The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients

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Background: Data concerning the association of juxtapapillary duodenal diverticula (JPDD) with biliopancreatic disorders are inconsistent, but an association between bile duct stones and JPDD is widely accepted. The aim of this study was to investigate the frequency of JPDD and its association with biliopancreatic disorders in patients undergoing ERCP.

Methods: A retrospective analysis was conducted of 5497 consecutive ERCP procedures performed in 2925 patients. Matched-pair analysis yielded 350 pairs of patients with and without JPDD, matched for definite risk criteria such as age, gender, and indication for ERCP.

Result: The incidence of JPDD was 12%. Patients with JPDD were significantly older than patients without JPDD (71 vs. 62 years; \( p < 0.0019 \)) and had a significantly higher bleeding rate after endoscopic sphincterotomy (8.8% vs. 4.8%; \( p = 0.039 \)). The presence of JPDD correlated with gallbladder stones (29.4% vs. 20.8%; \( p = 0.039 \)), bile duct stones (46% vs. 33.1%; \( p < 0.001 \)), and recurrence of bile duct stones (6.6% vs. 1.4%; \( p = 0.002 \)). There were no significant differences in frequency of acute and chronic pancreatitis as well as pancreas divisum. After multivariate logistic regression analysis, technically difficult ERCP, bleeding after endoscopic sphincterotomy, and bile duct stones remained as independent risk factors.

Conclusion: JPDD appears to be a risk factor for complications of endoscopic sphincterotomy and for gallbladder stones, bile duct stones, and their recurrence. (Gastrointest Endosc 2001;54:56-61.)

The juxtapapillary duodenal diverticulum (JPDD) was first described by Chomel in 1710.\(^1\) JPDD is an acquired lesion. Pathophysiologically it is pulsion or traction diverticula. Its incidence is estimated at 0.16% to 23%, depending on the method of identification, for example, radiography versus endoscopy. JPDD does not usually provoke symptoms by itself. Its prevalence rises with increasing age.\(^2\) In 1908 Rosenthal\(^3\) reported 3 cases of JPDD in combination with biliary obstruction. Since then, data concerning the association of JPDD with disorders of the biliopancreatic system have been inconsistent. Some investigators demonstrated an association of JPDD with bile duct stones, but among the many available studies, data on this point have not reached statistical significance.\(^4\)\(^-\)\(^12\) Other studies have found an increased prevalence of acute idiopathic pancreatitis.\(^5\)\(^,\)\(^7\) The largest published study to date, by Leivonen et al.,\(^5\) investigated 123 patients with JPDD. These investigators were able to show a significant association with bile duct stones but not with other biliopancreatic disorders. The aim of this retrospective analysis of the largest population ever studied was to investigate the frequency of JPDD and its association with disorders of the biliopancreatic system in patients undergoing ERCP.

PATIENTS AND METHODS

Between January 1991 and March 1996, 5497 ERCP procedures were performed in 2925 patients. The reports of these procedures and case records were transferred into a computer database (Microsoft Access 97, Microsoft Corp., Redmond, Wash.) and reviewed retrospectively. The median number of ERCP procedures per patient was 1.0 (range 1-25) with a mean of 1.88. For data analysis the first ERCP procedure was used in all cases except for those of recurrent stone disease and complications. Control patients were recruited from patients without JPDD.

Each case in the database was assigned a serial identification number according to the date of the first ERCP. After completion of database entry for each patient with JPDD, a matched case was selected in the non-JPDD group that had corresponding parameters for age, gender, and indication for ERCP. If there was more than one patient match in the non-JPDD group, the case with the lowest identification number was selected.
Three hundred fifty case pairs (with JPDD vs. without JPDD) matched for age, gender, and indication for ERCP were thus obtained. In this way two groups were defined with a comparable risk for developing gallstones (age and sex) and with identical symptoms leading to ERCP examination (Table 1).

Criteria for a technically difficult ERCP procedure were as follows: impeded access to the papilla and/or a time duration for cannulation of the papilla of 15 minutes or greater. Bleeding during endoscopic sphincterotomy (EST) was regarded as relevant if injection therapy with epinephrine and/or blood transfusion was necessary.

For statistical analysis of the qualitative characteristics, the chi-square test was used or Fisher exact test, when appropriate. To evaluate the effect of the continuous variable age, the Mann-Whitney U test was used. Odds ratios and their 95% confidence intervals were calculated with all analyses based on treating the samples of cases and controls as independent after matching. For adjustment for possible confounders and effect modifiers, a multivariate logistic regression model was used with duodenal diverticula as dependent variable and all 14 variables listed in Table 2 as independent variables. Statistical analysis was performed by SAS release 6.12 software (SAS Institute, Inc., Cary, N.C.).

**RESULTS**

There were 350 patients (12%) with 1 or more diverticula for whom sufficient data were available for this study. The median age of patients with JPDD was 71 years (range 23-98) versus 62 years (range 11-100) \((p < 0.0019)\) for those without JPDD. The male/female ratio was 44.6%/55.4% for patients without JPDD \((p = 0.075)\).

A single diverticulum was evident in 86% of patients with JPDD, 10.9% had 2 diverticula, and 3.1% had more than 2 diverticula. In 54.9% of patients with JPDD, the papilla was inside the diverticulum, 37.7% of patients had the papilla out-
side of the diverticulum, and in 7.4% the papilla was found on the bridge between 2 diverticula.

Patients without JPDD presented significantly more often with biliary colic than patients with JPDD (17.6% vs. 12.5%; \( p = 0.015 \)) but had symptoms of biliary obstruction less often, such as increased bile duct diameter, jaundice, and elevated biochemical parameters of cholestasis (41.3% vs. 56.2%; \( p < 0.0001 \)).

The ERCP procedure was described as being difficult more often in patients with JPDD than in control patients (12.5% vs. 5.1%; \( p < 0.001 \)). The success rate of cannulation of the papilla was 95.4% in patients with JPDD versus 98.9% in the control patients (\( p = 0.012 \)). Failure in cannulation of the papilla occurred in 62.5% with the papilla inside the diverticulum, in 25% with the papilla outside, and in 12.5% with the papilla on the bridge between 2 diverticula.

Among patients with JPDD, the complication rate for EST was higher. Significant bleeding occurred in 8.8% of patients with JPDD after EST versus 4.8% of control patients (\( p = 0.039 \)). All episodes of postinterventional bleeding were managed endoscopically by epinephrine injections. Severe postinterventional pancreatitis, defined as abdominal pain and serum amylase elevation of 3 times the normal value, was observed in 0.86% of control patients but in none of the patients with JPDD. Retroperitoneal perforation was rarely seen and no difference was detected in the perforation rate (0.86%) (Fig. 1). All perforations were managed by conservative treatment.

A slight difference in frequency of cholecystectomy was found but the difference was not significant (18.2% vs. 16.9%; \( p = 0.62 \)). Duodenal diverticula were correlated with gallbladder stones (29.4% vs. 22.6% in controls; \( p = 0.039 \)) and bile duct stones (46% vs. 33.1% in control patients; \( p < 0.001 \)). There was no difference in frequency of stones within the intrahepatic ducts.

Recurrent bile duct stones were seen in 6.6% of patients with duodenal diverticula compared with 1.4% of control patients (\( p = 0.002 \)) during the period of observation. The median time interval for stone recurrence was 10 months (range 2-58) for patients with JPDD and 4 months (range 2-15) for control patients. Purulent cholangitis occurred in 5.4% of patients with JPDD compared with 2.6% of the control patients (\( p = 0.059 \)) (Fig. 2).

Congenital alterations of pancreatic anatomy such as pancreas divisum were not found more often in patients with JPDD than in control patients (4% vs. 3.4%; \( p = 0.69 \)). In patients with JPDD, acute pancreatitis, defined as pain and serum amylase elevation more than 3 times normal value, was not found significantly more often than in control patients (11.4% vs. 8.9%; \( p = 0.261 \)). Chronic pancreatitis was found with equal frequency in both groups, 4.6% in JPDD vs. 6.9% (\( p = 0.196 \)) in controls (Fig. 3).

The above-mentioned univariate \( p \) values have to be regarded as descriptive. For adjustment for possible confounders and effect modifiers, a multivariate logistic regression model was used with 14 independent variables (Table 2). If those confirmatory multivariate \( p \) values are considered, only technically difficult ERCP (\( p = 0.0061 \)), significant bleeding

Table 2. Results of univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>JPDD (n = 350)</th>
<th>Control (n = 350)</th>
<th>( P ) univariate analysis</th>
<th>Odds ratio univariate analysis [95% confidence interval]</th>
<th>( P ) multivariate analysis</th>
<th>Odds ratio multivariate analysis [95% confidence interval]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.259</td>
<td>0.99 [0.980, 1.006]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female)</td>
<td>0.736</td>
<td>0.95 [0.682, 1.310]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ERCP/EST procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficult ERCP procedure</td>
<td>12.5%</td>
<td>5.1%</td>
<td>&lt; 0.001</td>
<td>2.65 [1.50, 4.69]</td>
<td>0.006</td>
<td>2.29 [1.267, 4.128]</td>
</tr>
<tr>
<td>Significant bleeding after EST</td>
<td>8.8%</td>
<td>4.8%</td>
<td>0.039</td>
<td>1.90 [1.03, 3.51]</td>
<td>0.006</td>
<td>2.34 [1.274, 4.294]</td>
</tr>
<tr>
<td>Retroperitoneal perforation</td>
<td>0.86%</td>
<td>0.86%</td>
<td>1.0</td>
<td>1.0 [0.20, 4.99]</td>
<td>0.735</td>
<td>0.61 [0.036, 10.525]</td>
</tr>
<tr>
<td>Biliary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior cholecystectomy</td>
<td>18.2%</td>
<td>16.9%</td>
<td>0.62</td>
<td>1.10 [0.75, 1.63]</td>
<td>0.664</td>
<td>1.10 [0.708, 1.718]</td>
</tr>
<tr>
<td>Gallbladder stones</td>
<td>29.4%</td>
<td>22.6%</td>
<td>0.039</td>
<td>1.43 [1.02, 2.01]</td>
<td>0.159</td>
<td>1.31 [0.899, 1.919]</td>
</tr>
<tr>
<td>Bile duct stones</td>
<td>46.0%</td>
<td>33.1%</td>
<td>&lt; 0.001</td>
<td>1.72 [1.27, 2.33]</td>
<td>0.012</td>
<td>1.56 [1.105, 2.210]</td>
</tr>
<tr>
<td>Intrahepatic duct stones</td>
<td>1.1%</td>
<td>0.6%</td>
<td>0.686†</td>
<td>2.01 [0.37, 11.05]</td>
<td>0.794</td>
<td>0.74 [0.081, 6.855]</td>
</tr>
<tr>
<td>Recurrent bile duct stones</td>
<td>6.6%</td>
<td>1.4%</td>
<td>0.002</td>
<td>4.85 [1.82, 12.92]</td>
<td>0.408</td>
<td>2.11 [0.361, 12.270]</td>
</tr>
<tr>
<td>Purulent cholangitis</td>
<td>5.4%</td>
<td>2.6%</td>
<td>0.059</td>
<td>2.17 [0.97, 4.88]</td>
<td>0.474</td>
<td>1.37 [0.576, 3.277]</td>
</tr>
<tr>
<td>Pancreatic disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas divisum</td>
<td>4.0%</td>
<td>3.4%</td>
<td>0.69</td>
<td>1.17 [0.53, 2.57]</td>
<td>0.567</td>
<td>1.27 [0.561, 2.871]</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>11.4%</td>
<td>8.9%</td>
<td>0.261</td>
<td>1.33 [0.81, 2.17]</td>
<td>0.069</td>
<td>0.57 [0.313, 1.045]</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>4.6%</td>
<td>6.9%</td>
<td>0.196</td>
<td>0.65 [0.34, 1.25]</td>
<td>0.389</td>
<td>0.74 [0.368, 1.477]</td>
</tr>
</tbody>
</table>

The multivariate logistic regression model included all listed variables as independent variables and JPDD as dependent variable.

*Per year.
†Fisher exact test.
after EST \( (p = 0.0061) \), and bile duct stones \( (p = 0.0116) \) remain significant (Table 2).

**DISCUSSION**

To our knowledge, this is the largest study yet published concerning juxtapapillary duodenal diverticula and their relationship to disorders of the biliopancreatic system (Table 3). Data concerning the association of JPDD and biliary lithiasis are inconsistent. Most investigators report a higher incidence of bile duct stones in patients with JPDD,\(^4\)-\(^{12}\) but the data were not statistically significant in all studies.\(^4\),\(^7\) In earlier studies by our group, JPDD is a main risk factor for bile duct stone recurrence.\(^14\) JPDD has been found to be associated with an increased frequency of biliary disease because of dysfunction of the sphincter of Oddi with consequently ascending bacterial infection from the duodenum. A correlation between bacteria and calcium bilirubinate pigment stones is widely accepted, and it has been suggested that bacteria may play an important part in the pathogenesis of bile duct stones.\(^10\),\(^15\),\(^16\)

JPDD is found in 10% to 15% of patients undergoing ERCP.\(^2\),\(^17\)-\(^19\) In the present study, 350 of 2925 patients (12%) had 1 or more duodenal diverticula. JPDD occurs in the elderly with a slightly higher frequency in women.\(^2\) In our study the median age of patients with JPDD was 71 years, 9 years more than the median age of patients without JPDD \( (p < 0.0019) \). Patients with JPDD had less abdominal pain and more symptoms of biliary obstruction than patients without JPDD. To eliminate these factors, matched-pairs were defined with best fit according to gender, age, and indication leading to ERCP.

In our retrospective analysis, an association of bile duct stones and their recurrence with JPDD was shown. Furthermore, a higher frequency of gallbladder stones was evident \( (29.4\% \text{ vs. } 22.6\%; \ p = 0.039) \). Our data are in accordance with those of other groups with respect to bile duct stones,\(^3\)-\(^8\),\(^10\) but they are contrary to those of other investigators with respect to gallbladder stones.\(^4\)-\(^6\),\(^9\)

Additionally, a higher rate of recurrent bile duct stones was detected \( (6.6\% \text{ vs. } 1.4\%; \ p = 0.002) \). To our knowledge this is the largest series outlining the association of recurrent bile duct stones and JPDD.

It is claimed that JPDD impedes cannulation of the major duodenal papilla.\(^20\) Chang-Chien could not demonstrate a difference in the failure rate of cannulation.\(^21\) The present study shows that cannulation of the papilla associated with JPDD is significantly more difficult \( (12.5\%) \) than cannulation in the absence of a diverticulum \( (5.4\%) \). Despite a reported failure rate of 8.1% to 8.49%\(^21\) in patients with JPDD, in our series cannulation of the papilla had a failure rate of only 4.6% as consequence of the diverticulum. The postinterventional complication rate for EST did not differ much from that in other series.\(^22\) Bleeding after EST was significantly more frequent in patients with JPDD \( (8.8\% \text{ vs. } 4.8\%) \), but was not as common as reported by Boender et al.\(^22\) \( (16\%-32\% \text{ vs. } 2.7\%) \).

Juxtapapillary duodenal diverticula have been found to be associated with an increased frequency of disorders of the biliopancreatic system due to dysfunction of the sphincter of Oddi with resultant biliary bacterial infection.\(^16\),\(^25\) In our series purulent cholangitis was more frequent in patients with JPDD \( (8.8\% \text{ vs. } 4.8\%) \), but was not as common as reported by Boender et al.\(^22\) \( (16\%-32\% \text{ vs. } 2.7\%) \).

### Table 3. Comparison of data from present study with published data

<table>
<thead>
<tr>
<th>Author</th>
<th>Incidence of JPDD</th>
<th>Prior cholecystectomy</th>
<th>Gallbladder stones</th>
<th>Bile duct stones</th>
<th>Acute pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy 1988 (^8)</td>
<td>47/250 (18.8%)</td>
<td>JPDD</td>
<td>–</td>
<td>25/47 (53%)</td>
<td>–</td>
</tr>
<tr>
<td>Skar 1989 (^11)</td>
<td>26/107 (24.3%)</td>
<td>Control</td>
<td>–</td>
<td>46/203 (22.7%)</td>
<td>–</td>
</tr>
<tr>
<td>Hagege 1992 (^9)</td>
<td>96/520 (19.8%)</td>
<td>JPDD</td>
<td>21/96 (21.9%)</td>
<td>17/96 (17.7%)</td>
<td>–</td>
</tr>
<tr>
<td>Uomo 1996 (^7)</td>
<td>58/433 (13.4%)</td>
<td>JPDD</td>
<td>80/424 (18.8%)</td>
<td>36/58 (62%)</td>
<td>–</td>
</tr>
<tr>
<td>Leivonen 1996 (^5)</td>
<td>84/1735 (4.8%)</td>
<td>JPDD</td>
<td>153/375 (40.8%)</td>
<td>93/375 (24.8%)</td>
<td>–</td>
</tr>
<tr>
<td>Own data</td>
<td>350/2925 (12%)</td>
<td>JPDD</td>
<td>103/320 (32.2%)</td>
<td>18/320 (5.6%)</td>
<td>–</td>
</tr>
</tbody>
</table>

\[ \text{Leivonen 1996} \]

\[ \text{Own data} \]

\[ \text{Kennedy 1988} \]

\[ \text{Skar 1989} \]

\[ \text{Hagege 1992} \]

\[ \text{Uomo 1996} \]

\[ \text{Leivonen 1996} \]

\[ \text{Own data} \]
pancreatitis in association with JPDD is mainly of biliary origin. However, Uomo et al.\textsuperscript{7} demonstrated an association of JPDD with acute idiopathic pancreatitis and postulated that the duodenal diverticulum is a risk factor for acute idiopathic pancreatitis. Our results do not support a correlation for JPDD with acute pancreatitis.

Despite some case reports suggesting an association of chronic pancreatitis with a diverticulum close to the major papilla,\textsuperscript{2} our patients with JPDD did not have chronic pancreatitis more frequently than the control patients.

Apart from univariate analysis of our results, a multivariate logistic regression model was used to adjust for possible confounders and effect modifiers. In this multivariate logistic regression model the 14 main variables listed in Table 2 were included. After this procedure the variables technically difficult ERCP procedure, significant bleeding after EST, and bile duct stones remained significant and therefore have to be regarded as independent risk factors associated with JPDD.

After the multivariate analysis, recurrent bile duct stones and gallbladder stones were no longer significant. One possible clinical explanation is that only patients with bile duct stones in their history can develop recurrent bile duct stones. After adjustment for bile duct stones in both groups, the significance must disappear because recurrent bile duct stones are dependent on the previous existence of bile duct stones. Another possible reason is that the number of pairs of patients studied (350) is too low for a multivariate regression model with 14 independent variables. The same reasoning may explain the change to a significant difference for gallbladder stones.

In our model, there is a trend toward more frequent purulent cholangitis in patients with JPDD. But according to the multivariate logistic regression model, it is not an independent risk factor associated with JPDD. This can be interpreted to mean that the higher cholangitis rate associated with JPDD is based only on the bile duct obstruction resulting from bile duct stones rather than on specific mechanisms associated with JPDD, for example, ascending bacteria. This is in contrast to the above-mentioned studies that maintain that bacteria ascending from the duodenum may play an important pathophysiologic role in patients with JPDD.\textsuperscript{10,15,16} The explanation for this might also be the high number of variables in comparison with the number of patients studied.

In conclusion, JPDD is associated with advanced age, a technically more difficult ERCP, and a higher bleeding rate after EST. Patients with duodenal diverticula have a higher frequency of bile duct stones, recurrent duct stones, and gallbladder stones. Acute pancreatitis is not associated with juxtapapillary duodenal diverticulum.

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**REFERENCES**


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