Is there a link between periampullary diverticula and biliopancreatic disease? An EUS approach to answer the question

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Abstract

Background: Many studies, almost all in an Endoscopic Retrograde Cholangiopancreatography (ERCP) setting, have been conducted to establish if a link exists between periampullary diverticula (PADs) and biliopancreatic diseases but the issue is still debated.

Aims: The objective was to clarify the link between PADs and biliopancreatic disease, for the first time using Endoscopic Ultrasound (EUS).

Methods: We retrospectively reviewed our database seeking patients scheduled for EUS with an indication that entailed the exploration of the second duodenum. For each patient with a PAD enrolled in the study, 6 controls were randomly selected.

Results: 2475 patients met the inclusion criteria. Among them, 185 subjects with a PAD were found (prevalence 7.5%), 1110 subjects served as controls. Patients with a PAD had more frequently a history of cholangitis (8.1 vs 2.2%; OR 3.99, $p<0.001$), a higher prevalence of common bile duct (CBD) dilation (44.3 vs 28.2%; OR 2, $p<0.0001$) and a higher prevalence of CBD stones (34.1 vs 19.6%; OR 2.1, $p<0.0001$). No differences were found about history of jaundice, acute/recurrent pancreatitis or EUS signs of chronic pancreatitis.

Conclusion: Whereas PADs were linked with history of cholangitis, CBD stones and dilation, no association was found with pancreatic diseases.

Keywords: choledocholithiasis; cholangitis; endosonography; pancreas.

Introduction

Periampullary diverticula (PADs) are duodenal extraluminal mucosal outpouchings located within 2–3 cm from the ampulla of Vater. If the diverticulum does not involve the ampulla of Vater per se it is termed juxtapapillary diverticulum (JPD), if the papilla is located within the diverticulum it is termed intradiverticular papilla (IDP) [1].

Most PADs are asymptomatic and found incidentally, but about 10% may be symptomatic and in 2% of cases they require surgical therapy. Complications include diverticulitis, haemorrhage, perforation [2]. The complications of the PADs are caused by inflammation or ulceration, or may arise from compression of the duodenal wall, the common bile duct (CBD) or the pancreatic duct due to the proximity to the engorged and distended diverticula. The potential effects of compression of the common bile duct include the formation of stones, pain and jaundice whereas the compression of the main pancreatic duct (MPD) may lead to acute and chronic pancreatitis [3].

It is difficult to establish the real prevalence of the PADs in the general population: the studies report a prevalence between 0.16 and 27%, a variability strictly related to the method used for the diagnosis. The prevalence in studies using barium meals is 0.6-6% [1]; in autopsy studies is 23-32% [4], while in Endoscopic Retrograde Cholangiopancreatography (ERCP) series is 5-27% [1]. In consideration of the possible complications of ERCP, in the last 20 years, with the advent of Endoscopic Ultrasound (EUS), the diagnostic role of ERCP has been reduced.

EUS performed with an oblique anterior viewing (that is a view intermediate between that of a gastroscope and of a duodenoscope) can easily detect PADs. Moreover, duodenal distension with water can allow echoendoscopic detection of PADs overlooked by endoscopic exploration.

Furthermore, in the diagnosis of chronic pancreatitis, EUS has a great sensitivity because it can recognize the presence of minimal pancreatic structural changes and, due to its high-resolution power, is able to diagnose the presence of microliths that could be missed by other diagnostic modalities [5].

With few exceptions [6,7] almost all Authors have found a causal relationship between PADs and lithiasis of the gallbladder and of the common bile duct [3,8-19], instead there is debate on a link with pancreatic disease, with only few papers claiming an increased risk [20-22]. The existence of a possible association between PADs and pancreatic disease remains an unresolved issue. All previous studies were conducted using ERCP or radiological methods (CT or MRCP). Our study, for the first time, had the objective of clarifying the hypothesis of a link between PADs and biliopancreatic disease using EUS, a less risky diagnostic method than ERCP, with a comparable sensitivity in the diagnosis of PADs and higher sensitivity in detecting microliths and subtle pancreatic changes.

Material and Methods

We retrospectively reviewed our Institutional Review Board–approved EUS database seeking patients that underwent EUS from January 2001 to December 2014.

Patients that had undergone EUS for an indication that required the exploration from the second duodenum were included:

- biliary-pancreatic pathology: obstructive jaundice, biliary duct dilatation, cholangitis, increase of cholestasis enzymes, increase of pancreatic enzymes, biliary pain, pancreatitis
- other indications: masses; neuroendocrine tumor; pancreatic cysts; polyps or submucosal lesions; ampulloma.

We excluded patients in whom, for anatomical reasons or previous surgical interventions (e.g., Billroth II gastric resection, pancreaticoduodenectomy), it was not possible to adequately visualize the papilla of Vater and patients in whom the test did not meet sufficient quality criteria (e.g., biliary or pancreatic stent that impaired the examination). We also excluded patients sent to perform EUS-guided fine needle aspiration (EUS-FNA), because in these patients, in which a diagnosis had already been made by another exam, the endoscopic and EUS exploration is more focused on the operative procedure rather than on a thorough investigation of the duodenum and neighbouring structures.

The diagnosis of cholangitis, acute and recurrent pancreatitis and obstructive jaundice was based on medical records. The diagnosis of CBD dilatation, choledocholithiasis, pancreatic duct dilatation was defined if present in the past medical history or found on EUS examination.

The diagnosis of chronic pancreatitis was made relying solely on EUS criteria (presence of at least five out of the nine well-known parenchymal and ductal criteria) [23].

Recurrent acute pancreatitis was defined by the occurrence of at least 3 episodes of acute pancreatitis after exclusion of a possible chronic pancreatitis [24].

The presence of bile gallstones >1 mm was considered biliary lithiasis.

The CBD was considered dilated if the diameter was more than 7 mm with the gallbladder in situ and more than 10 mm after cholecystectomy.

The upper normal limit of the main pancreatic duct diameter in the pancreatic head was set at 3.6 mm.

A PAD was diagnosed when endoscopically detected or when it became visible, after filling the lumen with water, as an extroflexion of the duodenal wall containing aerial microbubbles (Figure 1).

Figure 1.

The examinations were performed under conscious or deep sedation using radial echoendoscopes (GF UM 3, GF UM Q130, GF UM 160, GF UE 160) from Olympus (GmbH Hamburg, Germany) with a 50-55 degrees oblique viewing. All patients signed an informed consent before endoscopy. Three experienced endosonographers carried out the exams. It is our standardized practice to try to visualize endoscopically the papilla with the echoendoscope and then instil 100-200 ml of water through the biopsy channel to fill and extend the duodenal lumen to visualize it endosonographically.

The sample size was calculated based on the prevalence of idiopathic acute pancreatitis in periampullary extraluminal duodenal diverticula patients (13.7%) and in controls (1.8%) [21] and on the prevalence of relapsing or chronic pancreatitis (26% versus 14%) [20] obtained from the two studies in which a statistically significant difference resulted about pancreatic disease between patients with PAD and patients without PAD. Choosing the more stringent criterion, at least 103 patients with PAD and 618 patients without PAD were needed so that the study was adequately powered (for each patient with a PAD, 6 subjects were randomly selected and served as the control group: this ratio between cases and controls seemed adequate to widely overcome the minimum number of patients required to obtain a sufficient statistical power, considering the number of cases found in our study).

On an Excel® spreadsheet we recorded demographic data, EUS findings and relevant clinical data (history of CBD dilation, cholangitis, choledocholithiasis, pancreatitis).

Statistics

Continuous variables were expressed as mean ± standard deviation (SD). The Chi-square, or Fisher's exact test when appropriate, and the non-parametric Mann-Whitney U test were applied for categorical and continuous variables respectively. The multivariate analysis (Logistic regression) was performed to assess if the variables that were found statistically significant at the univariate analysis remained statistically significant after correction for age and gender biases. To calculate the required sample size of the two groups a type I error –

alpha of 0.05 and a type II error – beta of 0.2 were accepted. A p value of less than 0.05 was considered significant. A statistical software program (SPSS version 11.0, SPSS Inc., Chicago, IL) was employed.

Ethical considerations

All patients received a written information about the endoscopic procedure and gave informed consent for clinical data collection. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

Results

Two thousand four hundred seventy-five patients were included in the study. Among them, the presence of a PAD was diagnosed in 185 subjects (prevalence 7.5%). Among the 2290 patients without PADs, 1110 subjects were randomly selected and served as controls (6 controls were selected for each PAD patient) (Figure 2).

Figure 2.

Patients with PADs were older than controls: mean age 69.8 ± 11.3 vs 61.4 ± 13.9 years ($p<0.0001$); no statistically significant difference between PAD patients and controls was demonstrated about the gender (male/female =

89/96 among patients with PADs, 527/583 among patients without PADs, p = 0.94).

Data about biliary diseases are reported in Table 1.

Table 1.

Regarding the data obtained from the clinical history, a higher prevalence of cholangitis was found in PAD patients than in controls (8.1% vs 2.2%, OR 3.99, p<0.0001).

Concerning the data resulting from the clinical history or from EUS, patients with PAD had a greater prevalence of dilatation of the CBD (44.3% vs. 28.2%, OR 2.03; p<0.0001) and a higher prevalence of choledocholithiasis (34% vs. 19.6%, OR 2.11, p<0.0001) compared with controls. No statistically significant difference was found for the prevalence of obstructive jaundice.

Data about pancreatic disease are reported in Table 2.

Table 2.

No statistically significant difference was found for the occurrence of acute, recurrent or chronic pancreatitis or pancreatic duct dilatation between PAD patients and controls.

Patients with PADs were further divided according to the location of the papilla of Vater with respect to the diverticulum [25]: 55/185 had a type I-PAD

(intradiverticular papilla), 64/185 type II (juxtapapillary diverticulum) and 66/185 type III (periampullary diverticula). The three groups were similar for age and gender and no difference was found in the prevalence of biliopancreatic disease (Table 3).

Table 3.

Multivariate analysis

A clinical history of cholangitis was present in 39 out of 1295 subjects (3.01%).

At logistic regression analysis, male gender and presence of PAD were statistically associated with cholangitis (p=0.03 and p=0.0006, respectively); conversely age was not a risk factor for cholangitis (p=0.09). The male gender gave a cholangitis OR of 2.08 (IC 95% = 1.07 - 4.07), the presence of PAD gave an OR of 3.35 (IC 95% = 1.67 - 6.68).

The dilatation of the CBD (either in the clinical history or found at EUS) was found in 517 out of 1295 subjects (39.9%). At logistic regression analysis the age and the presence of PAD were statistically associated with the dilatation of the CBD (p<0.0001 and p=0.009, respectively); on the contrary gender was not statistically associated with the dilatation of the CBD (p=0.94). An older age had a CBD dilatation OR of 1.04 (IC 95% = 1.03 - 1.05), the presence of PAD gave an OR of 1.55 (IC 95% = 1.12 - 2.14).

Choledocholithiasis was present (in the clinical history or found at EUS) in 337 out of 1295 subjects (26%). At logistic regression analysis the age and the

presence of PAD were statistically associated with the dilatation of the CBD (p=0.004 and p=0.001, respectively); conversely no association was found with gender (p=0.62). A greater age gave a dilatation of the CBD OR of 1.01 (IC 95% = 1 - 1.02), the presence of PAD had an OR of 1.9 (IC 95% = 1.37 - 2.67).

Discussion

Many Authors have investigated whether a link exists between PADs and biliopancreatic disease. The early studies were based on autopsy findings or barium meal. In the 80s ERCP became the first-choice method in the diagnostic and therapeutic evaluation of pancreas and biliary tract and the most recent studies on the topic were almost all conducted using this method (Table 4).

Table 4 [3,6-10,12,14-16,18-22,26-44].

In most of these studies a link was found between PADs and choledocholithiasis, but controversy exists about a relationship with CBD dilation, history of jaundice and acute cholangitis.

The pathological mechanism of this association is explained by several hypotheses. The mechanical pressure exerted by the diverticula on the distal part of the CBD is the most quoted mechanism. The larger the PAD and the closer it is to the papilla, the more it may disturb the bile flow [32]. Another hypothesis is related to the dysfunction of the sphincter of Oddi (SO), which is believed to be caused by the accumulation of food in the diverticula,

compressing the end of the bile duct as well as SO and leading to stricture of the sphincter [1].

Some Authors claim that PADs may exert the same effect on the main pancreatic duct [45], but a link between PADs and pancreatic disease is far from being demonstrated: only few studies have addressed the topic and inconclusive results have been reached.

Uomo et al. [21], in a study conducted on 439 patients undergoing ERCP, showed a higher incidence of "idiopathic" acute pancreatitis among patients with diverticula than in patients without PAD, suggesting that this finding should be included in the possible causes of pancreatitis of unknown origin. However, the greater prevalence of pancreatitis as an indication to ERCP could be a bias.

The prevalence of PADs (7.5%) in our population was similar to that reported in the literature, even if a bit lower than the one found in an ERCP setting. The execution of ERCP, as a diagnostic or therapeutic method, is strictly related to a strong suspicion of biliopancreatic disease, and therefore it can be assumed that a higher prevalence of PADs can be due to a selection bias of the patients.

In other words, the prevalence we found could reflect the prevalence of PADs more accurately than in the studies conducted during ERCP.

From a demographic point of view, the previous studies have found a higher prevalence of PADs at an older age, while a clear gender correlation has not been demonstrated. Our results were consistent with the literature, showing that subjects with PADs were 8.4 years older than subjects without PADs, while no statistically significant differences were found for gender.

As far as biliary disease is concerned, our data agree with most of the previous literature: indeed, we found a higher prevalence of CBD dilation, cholelithiasis and history of cholangitis among patients with PADs.

On the other hand, our data agree with the studies that deny the existence of an association between PADs and pancreatic pathology: we did not find a link with acute pancreatitis, chronic pancreatitis and recurrent pancreatitis. Since we have used, for the first time in the literature, a diagnostic method (EUS) with a high sensitivity in the diagnosis of minimal pancreatic changes, we can suppose that a relationship between PAD and, at least, chronic pancreatitis can be ruled out with reasonable certainty.

Some limitations of our study must be discussed. Unlike Ozogul et al. [25], we did not find that the type of diverticulum had an influence on the risk of biliary or pancreatic pathology, but we cannot be sure that our classification of PADs, based on the echoendoscopic or endoscopic images (but using an instrument with anterior oblique viewing and not a lateral one), has been completely accurate. In the same way, we cannot be sure we have not overlooked some PADs, but an estimate of the PADs prevalence was not the primary goal of our study. Due to the limitations of the method we used, it has not been possible to analyse the effect of the diverticulum diameter, as its measurement with EUS cannot be considered reliable because it is influenced by the degree of water filling, by the peristalsis, and by artefacts produced by air or ingests in its lumen.

As in almost all the published studies, we performed a retrospective analysis; this is in part compensated by the large number of patients we analyzed. The mean age of the PAD group was greater than that of the control group and this

might in part explain the greater risk for cholangitis, choledocholithiasis and CBD dilatation. To overcome this bias, an adjustment about the confounding variables (multivariate analysis) has been performed to adjust for age and gender confounding factors: the history of cholangitis did not result influenced by the age and the presence of PAD resulted statistically associated to the CBD dilation and the cholelithiasis also at the multivariate analysis. Finally, the missing data concerning the previous cholecystectomy and the presence of cholelithiasis prevented us not only to assess whether there is a relationship between PADs and gallbladder disease, but also to determine if the stones we found in the common bile duct had to be considered migrated from the gallbladder or originated in the CBD itself. Another bias, directly connected with the retrospective nature of the study, was that the patients may have omitted to recall a previous episode of acute pancreatitis or cholangitis, but every effort was made to minimize this problem by a thorough consultation of the clinical data of the patients.

Finally, we did not analyse our data to asses if “old” echoendoscopes were less performant in terms of detection of subtle pancreatic changes than the “new” ones, but this possible bias in intrinsic in a study that spans so many years.

In conclusion, our study evaluated for the first time the prevalence of PADs with EUS. With this diagnostic modality we investigated the presence of a possible association with pancreatic and biliary disease. We confirmed, in agreement with the existing literature, an association between diverticula and choledocholithiasis, cholangitis and common bile duct dilatation. No statistical association was found between PADs and acute, recurrent or chronic

pancreatitis or with pancreatic duct dilatation. In this context the study we conducted, using EUS, must be considered very reliable due to the high sensitivity of this technique in diagnosing minimal and initial changes in the pancreatic parenchyma and in the pancreatic ductal system. Our results should be confirmed by prospective studies that will eliminate the bias of patients' omitted recall of a previous episode of acute pancreatitis, but this study is the first in the world that studied the clinical relevance of the occurrence of PAD with an EUS-approach.

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Figure 1. EUS image of a periampullary diverticulum: external to the duodenal wall and next to the common bile duct (asterisk) the artefacts produced by air in the diverticulum are visible (dotted circle)

Figure 2. Flow-chart of patient selection