Association of Periampullary Diverticula with Primary Choledocholithiasis but not with Secondary Choledocholithiasis

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- 국문초록 -
십이지장 유두주위 개설과 담석의 연관성
울산대학교 의과대학 서울중앙병원 소화기내과
명 승 재·김 명 휘·이 성 구
서 동 완·김 연 석·민 명 일

연구배경 및 목적: 십이지장 유두 주위 개설은 담석과 연관성이 알려져 있으나 담석을 해부학적 위치에 따라 구분하였을 때의 개설과의 연관성에 대한 연구 성적은 보고자에 따라 일정치 않다. 본 연구의 목적은 십이지장 유두부 개설과 담석의 관련성을 담석의 위치에 따라 알아보고 특히 담석의 성분 분석을 통하여 총담관 담석과 다른 부위의 담석과의 관계를 알아보고자 한 것이다.

대상 및 방법: 최근 10개월 간 서울중앙병원에서 ERCP를 시행 받은 632예 중 성공적으로 담관 조영을 할 수 있었던 611예를 대상으로 십이지장경상 유두주위 개설의 빈도 및 임상적 특성, 그리고 담석과의 판찰성 등을 전향적으로 분석하였다. 또한 담석은 부위에 따라 누수였으며, 그 외관 및 할면 소견, 그리고 적외선 분광계를 이용한 화학적 성분 등을 종합하여 분류하였다.

결과: 십이지장 유두주위 개설의 유병률은 27.0%(165/611)였으며 연령별 개설의 빈도는 연령이 증가할수록 유의하게 증가하였다(p<0.01). 담석증의 발생은 개설이 있던 군(95/165, 57.6%)에서 개설이 없었던 군(189/446, 42.6%)에 비해 더 흔하게 관찰되었다(p<0.01). 담석을 해부학적 위치에 따라 누수였을 때 총담관에만 담석이 존재했던 경우는 개설이 존재했던 증례에서 있었던 총례보다 유의하게 총담관 담석의 유병률이 높았으나 (24.2% vs. 8.3%, p<0.001) 기타 다른 부위에 담석이 존재했던 증례에서는 개설의 존재 유무에 따른 담석의 유병률에 유의한 차이가 없었다. 개설을 동반하여 총담관에만 담석이 있던 40예 중 32에는 담낭 결제술을 받은 경우였으며 이들의 담석 분석 결과 83%에서 갈색석이 해당하였고 원발성 총담관 담석으로 추정되었다. 한편 담낭이나 간내 담도에 담석이 같이 관찰되었던 총담관 담석의 경우, 총담관 담석은 외관 및 할면 소견 그리고 담석 성분에 있어 담낭 담석이나 간내 담석과 100% 일치하여 속발성 총담관 담석으로 수상되었고 개설의 유무에 따른 담석의 유병률의 차이는 없었다. 결론: 십이지장 유두부 주위 개설이 있는 경우 담석이 잘 발생할 수 있으며, 담석증에는 총담관 담석, 그 외에도 속발성이 아닌 원발성 총담관 담석의 형성이 유두부 주위 개설과 연관이 있다고 사료한다.

핵심단어: 십이지장 유두주위 개설, 담석, 원발성 총담관 담석, 속발성 총담관 담석

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INTRODUCTION

Duodenal diverticula are outpouchings of the mucosa and muscularis mucosae through the intestinal wall and the reported prevalence ranges between 1% and 22% according to the authors. This wide range of reported prevalence may be due to the difference in diagnostic methods (conventional x-ray studies vs. endoscopic examination) or research design (prospective vs. retrospective). The prevalence is expected to be higher in studies using endoscopic methods than x-ray studies, and in studies performed prospectively than retrospectively.

Most of the duodenal diverticula are commonly located close to the papilla of Vater and several endoscopic studies found an association between periampullary diverticula and biliary calculi. Some authors suggested an increased prevalence of periampullary diverticula in patients with gallbladder stones, on the other hand, others found an association of diverticula with common bile duct stones but not with gallbladder stones. However, none of these studies distinguished the common bile duct stones associated with gallbladder or intrahepatic calculi from those without. It is very important because the common bile duct stones are classified as primary and secondary according to the origin of the stones. A primary stone in the common bile duct indicates that the cause for its formation is within the duct. On the contrary, the presence of a secondary stone is indicative of its origin in the gallbladder from which it migrated through the cystic duct. Common bile duct stones with associated gallbladder stones may be regarded as secondary stones and those found after several years of symptom free interval following cholecystectomy are considered primary stones. In addition, most of the primary common bile duct stones are comprised mainly of brown pigment stones and in secondary common bile duct stones, cholesterol stones are the most frequent type. Therefore, when we evaluate periampullary diverticula as a pathogenetic predisposing factor for the common bile duct stone, we believe that it is essential to analyze the primary and secondary common bile duct stones separately because they might have different pathogenetic mechanism.

Therefore, we performed a prospective study using duodenoscopy during ERCP to evaluate the association of periampullary diverticula and gallstones. The gallstones were classified into gallbladder, common bile duct, and intrahepatic stones according to the anatomic location, and especially the common bile duct stones were divided into those with gallbladder or intrahepatic stones or those without. Furthermore, the composition of gallstones associated with periampullary diverticula were examined. The composition of gallbladder stones was analyzed earlier in patients with periampullary diverticula, however, there has been no report about the composition of common bile duct stones associated with periampullary diverticula.

MATERIALS AND METHODS

During a period of 10 months from January to October 1996, 632 consecutive patients were enrolled in our study. All were suspected of having biliary, or pancreatic diseases and admitted for ERCP. In 21 patients (3.3%), ERCP was unsuccessful due to failure to reach the papilla, insufficient cholangiography, or previous history of Billroth II operation. They were all excluded from the analysis and therefore, the results of 611 cases were analyzed. The diagnosis and determination of the location of the gallstones were based on ultrasonography, ERCP, and abdominal CT scan. Intrahepatic duct stones were defined as calculi located proximal to the confluence of the right and left hepatic ducts.

During the duodenoscopic procedure, a careful
examination of the entire midpart of the duodenum was performed. Periampullary diverticula were diagnosed when the center of the diverticula was located within 2 centimeters from the papilla of Vater.11

The stones were harvested by duodenoscopic or cholecdochoscopic stone extraction, or operation. They were bisected and initially grouped on the basis of their surface color, cross-sectional appearance and chemical composition into one of three categories: cholesterol, brown, and black pigment stones.12 The cholesterol stone was defined as one with a cholesterol content of 70% or more and showing a characteristic radial pattern emanating from the center on cross section. The pigment stones were classified as those with calcium bilirubinate for their major component and with cholesterol content less than 25% of the stones. Among the pigment stones, the brown pigment stones were classified as those with a brown-colored surface and having a characteristic concentric layer on cross section, on the other hand, the black pigment stones were defined as those with black-colored surface and amorphous appearance on cross section.13 The chemical composition of stones were measured by infrared spectroscopy.

Statistical analysis was performed using the Chi-square test with adjustment according to the Mantel-Haenszel procedure if necessary.

RESULTS

1. Prevalence of duodenal diverticula

Mean age of the 611 patients was 56±14 years and the male/female ratio was 354/257. Diverticula were found in 165 of 611 cases (27.0%) and there was a positive relationship between age and duodenal diverticula (p<0.01)(Table 1). However, a relationship between sex and duodenal diverticula was not found.

2. Relationship between duodenal diverticula and biliary calculi

Of 611 cases, 284 had gallstone diseases. The prevalence of biliary lithiasis was higher in the patients with periampullary diverticula (95/165, 57.6%) than without (189/446, 42.4%)(p<0.01, Table 2).

Considering the location of the gallstones, the patients were divided into 7 groups: 1) gallbladder only, 2) common bile duct only, 3) intrahepatic duct only, 4) gallbladder and common bile duct, 5) intrahepatic duct and common bile duct, and 6) gallbladder and intrahepatic duct, and 7) gallbladder, common bile duct and intrahepatic duct. The prevalence of gallstones with respect to whether or not they had periampullary diverticula was analyzed according to the groups separately. There were no significant differences in the mean ages of patients between these 7 groups. In the common bile duct stone only group, the rate of gallstones was significantly higher in patients with periampullary diverticula (24.2%) than in patients without (8.3%)(p<0.001)(Table 3). Of the 40 cases who contained stones only in common bile duct, 5 had stoneless gallbladder, and 35 had had a previous cholecystectomy. However, in other groups, there was no significant difference in the prevalence of gallstones according to the presence or absence of the periampullary diverticula(Table 3).

3. Analysis of the gallstone composition

Of the cases with periampullary diverticula, the gallstones were collected in 36 of 40 cases of common bile duct only group, in 16 from 20 cases of gallbladder and common bile duct group, and in 6 of 7 cases of intrahepatic duct and common bile duct group. The stones were analyzed chemically and classified into cholesterol, brown pigment, and black pigment stones according to the chemical composition and gross appearance.
The stones from 36 cases from common bile duct only group with periampullary diverticula were brown stones in 30 cases (83%), cholesterol stones in 5 cases (14%), and black pigment stone in 1 case (3%). Among these 36 cases, 32 cases had had a previous cholecystectomy. In 28 of these 32 cases, the recurrent stones were detected after at least a two year asymptomatic period (2~7 years) following their surgery and the stones from these cases were consistent with brown pigment stones in all cases. Of the 16 cases from gallbladder and common bile duct group, 12 (75%) had cholesterol stones, 4 (25%) had black pigment stones. The common bile duct stones from this group were as similar to their paired gallbladder stones in gross and cross-sectional appearance and in chemical composition in all the cases. In all cases from intrahepatic and common bile duct group, strictures of the intrahepatic duct were revealed from cholangiography. In these cases, most of the intrahepatic stones were located in dilated and static intrahepatic ducts proximal to a stricture and only one to three stones were found in common bile duct. The stones from six cases of intrahepatic and common bile duct group were analyzed. The gross and cross-sectional appearance were identical between common bile duct stones and their intrahepatic counterpart in all cases and all the stones were classified as brown pigment stones.

**DISCUSSION**

In our study, the diverticula were found in 27% (165/611) of the cases studied. This prevalence was rather higher than those of previous studies\(^1-^3\) and it may be because the diverticula have been sought prospectively with using duodenoscope. Moreover, we have studied a group of selected patients suspected of having biliary or pancreatic diseases and this may have contributed to the high prevalence also. The prevalence increased in older age groups and there was no sex predilection. These results were in accordance with previous reports (Table 1).\(^2-^4\)

There have been a number of studies about a periampullary diverticula and gallstones and several reports indicated that the prevalence of gallstones was higher in patients with periampullary diverticula.\(^2-^7\) However, Lotveit et al.\(^7\) suggested that periampullary diverticula were associated with gallbladder stones, while Hagege et al.\(^3\) implicated the association between periampullary diverticula and common bile duct stones, but not with the gallbladder stones. Therefore, the reports about the association between the diverticula and gallstone diseases are inconsistent when considering the anatomical location of gallstones. Moreover, Lotveit et al.\(^7\) studied the patients with gallstones only in gallbladder, and Hagege et al.\(^3\) did not analyze their patients with common bile duct stones separately into cases with or without gallbladder stones although they suggested the positive correlation between common bile duct stones and periampullary diverticula. The composition of gallbladder stones was analyzed earlier in patients with periampullary diverticula,\(^10\) however, no study had

### Table 1. Prevalence of periampullary diverticula according to the age group

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>Diverticulum</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>&lt;30</td>
<td>2(12.5)</td>
<td>14(87.5)</td>
</tr>
<tr>
<td>30~39</td>
<td>10(14.3)</td>
<td>60(85.7)</td>
</tr>
<tr>
<td>40~49</td>
<td>16(14.4)</td>
<td>95(85.6)</td>
</tr>
<tr>
<td>50~59</td>
<td>51(31.5)</td>
<td>111(68.5)</td>
</tr>
<tr>
<td>60~69</td>
<td>37(27.4)</td>
<td>98(72.6)</td>
</tr>
<tr>
<td>70~79</td>
<td>38(41.8)</td>
<td>53(58.2)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>11(42.3)</td>
<td>15(57.7)</td>
</tr>
<tr>
<td>Total</td>
<td>165(27.1)</td>
<td>446(72.9)</td>
</tr>
</tbody>
</table>

( ) indicates percents.
analyzed gallbladder, common bile duct, and intrahepatic stones simultaneously in patients with periampullary diverticula.

The common bile duct stones are classified as primary or secondary. Primary stones are defined as calculi originated in common bile duct, and secondary stones are initiated in the gallbladder and then moved down the cystic duct into the common bile duct. The presence of secondary stone is indicative of its main pathology in the gallbladder, on the other hand, a primary stone in the common bile duct indicates that the cause for its formation is within the duct itself including sphincter of Oddi. Therefore, it is more probable that periampullary diverticula are associated with primary common bile duct stones than with secondary ones because periampullary diverticula may cause functional biliary stasis possibly due to a compression of the distal common bile duct, or also induce reflux of duodenal contents including bacteria into the bile ducts caused by the insufficiency of the choledocho-duodenal sphincter. The data shown in studies of the choledocho-duodenal sphincter and bacteriological examinations peroperatively taken from the common bile duct in patients with periampullary diverticula support this hypothesis. Although the prevalence of the gallstones was significantly higher in patients with periampullary diverticula (including all the gallstones regardless of their location, Table 2), when considering their anatomical location, this significance was found only in patients with common bile duct stones but without gallbladder or intrahepatic stones (Table 3). These results implicate that only primary common bile duct stones might be associated with periampullary diverticula. Since most of our cases with common bile duct stones had had a two or more year asymptomatic period following cholecystectomy and their stones were brown pigment stone, we could assume that most of the stones in our cases from the common bile duct only group were primary common bile duct stones. It is well-known that the bile stasis and bacterial infection are associated with the pathogenesis of brown pigment stones.

The common bile duct stones with associated gallbladder stones were almost identical with their paired gallbladder stones not only in gross appearance but in composition and most of these stones were cholesterol stones. These findings implies that these stones are secondary stones migrated from the gallbladder. Therefore, it is presumed that in cases

| Table 2. Correlation between periampullary diverticula and gallstones |
|----------------------------------|-----------------|-----------------|
| Diverticulum | Gallstones | Total |
| Present | 95(57.6)* | 70 | 165 |
| Absent | 189(42.4) | 257 | 446 |
| Total | 284 | 327 | 611 |

( ) indicates percent; *χ² test: p<0.01.

| Table 3. Periampullary diverticula and gallstones according to the anatomical location |
|----------------------------------|-----------------|-----------------|
| Location of gallstones | Diverticulum | P-value |
| Present | Absent | GB only | CBD only | IHD only | GB+CBD | IHD+CBD | GB+IHD | GB+IHD+CBD | Others |
| GB only | 13(7.9) | 48(10.8) | NS |
| CBD only | 40(24.2) | 37(8.3) | <0.001 |
| IHD only | 6(3.6) | 21(4.7) | NS |
| GB+CBD | 20(12.1) | 45(10.1) | NS |
| IHD+CBD | 9(5.5) | 23(5.2) | NS |
| GB+IHD | 3(1.8) | 4(0.9) | NS |
| GB+IHD+CBD | 4(2.4) | 11(2.5) | NS |
| Others | 70(42.4) | 257(57.6) | |

( ) indicates percent; * Others are patients without gallstone diseases.
with stones in both the common bile duct and the gallbladder, the association of periampullary diverticula and gallstone prevalence could not be found. As for the common bile duct stones with intrahepatic stones in present study, these stones may be regarded as secondary ones migrated from intrahepatic duct because intrahepatic strictures were noted in all cases and most of the stones were located proximal to the strictures. Therefore, since the main cause for the formation of these stones might lie in the intrahepatic duct, the association between periampullary diverticula and choledocholithiasis was not documented in those patients.

These results also have therapeutic implications. In secondary common bile duct stones, cholecystectomy and removal of choledocholithiasis is enough for the treatment. However, primary common bile duct stones associated with periampullary diverticula, because of their pathogenic foci in the common bile duct and not in the gallbladder, may recur after cholecystectomy and common duct exploration, unless biliary stasis or ascending infection is corrected.

In conclusion, the prevalence of gallstone disease was significantly higher in periampullary diverticula, and considering the location and the origin of the gallstones, the association between diverticula and gallstones is significant in patients with primary common bile duct stones but not with the secondary ones.

**SUMMARY**

**Background/Aims:** Several endoscopic studies found an association between periampullary diverticula and biliary calculi, however, the results of the reports are inconsistent when considering the anatomical location of the stones. The aims of our study are to evaluate the association between periampullary diverticula and gallstones according to their location and to clarify the origin of the common bile duct stones by analyzing the composition of the stones. **Methods:** During a period of 10 months, 611 of 632 consecutive cases of endoscopic retrograde cholangiopancreatography (ERCP) were prospectively enrolled. The data of periampullary diverticula and gallstones were analyzed according to the location of the stones. The stones available were initially grouped on the basis of their gross morphology and cross-sectional appearance, and finally analyzed by quantitative infrared spectroscopy. **Results:** Diverticula were found in 165 of 611 cases (27.0%) and there was a positive relationship between age and duodenal diverticula (p<0.01). The prevalence of biliary lithiasis was higher in patients with periampullary diverticula (95/165, 57.6%) than without (189/446, 42.4%)(p<0.01). Considering the location of the gallstones, this significance was found only in patients with common bile duct stones not associated with gallbladder or intrahepatic duct stones (p<0.001). Of these 40 cases with gallstones only in common bile duct, 32 had had a history of cholecystectomy with more than a two year asymptomatic period following their surgery, and on analysis, most of the stones (30/36, 83%) were classified as brown pigment stones. Therefore, these stones were presumed to be primary common bile duct stones. On the contrary, the common bile duct stones with associated gallbladder or intrahepatic stones were identical with their paired gallbladder or intrahepatic stones in gross and cross-sectional appearance and chemical composition. They were assumed to be secondary common bile duct stones and the difference in prevalence of calculi according to the **Conclusion:** The prevalence of gallstones was significantly higher in periampullary diverticula, and considering the location and the origin of the gallstones the association between diverticula and gallstones is significant in patients with primary common bile duct stones but not with the secondary one.
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Key Words: Periampullary Diverticulum, Cholecystolithiasis, Primary Common Bile Duct Stone, Secondary Common Bile Duct Stone

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