Clinical and Nutritional Study on Gallstone Disease in Japan

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The dietary factors, as a cause on increasing incidence of gallstones in Japan, were studied. The increase in the incidence of gallstones at autopsy was nearly paralleled with that of fat intake on a line graph and reversely the carbohydrate intake including crude fiber showed a decreasing trend. In the nutritional survey of patients with gallstone, the fat intake was 22% higher than that of the control group, and the crude fiber intake was 18% lower. Comparing the incidence of cholesterol stones during each 10 years of 1953–1962 and 1969–1980 with the nutritional intake, the incidence of gallstones increased by 25% and the fat intake by 120%, but the carbohydrate intake including crude fiber decreased by 14%. From the above, it was considered that the increase of the incidence of cholesterol gallstones was related to the increase of the fat intake and the decrease of the crude fiber intake. A study on black stone was carried out with an infrared spectroscopic analysis and scanning electron microscopic observation, and we now proposed a new classification of this type of stones.

Key Words: Gallstone, Black stone, Crude fiber, Fat intake

Recently the increase in the incidence of gallstones in Japan has been recognized. As we reported\(^1\), the incidence of gallstones at autopsy was 8.2% in the total materials, and 15.5% in recent 4 years. Furthermore, in clinical study, we reported that cholesterol stones comprised as higher as 71.7% of cases in recent years. Because it was assumed that dietary factor was related to this increase of the incidence of gallstones, particularly of cholesterol stones among Japanese, comparative studies between the disease and nutritional state in Japan were conducted using autopsy and clinical materials.

The mechanism of black stone formation, and its pathophysiological and clinical implication has the topic of discussion lately. The classification of black stone is still ambiguous.

MATERIALS

1) Statistical analysis

The records of 18,307 autopsies performed in the Departments of Pathology, Faculty of Medicine, University of Tokyo, and The Jikei University School of Medicine, during a period of 29 years, i.e. from 1949 to 1977, were reviewed. These materials were included 11,441 males and 6,866 females.

The gallstones obtained surgically in 1,512 Japanese patients from 15 hospitals during the twelve years period (1969–1980) were studied. No geographical preference was present.

2) Nutritional study

Twenty-five subjects (10 males and 15 females) of cholelithiasis which were presumed
cholesterol gallstones radiographically in recent clinical cases in our hospital were studied.

3) Black stone

Fifty-two gallstones which had black-toned surface were selected as materials obtained from 1,512 cases surgically.

METHODS

1) Statistical analysis

The incidence of gallstones were calculated per annum by percentage. All cases which had cholecystectomy because of cholelithiasis were considered as having gallstones. The incidence of gallstones was compared with the change of nutritional intake in Japan which was reported by the Ministry of Welfare during sequential years.

Infrared spectroscopic analysis of the gallstones was carried out with recording spectrophotometer by potassium bromide disc method and the stones were classified by the major component as follows; Cholesterol gallstone, Pigment gallstone and Rare gallstone. The results were compared with that of 1953–1962 in the same method reported previously. Furthermore, the frequency of cholesterol stone was compared with the mean of national nutritional intake.

2) Nutritional study

Daily intake of energy, protein, fat, carbohydrate and crude fiber were calculated by using a 1-week recall method. These components were compared with the nutritional survey of the Japanese that was reported by the Ministry of Welfare.

3) Analysis of black stones

Stones with the black-toned surface were analyzed by a infrared spectroscopic method and observed by scanning electron microscopy.

RESULTS

1) Statistical analysis

Annual changes of the incidence of gallstones at autopsy and of the intake of nutritional elements (amounts consumed per day) reported by the national nutritional survey, were shown in Table 1. Protein intake was 68.0 g/day in 1950, 69.7 g/day in 1960 and 78.4 g/day in 1979. The increase in protein intake during these sequential years, was considered moderate. Fat intake was 18.0 g/day in 1950, 36.0 g/day in 1965 and 54.8 g/day in 1979. This increase in fat intake was considered remarkable. Conversely, carbohydrate intake including sugar and crude fiber was 410 g/day in 1950, 310 g/day in 1979, showing a decreasing trend. The incidence of gallstones at autopsy was 2.7% in 1950, 7.6% in 1965 and 15.1% in 1975. Comparing the incidence of gallstones with the intake of nutritional elements, an increase in the incidence of gallstones in Japan, was paralleled by an increase in the fat intake, and was reversely correlated by the carbohydrate intake on a line graph.

Next, the results of infrared spectroscopic analysis in 1,512 cases were shown at Table 2, comparing with the previous report. As cholesterol stone formation was considered to be affected by changes in food intake, we compared this frequency of cholesterol stones with the mean of national nutritional intake during the same period (Table 3). During this 15 years, the frequency of cholesterol stones had increased from 46.6% to 68.9%. The energy intake had increased 5%, the protein intake 15%, the fat intake 120%, and the carbohydrate intake had decreased 14%.
Table 2. The results of infrared spectroscopic analysis

<table>
<thead>
<tr>
<th>Class of gallstone</th>
<th>No.</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol gallstone</td>
<td>1,042</td>
<td>68.9</td>
<td>46.6</td>
</tr>
<tr>
<td>Pigment gallstone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium bilirubinate stone</td>
<td>336</td>
<td>22.3</td>
<td>41.5</td>
</tr>
<tr>
<td>Black stone</td>
<td>96</td>
<td>6.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Rare gallstone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty acid calcium stone</td>
<td>4</td>
<td>0.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Miscellaneous stone</td>
<td>34</td>
<td>2.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Total</td>
<td>1,512</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 3. The incidence of cholesterol stones and the nutritional intakes.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>The incidence of cholesterol gallstones (%)</td>
<td>46.6</td>
<td>68.9</td>
</tr>
<tr>
<td>Energy (Kcal)</td>
<td>2,094</td>
<td>2,205</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>69.5</td>
<td>79.6</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>23.2</td>
<td>51.1</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>402</td>
<td>346</td>
</tr>
</tbody>
</table>

Table 4. The nutritional survey of gallstone patients

<table>
<thead>
<tr>
<th></th>
<th>Energy Kcal</th>
<th>Protein g</th>
<th>Fat g</th>
<th>Carbohydrate g</th>
</tr>
</thead>
<tbody>
<tr>
<td>The national nutritional survey (means in recent 5 years)</td>
<td>2,214</td>
<td>79.7</td>
<td>50.8</td>
<td>350</td>
</tr>
<tr>
<td>Gallstone patients</td>
<td>2,124</td>
<td>81.2</td>
<td>62.0</td>
<td>280</td>
</tr>
</tbody>
</table>

(Average intakes per capita per day)

2) Nutritional study

We compared the national nutritional intakes reported by the Ministry of Welfare in recent 5 years (control group), with the nutritional survey made retrospectively on subjects of cholelithiasis prior to discovery of gallstone (Table 4). The daily intake of energy for control group was 2,214 Kcal/day, comprising of 79.7 g/day of protein, 50.8 g/day of fat and 350 g/day of carbohydrate. The daily intake of each in patients with gallstone was 2,124 Kcal/day, 81.2 g/day, 62.0 g/day, 280 g/day respectively. The protein intake in patients with gallstone was similar to that in control group. The fat intake was higher than that in control group and the crude fiber intake was lower (4.6 g/day) than in control group (5.6 g/day). Patients with gallstone had lower intake in each nutritional element by 20–30%, after gallstone had been found.

3) Black stone

Gallstone are roughly classified either as cholesterol stone or bilirubin calcium stone. But there are few black stones, fatty acid calcium stones and miscellaneous stones. Black stones are different from bilirubin calcium stones in that they are small stones limited within gall-bladder and occasionally radio-opaque (Fig. 1). As shown in Fig. 2, black and grossy and confetto-like appearance is typical of black stone. In Europe and America,
Table 5. Black stone and black stone-like gallstone

Group 1. Black surface and black cut-surface (30.0%)
Confetto-like or mulberry-like appearance
with diameter of 5 mm or less

Group 2. Black surface and black cut-surface (52.5%)
Various external appearances in shape and
size (i.e. cubic)

Group 3. Black surface (17.5%)
Dark-brownish cut-surface with laminate-like
structure (sub-black stone)

Group 4. Black-toned surface
Brownish cut-surface with lamination
(excluded from black stone)

Table 6. Analysis of black color stones

<table>
<thead>
<tr>
<th>Main component</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>(Group 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin calcium</td>
<td>5 (41.7)</td>
<td>13 (61.9)</td>
<td>3 (42.9)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>3 (25.0)</td>
<td>5 (25.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>1 (8.3)</td>
<td>1 (4.8)</td>
<td>2 (28.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (25.0)</td>
<td>2 (9.5)</td>
<td>0 (0)</td>
<td>1 (8.3)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (100.0)</td>
<td>21 (100.0)</td>
<td>2 (100.0)</td>
<td>12 (100.0)</td>
</tr>
</tbody>
</table>

DISCUSSION

Recently the incidence of cholesterol gallstones has increased in Japan and became similar to that in Europe and America. It was recognized that the formation of gallstone was caused by abnormality of bile components, inflammation of bile duct, abnormality of systemic metabolism and so on. Furthermore, it was considered that the formation of gallstone was closely related to dietary life. Tanimura, et al. reported the pro-
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duction of pure cholesterol gallstones using lithogenic diet in hamsters, and Osuga, et al.\textsuperscript{5} reported the same in squirrel monkeys. It was reported that bile became lithogenic in human when he took cholesterol in excess of 1,000 mg/day for over 2 months, or 2,000 mg/day for over 3 weeks\textsuperscript{6}. In the present study, it was apparent that the incidence of gallstones in Japan was increasing annually in parallel with daily fat intake on a line graph, and the patient of cholelithiasis took 22% more fat than control, and less sugar and crude fiber. Sarles\textsuperscript{7} had reported that small intake of green vegetables and fruits was related to the formation of gallstones. In Japan, the intake of carbohydrate including crude fiber was decreasing. It was considered that the increase of gallstones in Japan was closely related to food intake, especially to large fat intake and a little crude fiber consumption.

Regarding black stone, Suzuki\textsuperscript{8} reported that the characteristic grossy black substance was bilirubin polymer. Detailed biochemical investigation was necessary for component analysis of black stone, because there were unidentified substances present at infrared spectroscopic analysis. However, it was highly possible that the major component of black stones was bilirubin polymer or bilirubin-like substance on infrared absorption spectra, because a typical black stone was nearly amorphous on scanning electron micrograph and similar to bilirubin calcium and to bilirubin polymer which was synthesized by Suzuki. The stones of group 4 were similar to bilirubin calcium stone in structure, components and clinical manifestations and were considered to be excluded from black stone. The stones of group 1, 2 and 3 were all limited within the gallbladder. The mechanism of black stone formation is unknown, but it is said to be different from that of bilirubin calcium stone on clinical manifestation probably\textsuperscript{8}. Further examination will be needed for this question.

The gallstones were classified as in Table 7.

Table 7. Classification of gallstones

<table>
<thead>
<tr>
<th>I. Cholesterol gallstone</th>
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<tbody>
<tr>
<td>1. Pure cholesterol stone</td>
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<tr>
<td>2. Mixed stone</td>
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<tr>
<td>3. Combination stone</td>
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</table>

<table>
<thead>
<tr>
<th>II. Pigment gallstone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Calcium bilirubinate stone</td>
</tr>
<tr>
<td>2. Black stone</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>III. Rare stone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Fatty acid calcium stone</td>
</tr>
<tr>
<td>2. Miscellaneous stone</td>
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</table>

based on the discussions given above, namely in relation to studies in Europe and America, the characteristics of gallstones and their clinical implications. That is, there are three groups. Group 1 is cholesterol stone including pure cholesterol stone, mixed stone and combination stone. Group 2 is pigment stone including calcium bilirubinate stone and black stone. Group 3 is rare stone including fatty acid calcium stone and miscellaneous stone.

REFERENCES