Among 594 patients treated with PCCL, 370 were followed up, the follow-up rate being 62.3%. There were 262 cases with non-recurrence and 108 with recurrence. Seven of them were treated surgically, the others received consecutive treatment, and 224 patients were lost to follow-up. The recurrence rate of gallstone was 8.8%, 22.4%, 29.5%, 36.7%, 47.4% respectively within 1, 2, 3, 4 and 5 years. The total recurrence rate was 29.9%.

**Follow-up and stone recurrence rate after ODG**

Nine of 10 patients treated with ODG were followed up. The stone recurrence occurred in 8 patients. One case was lost to follow-up. Average follow-up length was 5 years and 4 months. The stone recurrence rate was 88.9%.

**DISCUSSION**

**Recurrence rate of gallbladder stone**

According to the literature, the recurrence rate of cholelithiasis is about 7%-11.8% after ODG, ESWL, PTGC and PCCL treatment[1-3]. In this study, the 1-year stone recurrence rate was 8.8%-11.9%, similar to the literature. It has been reported that the stone recurrence rate increases by about 10% each year, and by the fifth year it reaches 50%. After 5 years, a plateau with no further recurrence is usually seen[4]. The recurrence rates after ESWL, PCCL and ODG in the fifth year were 35.7%, 47.7% and 88.9% in this study. The lower gallstone recurrence rate after ESWL was probably related to strict selection of cases and higher ratio of solitary stone. More research should be done about
the relatively high recurrence rate of gallstone, otherwise the non-surgical therapy of gallbladder stone will lose their clinical application value.

Risk factors for recurrence of gallstone

The occurrence and the recurrence of the gallbladder stone probably have similar physiopathologic mechanism. It is related to many factors such as sex, age, weight index, diet hobby, labor strength, endocrine and metabolism, the size, number and character of the gallstone. In our study, no difference exists between recurrence and non-recurrence groups on such items as sex, average age, average weight/height, thickness of gallbladder wall, average ratio of gallbladder constiction, average degree of liver lipid infiltration and related diseases (diabetes, coronary heart disease, etc). Some items have significant difference between the two groups. The following in the recurrence group were significantly different from the non-recurrence groups: more clinical symptoms, more patients receiving medical treatment, low mean value of serum insulin and high mean value of serum TBA. The group with multiple gallstones, family history of gallstone and intake of greasy food has a higher recurrence rate. All of these differences are statistically significant \( P<0.05 \).

Multiple gallstones seem to recur more often than solitary stone probably because ① most of solitary stones are cholesterol calculus, and lithotripsy and litholysis are effective treatment. The proportion of combined calculus is quiet higher in multiple stones. The insoluble bile sludge after lithotripsy and dissolution might become the nuclear of the recurrence stone. ② Solitary stone is easier to be hit during the lithotripsy. The treatment takes less time and the broken stones are easier to be removed. There were less fine stones left and less injury to the gallbladder, while results were different for multiple stones.

Patients with family histories of gallstone had higher recurrence rates probably because of similar component and hobby of the diet, and hereditary factors.

Most literature reports that the serum insulin level in patients with gallstone is high\(^5\). The mechanism might be that insulin activates the cholesterol synthesis reductase of liver, causing the increase of cholesterol synthesis and accelerating gallstone formation. Some authors have found no statistical difference in serum insulin level between diabetes patients with or without gallstone. In our cases, the mean serum insulin level in stone recurrence and multiple stone groups is significantly lower than in non-recurrence and solitary stone groups. When insulin is deficient, most glucose produced by glyconeogenesis was consumed, and the amount of pyrurate used to synthesize acetyl coenzyme A is decreased. Most of acetyl coenzyme A is derived from lipose. A great quantity of acetyl coenzyme A provides the material for cholesterol synthesis. At the mean time, the deficiency of insulin reduces the capability of cholesterol utilization of liver, resulting in the hypercholesterolemia. This abnormal metabolism of lipid is often related to the formation of gallstone.

It has been proven that food is closely related to gallbladder stone. Epidemiological investigation also indicated that the high morbidity of cholecystolithiasis is correlated with the intake of low fiber and refined food in some developed countries. With the changing of the food components and reduction of the labor intensity, the morbidity of cholecystolithiasis is rising progressively.

Content and hobby of diet, over intake and low consumption of high fat and cholesterol food, relative deficiency of serum insulin, abnormal metabolism of glucose and lipose, liver disease and dysfunction of gallbladder might be all related to the formation of gallstone. Effective propaganda and education, reasonable diet structure, constant physical exercise and a certain amount of labor might help control the occurrence and recurrence of cholecystolithiasis.

REFERENCES

1. Schoenfield L.J. Oral dissolution of gallstones. Am J Surg, 1993;165:427-430
2. Sackmann M, Nillier H, Kluempelberg U, Von Ritter C, Pauletzi J, Hoff J. Gallstone recurrence after shock-wave therapy. Gastroenterology, 1994;106:225-230.
3. Mc Dermott VG, Arger P, Cope C. Gallstone recurrence and gallbladder function following percutaneous cholecystolithotomy. J Vasc Interv Radiol, 1994;5:437-438.
4. O’Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gallstones after medical dissolution: a long term follow-up. Gut, 1988;29:655-658.
5. Han TQ, Zhang SD, Chen S, Yi F, Shi RT, Jiang ZH. A case control study on risk factors of cholelithiasis. Chin J Experiment Surg, 1995;12:99-100.

Edited by MA Jing-Yun