Functional Gallbladder and Sphincter of Oddi Disorders

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The functional disorder of the gallbladder (GB) is a motility disorder caused initially either by metabolic abnormalities or by a primary motility alteration. The functional disorders of the sphincter of Oddi (SO) encompass motor abnormalities of either the biliary or the pancreatic SO. Dysfunction of the GB and/or biliary SO produce similar patterns of pain. The pain caused by a dysfunction of the pancreatic SO can be similar to that of acute pancreatitis. The symptom-based diagnostic criteria of motility dysfunction of the GB and biliary SO are episodes of moderate to severe steady pain located in the epigastrium and right upper abdominal quadrant that last at least 30 minutes. GB motility disorder is suspected after gallstones and other structural abnormalities have been excluded. This diagnosis should then be confirmed by a decreased GB ejection fraction induced by cholecystokinin at cholescintigraphy and after disappearance of the recurrent biliary pain after cholecystectomy. Symptoms of biliary SO dysfunction may be accompanied by features of transient biliary obstruction, and those of pancreatic SO dysfunction are associated with elevation of pancreatic enzymes and even pancreatitis. Biliary-type SO dysfunction is more frequently recognized in postcholecystectomy patients. SO manometry is valuable to select patients with sphincter dysfunction; however, because of the high incidence of complications, these patients should be referred to an expert unit for such assessment. Thus invasive tests should be performed only in the presence of compelling clinical evidence and after noninvasive testing has yielded negative findings. The committee recommends that division of the biliary or pancreatic sphincters only be considered when the patient has severe symptoms, meets the required criteria, and other diagnoses are excluded.

The biliary tract transports, stores, and regulates the continuous secretion of hepatic bile. Bile is transported by the intra- and extrahepatic bile ducts and delivered into the duodenum to contribute to the digestion and absorption of fats. During the interdigestive phase, the resistance of the sphincter of Oddi (SO), mainly because of its phasic contractions, increases intraductal pressures triggering a choledocho-cystic duct reflex that relaxes the gallbladder (GB).[1,2] These pressure changes create a gradient between the common bile duct and the GB diverting the bile flow toward the GB through the cystic duct. However, about 25% of the hepatic bile manages to enter into the duodenum probably in between phasic contractions of the SO.[3] It also appears that during the interdigestive and digestive phases bile is continuously mobilized by propulsive and nonpropulsive contractions within the GB and through the cystic duct. The bile flow through the cystic duct is complex, and several studies have shown that the flow through the cystic duct is bidirectional. The bidirectional flow through the cystic duct can be best explained by the GB functioning as a bellows contracting and relaxing intermittently.[4,5] The net effect during the interdigestive phase is storage, whereas in the digestive phase it is net emptying of bile from the GB. Some of the contractions are associated with emptying, whereas others are nonpropulsive and simply appear to stir its bile contents.[6] The physiological significance of the nonpropulsive contractions is unclear, although they may stir the GB contents to avoid precipitation of relatively insoluble constituents such as cholesterol and bilirubin. These propulsive contractions become stronger and propulsive during the phase III of the migrating motor complex of the antrum, resulting in partial GB emptying. In the digestive phase, there is net bile emptying into the duodenum because of the GB contraction and SO relaxation initiated by the sequential activation of cephalic, antral, and intestinal neurohormonal mechanisms. The SO also plays a rel-

Abbreviations used in this paper: ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; GB, gallbladder; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; MRCP, magnetic resonance cholangiography; SO, sphincter of Oddi; SOM, sphincter of Oddi manometry; US, ultrasonography.

0016-5085/06/$32.00
doi:10.1053/j.gastro.2005.11.063

evant role in regulating the flow of pancreatic secretions into the duodenum. Derangements of any of these components may lead to intermittent upper abdominal pain, transient elevations of liver or pancreatic enzymes, common bile duct dilatation, or episodes of pancreatitis.

E. Functional GB and SO Disorders

GB and SO dysfunctions are relatively rare conditions, but their main clinical presentation, pain in the upper right abdominal quadrant and in the epigastrum, is not easily distinguished from that occurring in high prevalence conditions such as gastroesophageal reflux disease (GERD), irritable bowel syndrome (IBS), functional dyspepsia, and cholelithiasis and in high risk complications caused by cholecystitis and pancreatitis. In addition, SO dysfunction itself can be the cause of liver and pancreatic abnormalities. Therefore, these disorders need to be excluded before patients suspected of having functional disorders of the GB and SO are submitted to extensive investigations with invasive procedures and to inappropriate endoscopic and surgical treatments.

The present diagnostic criteria and guidelines for clinical evaluation and treatment have been developed taking into consideration the peculiar aspects of functional disorders of GB and SO that differ substantially from other functional gastrointestinal disorders. As noted in Table 1, the functional GB and SO disorders (category E) are subcategorized into functional GB disorder (E1), functional biliary SO disorder (E2), and functional pancreatic SO disorder (E3). In comparison to the previous Rome II criteria, the major change in the proposed criteria is to make them more stringent to reduce the number of unnecessary invasive procedures and surgical operations in patients presenting with upper abdominal pain. Biliary and pancreatic pain should be defined by site, severity, modality of onset, duration and by the absence of typical symptoms of GERD, functional dyspepsia, and IBS. The characteristics of biliary and pancreatic pain in these functional disorders of the GB and SO are not substantiated by any published evidence. They are based on similarities with the characteristics of the pain experienced by patients with biliary lithiasis and in those with pancreatitis. It is also based on the consensus reached by the authors of this article. Consequently, these consensus-based symptomatic criteria should be considered only as a generalization that does not necessarily hold true in every patient. However, by excluding GERD, IBS, functional dyspepsia, and chronic abdominal pain, it will be possible to reduce unnecessary invasive procedures and surgical interventions. Psychosocial aspects appear to be variably interrelated with functional gastrointestinal disorders. These relationships also may occur in patients with functional disorders of the GB and SO. Our knowledge of their influence in these disorders is limited because appropriate epidemiological studies have not been performed because of the lack of uniform diagnostic criteria of these conditions.

It is also possible that the syndrome of chronic functional abdominal pain (see "Functional Abdominal Pain Syndrome" on page 1492 in this issue) may manifest itself with clinical characteristics similar to biliary pain. This condition should be suspected in those patients in whom repeated episodes of biliary-like pain are not associated with any laboratory, endoscopic, ultrasonographic, radiologic, scintigraphic, or manometric findings that support the presence of biliopancreatic alterations.

Patients with upper abdominal pain who do not meet the Rome III symptom-based criteria for functional GB and SO pain should not be submitted to endoscopic retrograde cholangiopancreatography (ERCP) or other invasive procedures. Those qualifying with the Rome III criteria should be assessed initially with noninvasive procedures and eventually with therapeutic trials that will more likely identify the majority of patients whose pain is not of biliopancreatic origin and therefore will not require any further investigation. This approach will also select a small minority of those patients who may require further invasive procedures and who should be referred to dedicated centers to the study and treatment of biliopancreatic disorders with proper equipment and trained staff (see clinical evaluation). Furthermore, the Geenen–Hogan biliary subtypes classification of SO dysfunction has been revised to avoid early ERCP investigation by using noninvasive imaging tests.

The caution to avoid performing unnecessary ERCPs is because of the potential complications of this procedure, mainly pancreatitis, which vary widely with the experience of the endoscopist and whether it is performed for diagnostic or therapeutic purposes. In the literature, the incidence of postprocedure pancreatitis can approach 24%, and major complications and death have been reported to vary from 1.4% to 1.8% and 0% to 0.3%, respectively, for diagnostic procedure, and 5.0% to 9.0% and 0.5% to 0.9%, respectively, for therapeutic procedure.

Table 1. Functional Gastrointestinal Disorders

E. Functional gallbladder and sphincter of Oddi disorders
E1. Functional gallbladder disorder
E2. Functional biliary sphincter of Oddi disorder
E3. Functional pancreatic sphincter of Oddi disorder

E. Diagnostic Criteria for Functional GB and SO Disorders

Must include episodes of pain located in the epigastrium and/or right upper quadrant and *all* of the following:

1. Episodes lasting 30 minutes or longer
2. Recurrent symptoms occurring at different intervals (not daily)
3. The pain builds up to a steady level
4. The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5. The pain is not relieved by bowel movements
6. The pain is not relieved by postural change
7. The pain is not relieved by antacids
8. Exclusion of other structural disease that would explain the symptoms

Supportive criteria

The pain may present with 1 or more of the following:

1. Pain is associated with nausea and vomiting
2. Pain radiates to the back and/or right infrasubscapular region
3. Pain awakens from sleep in the middle of the night

E1. Functional GB Disorder

Definition

GB dysfunction is a motility disorder of the GB that manifests symptomatically with biliary pain as a consequence of either an initial metabolic disorder (ie, supersaturated bile with cholesterol[7]) or a primary motility alteration of the GB in the absence, at least initially, of any abnormalities of bile composition.[8] It is likely that the latter condition, by causing bile stasis, may alter over a period of time, bile recycling and bile composition within the GB. Both conditions may eventually lead, over a period of time, to the development of organic abnormalities (eg, gallstones and acute cholecystitis). The symptoms of these organic and functional conditions appear to be indistinguishable from one another, and therefore their differential diagnoses require a careful diagnostic workup.

Epidemiology

The prevalence of GB dysfunction is not known. Large population-based studies have reported that prevalence of biliary pain in ultrasonography (US)-negative subjects with GB in situ varies from 7.6% in men to 20.7% in women.[9,10]

E1. Diagnostic Criteria for Functional GB Disorder

Must include *all* of the following:

1. Criteria for functional GB and SO disorders
2. GB is present
3. Normal liver enzymes, conjugated bilirubin, and amylase/lipase

Clinical Presentation

The most specific symptom attributed to functional disorders of the GB appears to be biliary pain, and therefore the crucial steps in the diagnosis are a thorough history supported by objective evidence of GB dysfunction and exclusion of structural abnormalities. However, further research will be necessary to assess whether these rigidly defined criteria will be able to select patients with functional GB disorders. These patients will need to be evaluated with longer follow-ups for at least 1 year after cholecystectomy. In the meantime, we are proposing the following criteria for this diagnosis:

1. Absence of gallstones, biliary sludge, or microlithiasis
2. An abnormal GB ejection fraction of less than 40% by using a continuous intravenous cholecystokinin octapeptide infusion over a 30-minute period
3. A positive therapeutic response with absence of the recurrent pain for longer than 12 months after cholecystectomy

Laboratory and Instrumental Investigations

The symptoms of GB dysfunction must be differentiated from organic disease and other more common functional disorders including functional dyspepsia and IBS in which symptoms do occur daily for at least short intervals (few days or weeks).

Tests of liver biochemistries and pancreatic enzymes should be obtained in those patients with the previously mentioned symptomatic criteria. These tests are normal in the presence of GB motility dysfunction. The findings of abnormal liver or pancreatic enzyme levels or both indicate that other diagnoses should be considered. To rule out calculus biliary disease, which can produce similar symptoms, the following investigations need to be performed; however, some of them may not be available and some are obsolete.

Ultrasound. Transabdominal ultrasonographic study of the entire upper abdomen is mandatory in

patients with the previously mentioned symptoms. In the presence of GB dysfunction, the biliary tract and pancreas appear normal on US. In particular, gallstones or sludge cannot be shown. US usually detects stones within the GB equal to or greater than 3 to 5 mm in diameter, but it has a low sensitivity to detect smaller stones.[11] US detection of stones or sludge within the common bile duct is even more difficult. Endoscopic US is more sensitive than traditional transabdominal US in detecting microlithiasis (tiny stones <3 mm) and sludge within the biliary tract.[12]

Endoscopy. In the presence of normal laboratory and ultrasonographic findings, an upper gastrointestinal endoscopy is usually indicated. The diagnosis of GB dysfunction is suspected in the absence of significant abnormalities in the esophagus, stomach, and duodenum.

Microscopic bile examination. To exclude microlithiasis as a cause for these symptoms, a careful microscopic examination of GB bile could be performed. The detection of microlithiasis and cholesterol microcrystals is best accomplished by a careful examination of GB bile obtained directly at the time of ERCP or by aspiration from the duodenum during endoscopy after cholecystokinin (CCK) stimulation. The resultant bile should appear deep golden yellow to dark green-brown. Pale yellow bile from the common duct is not appropriate. Even in those patients with cholesterol gallstones or sludge, this hepatic bile is often free of cholesterol microcrystals being insufficiently concentrated to nucleate. The collected bile should be immediately centrifuged and examined. Two types of deposits may be evident: cholesterol crystals and/or calcium bilirubinate granules. Cholesterol microcrystals are birifringent and rhomboid shaped and best visualized by polarizing microscopy. The presence of cholesterol crystals provides a reasonably high diagnostic accuracy for microlithiasis[13–15] if properly performed. Bilirubinate granules are red-brown and can be detected by simple light microscopy. These crystals are significant only in freshly analyzed bile.

Tests of GB motor dysfunction are shown in Figure 1.

Assessment of GB emptying by cholescintigraphy. Cholescintigraphy is performed after the administration of technetium 99m–labelled iminodiacetic acid analogs. These compounds have a high affinity for hepatic uptake, are readily excreted into the biliary tract, and concentrated in the GB. The net activity-time curve for the GB is then derived from subsequent serial observations, after either CCK administration or the ingestion of a meal containing fat. GB emptying is usually expressed as GB ejection fraction, which is the percentage change of net GB counts after the cholecystokinetic stimulus. A low GB ejection fraction has been considered

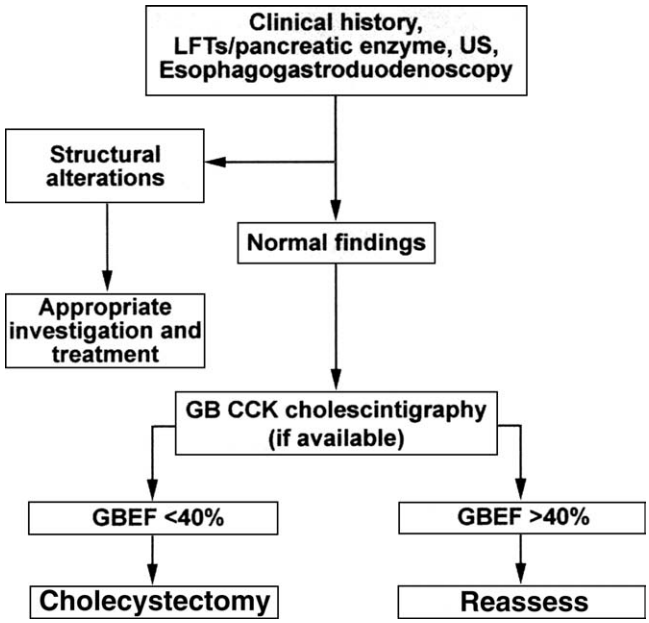

Figure 1. Algorithm of the diagnostic workup and management of functional GB disorders.

evidence of impaired GB motor function that, in the absence of lithiasis, could identify patients with primary GB dysfunction.

The most widely used and validated stimulus to contract the GB has been the slow intravenous infusion of CCK analogs, especially CCK-8 over a 30-minute period.[16,17] In some countries, CCK preparations have not been approved for human use. Fatty meals and variable bolus injections of CCK do not yield consistent results.

Reduced emptying can arise from either impaired GB contraction or increased resistance of the SO because of an elevated basal tone. Furthermore, several other conditions that do not necessarily present with biliary pain can be associated with reduced GB emptying such as obesity, diabetes, and several drugs (eg, calcium channel antagonists and oral contraceptives). An accurate medical history should exclude secondary causes of impaired GB motility. Two systematic reviews that did not discriminate between slow and rapid intravenous infusion of CCK have concluded that there is no sufficient evidence to recommend the use of CCK cholescintigraphy to select patients for cholecystectomy.[18,19]

Assessment of volume changes by transabdominal real-time US. Unlike cholescintigraphy, this method measures GB volume and obtains serial measurements during fasting or after a meal or the intravenous infusion of CCK analogs. In addition, US allows for assessment of residual volume after emptying and the rate of refilling after GB contraction.

US may be helpful when radiation should be avoided. One deficiency in the technique is the fact that it is

operator dependent, and the results may not be reproducible between different centers; therefore, the diagnostic role, if any, of ultrasonographic assessment of GB emptying has not become the standard in GB dysfunction. Further prospective randomized studies are needed to better understand the predictive value of CCK cholescintigraphy or CCK US to recommend cholecystectomy in patients with suspected GB motility dysfunction.

Pain provocation test. A stimulation test with CCK attempting to duplicate biliary pain has been historically used as a diagnostic investigation. This test has low sensitivity and specificity in selecting patients with GB dysfunction who respond to therapy. This may relate to problems in the subjective assessment of pain and the use of bolus injections of CCK. The latter can induce pain by stimulating intestinal contractions.

Diagnostic Workup for Patients With Suspected Functional GB Disorder

Based on the consensus reached by the authors of this article, the diagnostic workup reported in Figure 1 is recommended. The following comments summarize the proposed diagnostic workup.

1. Symptoms consistent with a biliary tract etiology should be evaluated by US examination of the biliary tract, liver biochemistry, and pancreatic enzyme measurements. If the results are normal, upper gastrointestinal endoscopy is recommended.
2. If any of these investigations detect abnormalities, appropriate investigation and treatment should follow.
3. If no abnormal findings are detected, a dynamic cholescintigraphic GB study with the administration of a CCK analog should be performed.
4. If GB emptying is abnormal (<40%) and there are no other conditions associated with reduced GB emptying, the diagnosis of GB dysfunction is likely; cholecystectomy is therefore the most appropriate treatment.

E2. Functional Biliary SO Disorder

Definition

SO dysfunction is the term used to define motility abnormalities of the SO associated with pain, elevations of liver or pancreatic enzymes, common bile duct dilatation, or episodes of pancreatitis. The SO is situated strategically at the duodenal junction of the biliary and pancreatic ducts. SO dysfunction may result in either biliary or pancreatic disorders. Although SO dysfunction may be present in patients with an intact GB, most of the clinical data concerning SO dysfunction has been obtained from postcholecystectomy patients.

E2. Diagnostic Criteria for Functional Biliary SO Disorder

Must include *both* of the following:

1. **Criteria for functional GB and SO disorder**
2. **Normal amylase/lipase**

Supportive criterion

Elevated serum transaminases, alkaline phosphatase, or conjugated bilirubin temporally related to at least two pain episodes

Epidemiology

The prevalence of symptoms suggesting SO dysfunction was noted in 1.5% of cholecystectomized patients in a survey on functional gastrointestinal disorders.[20] This survey confirmed that SO dysfunction affects females more frequently than males and indicated a high incidence of work absenteeism, disability, and health care use.[20] SO dysfunction has been detected in less than 1% of a large consecutive series of cholecystectomized patients and in 14% of a selected group of patients complaining of postcholecystectomy symptoms.[21]

Patients with biliary SO dysfunction after cholecystectomy have been arbitrarily classified according to their clinical presentation, laboratory results, imaging tests, and ERCP findings.[22] The authors of this article have revised this classification system to make it more applicable to clinical practice and, whenever possible, to avoid the invasive ERCP procedure. In this revised classification system, noninvasive methods, instead of ERCP, are used to measure the common bile duct diameter and suggest that contrast drainage times are not required. This revision is in accordance with the use of noninvasive imaging technique, namely US, in the early phases of the diagnostic workup of biliopancreatic disease and does not require contrast drainage times. The authors of this article acknowledge that such revised classification system is based on opinion and should be validated in future clinical studies. Type I patients present with biliary-type pain; abnormal aspartate aminotransferase, alanine aminotransferase, bilirubin, or alkaline phosphatase >2 times normal values documented on 2 or more occasions; and dilated bile duct greater than 8 mm diameter at US. In biliary type I, 65% to 95% of the patients have manometric evidence of biliary SO dysfunction, mainly because of what is thought to be structural alteration of

the SO (stenosis).[22,23] Type II patients present with biliary-type pain and one of the previously mentioned laboratory or imaging abnormalities. In biliary type II, 50% to 63% of the patients have manometric evidence of biliary SO dysfunction.[22,23] Type III patients only complain of recurrent biliary-type pain and none of the previously mentioned laboratory or imaging criteria. In biliary type III, 12% to 59% of the patients have manometric evidence of biliary SO dysfunction.[22,23]

SO dysfunction can involve abnormalities in the biliary sphincter, pancreatic sphincter, or both. The true frequency would then depend on whether 1 or both sphincters were studied. One sphincter could be abnormal and the other normal. In a study that investigated 360 patients by using biliary and pancreatic manometry,[24] basal sphincter pressures higher than 40 mm Hg were present in 11.4% in the biliary SO alone, in 18.9% in the pancreatic SO, and in 31.4%, both sphincters were involved. Furthermore, the frequency of SO dysfunction did not differ whether they were typed by biliary or pancreatic criteria. These findings were supported by a second study[25] with 214 patients, who were labelled type III; 31% had both sphincter pressures elevated, 11% had the biliary one alone, and 17% had the pancreas one alone. Overall, 59% of patients were found to have abnormal basal sphincter pressures. In the same study, among the 123 patients categorized as biliary type II, both sphincters were elevated in 32%, the biliary sphincter alone in 11%, and the pancreas alone in 22%. Overall, 65% of type II patients had an abnormal SO manometry.

Clinical Presentation

Patients present with intermittent episodes of biliary pain sometimes accompanied by biochemical features of transient biliary tract obstruction: elevated serum transaminases, alkaline phosphatase, or conjugated bilirubin (Table 1). SO dysfunction may exist in the presence of an intact biliary tract with the GB in situ.[26,27] Because the symptoms of SO or GB dysfunction cannot be readily separated, the diagnosis of SO dysfunction is usually made after cholecystectomy or, less frequently, after proper investigations have excluded GB abnormalities (normal ejection fraction).

Laboratory and Instrumental Investigations

The symptoms of SO dysfunction must be differentiated from organic disease and other more common functional disorders including functional dyspepsia and IBS in which the pain does occur daily for at least short intervals (few days or weeks). The only method that can directly assess the motor function of the SO is manometry. This technique is not widely available and is invasive with potential and frequent complications. Prolonged studies in expert hands not only result in suboptimal investigations but also may be associated with increased risk of complications, often pancreatitis. In such circumstances, less invasive procedures should be considered first, and if a conclusion cannot be made with this approach, the patient should be referred to an expert biliopancreatic unit for further assessment.

Noninvasive Indirect Methods

Serum biochemistry. SO dysfunction should be suspected in patients with recurrent and transient elevation of liver tests in close temporal relationship to at least 2 episodes of biliary pain. However, the diagnostic sensitivity and specificity of these abnormal liver tests are relatively low.[28]

Magnetic resonance cholangiopancreatography. When SO dysfunction is suspected, it is essential to rule out stones, tumors, or other obstructing lesions of the biliary tree that may mimic SO dysfunction. Magnetic resonance cholangiopancreatography is the best noninvasive method to obtain a cholangiogram or a pancreatogram.[29]

Pain provocative test using morphine (± prostigmine) to detect SO dysfunction was greatly limited by a low sensitivity and specificity. They are no longer recommended.

Ultrasonographic assessment of duct diameter. In the fasting state, the maximal diameter of common hepatic bile duct is normally 6 mm or less.[30] A dilated common bile duct of 8 mm or greater usually indicates the presence of increased resistance to bile flow at the level of the SO; however, the diagnostic usefulness of this finding may be limited because 3% to 4% of asymptomatic cholecystectomized subjects have a dilated common bile duct.[21]

In the fatty meal (cholecystokinin) stimulation test, the fatty meals increase the bile flow caused by the endogenous release of CCK without increasing the bile duct diameter. However, in the presence of a dysfunctional SO, the duct dilates because of obstruction to the flow.[31] Typically, the bile duct diameter is monitored by transabdominal US. The diagnostic yield of this test has not been satisfactory when compared with the results of SO manometry. It is likely that sensitivity and specificity of the test decrease markedly from group I to group III.[31] However, an advantage of the US with a fatty meal is that it can be used in patients with a functioning GB. Its diagnostic usefulness is limited, but it can be used to screen high-risk patients with suspected partial bile duct obstruction.

Table 2. Pressure Profile of Sphincter of Oddi Measured at Common Bile Duct and Pancreatic Duct

	Normal[a]		Abnormal[b]
	CBD	PD	CBD and PD
Duct pressure (*mm Hg*)	7.4 ± 1.7	8.0 ± 1.6	
Basal pressure (*mm Hg*) (8–26)	16.2 ± 5.8	17.3 ± 5.8	>40 mm Hg
Phasic contractions	136.5 ± 25.9	127.5 ± 21.5	>350 mm Hg
Amplitude (*mm Hg*)	(82–180)	(90–160)	
Duration (*sec*)	4.7 ± 0.9	4.8 ± 0.7	
	(3–6)	(4–6)	
Frequency (*/min*) (3–10) (3–10)	5.7 ± 1.4	5.8 ± 1.5	>7/min
Propagation sequence (*%*)			
Simultaneous	55 (10–100)	53 (10–90)	
Antegrade	34 (0–70)	35 (10–70)	
Retrograde	11 (0–40)	12 (0–40)	>50%

CBD, common bile duct; PD, pancreatic duct.
[a]Values are means ± standard deviations; ranges are given in parentheses.
[b]Abnormal values for the CBD[36] and the PD.[37]

Choledochoscintigraphy ([99mTc]/HIDA [hepatic iminodiacetic acid] scan). Dysfunction of the biliary sphincter in postcholecystectomy patients may become apparent when the radionuclide flow into the duodenum is delayed. Several variables have been used to define a positive (abnormal) study. A prolonged duodenal arrival time (choledochoscintigraphy) and a high Johns–Hopkins scintigraphic score have been used.[32,33] There is a good direct correlation between choledochoscintigraphy and SO manometry.

Irrespective of the variable and method used, the specificity of hepatobiliary scintigraphy was at least 90%.[34] The level of sensitivity has been reported to vary substantially according to the investigated variable and the method used. Moreover, case studies have shown that choledochoscintigraphy may predict the outcome of sphincterotomy in SO dysfunction,[32] but randomized studies are needed to support this conclusion. Its role in the selection of patients for the treatment of biliary SO dysfunction awaits future studies.

Invasive Indirect Methods

ERCP. Certain radiologic features during ERCP such as a common bile duct diameter exceeding 12 mm may suggest SO dysfunction.[22] However, the radiographic findings obtained at ERCP are not diagnostic of SO dysfunction. ERCP alone is generally not recommended in the assessment of patients with suspected SO dysfunction because of the frequency of complications. If SO dysfunction is suspected, ERCP must be coupled with a diagnostic SO manometry (SOM), possibly dual endoscopic sphincterotomy (ES), and possibly placement of a pancreatic stent. ERCP with SOM and ES should ideally be performed at referral centers dedicated to the study of biliopancreatic disorders that may include these patients in randomized controlled trials to examine the impact and timing of these therapeutic maneuvers on clinical outcome.[35]

Invasive Direct Methods

Manometry. SO manometry is performed at the time of ERCP. The variables customarily assessed at SO manometry are basal pressure and amplitude, duration, frequency, and propagation pattern of the phasic waves. Normal and abnormal reference values for the SO measured at the common bile duct and Wirsung duct are reported in Table 2.[36,37]

Basal sphincter pressures higher than 40 mm Hg are the only manometric criterion used to diagnose SO dysfunction. Other manometric abnormalities of the SO include increased amplitude of phasic waves, paradoxic response to CCK analogs, increased frequency of phasic waves, and increased number of retrograde waves. More than one of these manometric findings may be found in postcholecystectomy patients with no apparent organic alterations. However, most authorities accept only the basal sphincter pressure as an indicator of SO dysfunction.

Diagnostic Workup for Patients With Suspected Functional Biliary SO Disorder in Cholecystectomized Patients

The diagnostic workup of patients without a GB for suspected SO dysfunction as a cause of biliary-type pain begins with liver biochemistries and pancreatic enzymes, plus a careful elimination of potential structural abnormalities of the biliary and gastrointestinal tract. This would include transabdominal US, computed tomography scan, endoscopic US, magnetic resonance cholangiography (MRCP), and ERCP, depending on the

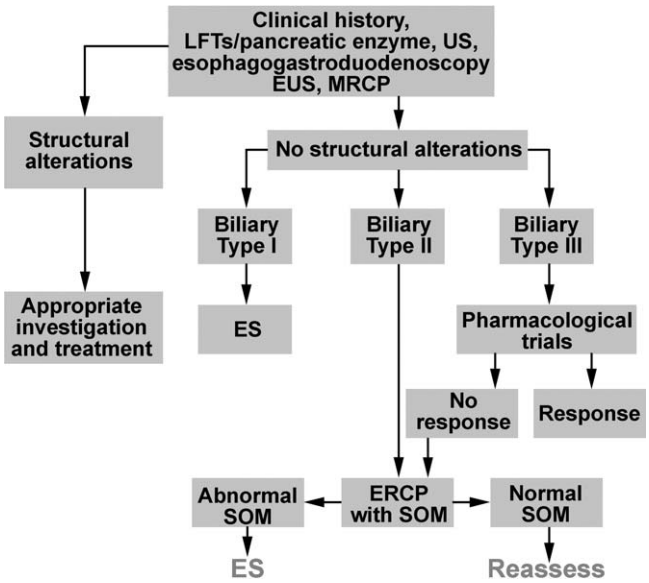

Figure 2. Algorithm of the history, diagnostic workup, and treatment of patients suspected with types I, II, and III functional biliary SO disorder.

resources available. The most practical diagnostic sequence suggested by the authors of this article is as follows: liver and pancreatic enzymes followed by an US, MRCP, and then ERCP with SO manometry as needed (Figure 2).

Choledochoscintigraphy may be a valuable noninvasive test before a decision to undertake SO manometry is made. SO manometry is recommended in biliary type II patients. In patients with biliary type III, invasive procedures should be avoided unless a proper clinical assessment has concluded that potential benefits exceed the risk of complications. Noninvasive investigations and therapeutic trials with proton pump inhibitors, spasmolytic drugs, calcium blockers (nifedipine), and psychotropic agents should be attempted before performing ERCP and SO manometry.

ERCP with SO manometry is indicated if the pain is disabling, noninvasive investigations have not detected structural abnormalities, and there is no favorable response to conservative therapy. As stated in the National Institutes of Health State of the Sciences Conferences in ERCP, perendoscopic SO manometry should ideally be performed at specific referral centers.[35] Endoscopic sphincterotomy is the treatment of choice if SOD is detected at manometry.

Treatment

Patients presenting with the characteristics of biliary type I SO dysfunction may undergo endoscopic sphincterotomy without SO manometry. Nifedipine has been reported to benefit biliary type II patients and a therapeutic trial with this drug may be warranted before submitting the patients to invasive procedures.[36] Two crossover clinical trials of relatively short duration (~12 or 16 weeks) showed symptomatic improvement over placebo.[38,39] However, these therapies need to be evaluated with long-term double-blind clinical trials. If SO dysfunction is detected at manometry in biliary type II and III patients not responding to conservative treatment, endoscopic sphincterotomy is indicated.

Patients with GB in situ. The diagnostic workup of patients with GB in situ is part of the same diagnostic algorithm that has initially excluded the presence of a GB dysfunction. Two main indications are biliary pain in subjects with normal GB ejection fraction and idiopathic recurrent pancreatitis.

E3. Functional Pancreatic SO Disorder

The association between the dysfunction of the SO motility and recurrent episodes of pancreatitis has been reported in case series.[40,41] It has also been reported[41,42] that total division of the SO in manometrically identified patients with SO dysfunction results in abolition of the recurrent episodes of pancreatitis. However, randomized controlled studies are needed.

Patients report recurrent episodes of epigastric pain that are usually not distinguishable from biliary pain, although it can radiate through to the back. The pain episode is accompanied by elevated serum amylase and/or lipase. In the absence of the traditional causes of pancreatitis (no stones, alcohol abuse, pancreas divisum, or any other uncommon causes of pancreatitis), the diagnosis of idiopathic recurrent pancreatitis should be considered. In the last decade, there have been a number of studies that have looked at the genetic makeup of patients with idiopathic recurrent pancreatitis. These have resulted in mutations and polymorphisms that have been described. Mutations in 3 genes, *PRSS1*, *CFTR*, and *SPINK1*, have been associated with pancreatitis.[43,44] These genetic mutations have been associated with early onset of pancreatitis. In addition, R122H or N29I mutations in cationic trypsinogen gene (*PRSS1*) responsible for classic autosomal dominant form of hereditary pancreatitis have been noted in patients with nonhereditary idiopathic recurrent pancreatitis. Although these mutations have been identified, their penetrance is low and indeed may only be sporadic in relationship to idiopathic recurrent pancreatitis. Their role in the pathogenesis of this disease has not been defined.

Epidemiology

The majority of patients who present with SO dysfunction causing recurrent episodes of acute pancreatitis are female.[45] This is similar to the incidence for biliary SO dysfunction. In populations of patients with idiopathic recurrent pancreatitis, patients have a median age in the 40s. The manometric evidence of pancreatic SO dysfunction has been reported in these patients to vary from 15% to 72%.[23,24,46,47]

E3. Diagnostic Criteria for Functional Pancreatic SO Disorder

Must include *both* of the following:

1. **Criteria for functional GB and SO disorder**
2. **Elevated amylase/lipase**

Clinical Presentation

Patients present with intermittent episodes of pain that occur at intervals of months rather than days and are usually associated with a significant rise in serum amylase and lipase. Liver enzymes or bilirubin may also be elevated, depending on the severity of the pancreatitis. According to the anecdotal experience of the authors of this article, in most instances, pancreatitis is not severe when standard severity scores are used to evaluate these patients.

Instrumental Investigations

Noninvasive procedures should be considered first.

Noninvasive procedures. US of the upper abdomen excludes the presence of gallstones, but it does not usually reveal any abnormalities during an episode of acute pancreatitis. However, in the investigation of these patients, US has been used to monitor the diameter of the pancreatic duct during secretin infusion. After the infusion of secretin (1 U/kg per minute) in normal subjects, the pancreatic duct dilates as secretin causes increased secretion of pancreatic juice. On cessation of the secretin infusion, the duct diameter returns to normal within 15 minutes. In patients with pancreatic SO dysfunction, the pancreatic duct may remain dilated for a longer period.[48] This method has been suggested to diagnose SO dysfunction, but it is not widely used because of its low sensitivity.[49]

MRCP. MRCP has been used more recently to evaluate the pancreatic duct in patients presenting with recurrent episodes of pancreatitis. Secretin infusion has also been used to enhance the MRCP images of the pancreatic duct, and these studies have defined abnormalities in the duct that were hitherto unidentified.[50,51] However, the sensitivity and specificity of this investigation have not as yet been determined.

Endoscopic US. Endoscopic US has also been used in patients who present with recurrent pancreatitis, and this investigation has been important in identifying patients with microlithiasis as the cause of the recurrent episodes of pancreatitis. The value of endoscopic US is in its ability to select patients in whom a motility disorder of the sphincter may not be the primary cause of the episodes of pancreatitis.[52]

Invasive Methods

Manometry. Manometry of the SO during ERCP, which was first described over 30 years ago, remains the most direct and objective investigation that selects patients with pancreatic SO dysfunction associated with recurrent episodes of pancreatitis. The manometric technique has been well described previously.[47] It is important to note that recording from the pancreatic SO in patients with recurrent pancreatitis is important because a normal biliary SO may exist in the presence of an abnormal pancreatic SO.[53,54] The major complication after SO manometry is pancreatitis that may require hospital treatment for 48 to 72 hours. It seems that certain types of patients, rather than SO manometry per se, play a major role in postmanometry pancreatitis.[55] To minimize this complication, some units routinely use pancreatic duct stenting after the procedure.[56] Others use an aspiration manometry catheter[57] or electronic microtransducers[58] in the belief that water perfusion is the cause of the pancreatitis. Although all of these techniques have been suggested to reduce the incidence of complications, none have been universally adopted because there are no major studies that have shown their efficacy. Most recently, a back-perfused sleeve manometric device has been developed.[59] Such a device accurately records SO pressures without perfusing water into the pancreatic duct. Its efficacy and safety have not been determined as yet.

Botulinum toxin. More recently, injection of Botox into the SO has been used to select patients who will respond to division of the pancreatic sphincter.[60] Botulinum toxin produces a chemical sphincterotomy that lasts for approximately 3 months. In a limited study, it has been shown to select patients who will respond well to division of the sphincter. Further studies are required before this test can be recommended for this indication.

Stent drainage. Drainage of the pancreatic duct by inserting a stent has also been used to select patients who may subsequently respond to sphincterotomy.[61] The results of this approach have varied in different units, and

there are questions regarding possible damage on the pancreatic duct by the stent.

Diagnostic Workup for Patients With Suspected Functional Pancreatic SO Disorder

The diagnostic workup of patients presenting with pain episodes associated with elevated amylase/lipase requires a careful exclusion of potential structural abnormalities such as microlithiasis or pancreas divisum as the cause of pancreatitis. This includes transabdominal US, computed tomography scan, endoscopic US, MRCP, and ERCP, depending on the patient's clinical picture and resources available. The most practical diagnostic sequence in these patients suggested by the authors of this article in these patients is as follows: after all the traditional aetiologies of pancreatitis have been excluded, patients should undergo liver biochemistry and pancreatic enzymes followed by an US, endoscopic US and/or MRCP, and then ERCP with bile analysis and SO manometry as needed.

The investigation that has stood the test of time in selecting patients who will respond best to division of the sphincter is SO manometry.[51] In a patient with the appropriate clinical presentation, a manometric finding of SO basal pressures in excess of 40 mm Hg does result in a successful clinical outcome to treatment.[45] In patients with idiopathic recurrent pancreatitis, it is important to record from both the biliary and the pancreatic duct sphincter because on occasion abnormalities in the pancreatic SO may be noted in the presence of a normal manometry in the biliary SO.

Treatment

The best available treatment for SO dysfunction that produces recurrent episodes of pancreatitis is total division of the SO.[40–42] The division ensures that both the biliary and the pancreatic sphincters are divided to allow free drainage of pancreatic juice and bile into the duodenum.[62] This treatment is recommended only in patients who have been shown by endoscopic manometry to have abnormal SO dysfunction as demonstrated by an elevated SO basal pressure in excess of 40 mm Hg.

Traditionally, total division of the SO has been performed by an open transduodenal approach to the SO.[40] Nowadays, the treatment of choice for pancreatic SO dysfunction is the endoscopic division of the pancreatic sphincter.[42] Similar to the surgical approach, these patients undergo division of the biliary sphincter and subsequently division of the septum between the biliary and pancreatic ducts using diathermy techniques. The stent is often left in the duct after the procedure using a small diameter stent for a short period of time.[41] The use of stents has reduced the incidence of post-ERCP pancreatitis.[63] The initial results of endoscopic treatments show an efficacy that is similar to that of the surgical approach. However, long-term results of this endoscopic treatment are not available at this time.

Botulinum toxin has been used to treat patients with SO dysfunction. However, botulinum is not effective because its effects are temporary. Similarly, it has not been shown that stenting of the pancreatic ducts has a long-term positive outcome.

Conclusion and Future Directions

Functional disorders of the GB and biliopancreatic SO cause significant clinical symptoms that are clearly associated with motility abnormalities of the GB and SO. However, several aspects of their pathophysiology and clinical symptomatology remain to be clarified.

Future investigations should include clinical studies to study the following:

1. The natural history of functional GB disorders clearly distinguished from those associated with lithogenic bile with excess cholesterol; therefore, it should include analysis of the GB bile constituents and histological and biochemical parameters of inflammation in cholecystectomized specimens
2. The potential role of psychosocial conditions and genetic factors on the pathogenesis of functional biliary and pancreatic SO disorders
3. The relation of these biliopancreatic disorders with other GI functional disorders particularly with IBS and nonulcer dyspepsia
4. The relation to functional GB disorders with or without lithogenic bile with functional SO motility abnormalities
5. The origin and pathogenesis of biliary pain in these functional conditions and whether they are associated with visceral hyperalgesia, particularly in the controversial biliary SO dysfunction type III

A number of noninvasive investigations have been developed that help to confirm the diagnosis of these conditions; however, further evaluations are needed to assess the specific roles of cholescintigraphy in the diagnosis and therapeutic outcome prediction of symptomatic functional disorders of the GB and SO and MRCP in the visualization and dynamic assessment of the papillary region.

Multicenter randomized clinical trials should be directed to the therapy of these conditions to assess the following:[14,15]

1. The medical treatment of functional disorders of the GB and SO (from bile acids [ursodeoxycholic acid], prokinetics, and relaxants to targeted analgesics). Ursodeoxycholic acid may have a therapeutic potential because it has been recently shown that this hydrophilic acid not only decreases the excess of cholesterol from muscle cells in GBs with lithogenic bile but also normalizes the effects of oxidative stress, which may be applicable to the treatment of functional GB disorders.
2. Improved modes of evaluation of outcome studies.

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Received March 15, 2005. Accepted November 3, 2005.

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