Functional Gallbladder Disorder: Gallbladder Dyskinesia

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The occurrence of abdominal pain thought is to resemble gallbladder pain but in the absence of gallstones confronts the clinician with regularity and results in significant health care costs.[1] The estimated prevalence of this disorder is about 8% in men and 21% in women according to population-based studies involving persons with biliary-like pain and normal gallbladder ultrasounds.[2–4] The pathogenesis of this condition, referred to by various names including gallbladder dyskinesia, chronic acalculous gallbladder dysfunction, acalculous biliary disease, chronic acalculous cholecystitis, and biliary dyskinesia, is poorly understood. The term functional gallbladder disorder is currently the accepted Rome consensus nomenclature for this condition and will be used throughout this article. The aim of this article is to clarify the identification and management of patients with suspected functional gallbladder disorder.

CLINICAL PRESENTATION

A critical question that has plagued clinicians for many years is what exactly constitutes biliary-like abdominal pain? Biliary-like abdominal pain originally was described as a pain in the right upper quadrant that was colicky in nature and associated with fatty food intake and various nonspecific gastrointestinal (GI) symptoms.[5] In contrast, the definition recently endorsed by the Rome committee on functional biliary and pancreatic disorders describes biliary-like pain as episodic, severe, steady pain located in the epigastrium or right upper quadrant that lasts at least 30 minutes and is severe enough to interrupt daily activities or require consultation with a physician (**Box 1**).[6,7] The pain may be accompanied by nausea and vomiting, radiate to the back or infrascapular region, or awaken the patient from sleep. In general, an irregular

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Box 1
Rome III criteria for the diagnosis of functional gallbladder disorder

Episodes of pain in the right upper quadrant or epigastrium and all of the following:

Gallbladder is present

Normal liver enzymes, conjugated bilirubin, amylase and lipase

Pain lasts 30 minutes or longer

Recurrent episodes occur at different intervals (not daily)

Pain builds up to a steady level

Pain is severe enough to interrupt the patient's current activities or lead to a visit to a clinician/emergency room

Pain is not relieved by bowel movements, postural change, or antacids

Other structural diseases that may explain the symptoms have been excluded

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periodicity between episodes is characteristic, and the relationship to eating is unreliable. Importantly, pain lasting more than 6 hours is unlikely to be related to the gallbladder when gallstones are not present, and serologic liver and pancreas tests are normal unless due to a complication of gallstone disease (eg, acute cholecystitis, pancreatitis). Despite this clarification of the clinical criteria, there continues to be confusion and significant overlap with other functional GI disorders requiring further validation of these criteria.

PATHOGENESIS

Presumably, the pain associated with functional gallbladder disorder may occur due to increased gallbladder pressure caused by either structural or functional outflow obstruction. Similar to other functional GI disorders, the pathophysiology of functional gallbladder disorder remains poorly understood and may, in fact, represent a constellation of mechanisms. Multiple theories of pathogenesis have been proposed including cholesterolosis, microlithiasis, biliary sludge, chronic cholecystitis, gallbladder dysmotility, narrowed cystic duct, cystic duct spasm, sphincter of Oddi dysfunction, and visceral hypersensitivity.[2,8–10] Two studies, one by Velanovich[11] and one by Brugge,[12] reported a significant association between crystal formation in the bile or in the walls of the gallbladder in patients with functional biliary pain who had undergone cholecystectomy, suggesting that bile saturation or gallbladder dysmotility may lead to crystal growth and eventually gallstones or chronic inflammation. Presumably, pain may occur at any point during the process. Abnormal gallbladder histology, however, has not been a universal finding in patients who experience symptom relief following cholecystectomy for presumed functional biliary pain, with studies reporting changes of chronic cholecystitis ranging from 44% to 100%.[13–15] Furthermore, it remains unclear whether the histologic changes in the gallbladder are a cause or an effect of poor gallbladder contractility.

Impaired gallbladder emptying resulting from hypokinesia of the gallbladder or dyskinesia due to partial obstruction distal to the gallbladder, either structural or functional, also might be responsible for functional gallbladder disorder.[16] Interestingly, given the not uncommon occurrence of abnormalities in gastric emptying and colon transit in these patients, it has been suggested that functional gallbladder disorder

may reflect a panenteric motility disorder.[17] The role of dysfunction at the level of the sphincter of Oddi in patients with presumed functional gallbladder disorder remains unclear.[18–20] To clarify this relationship, Ruffolo and colleagues[19] conducted a prospective study of patients with biliary-type pain and normal-appearing gallbladder. Patients were tested extensively with quantitative cholescintigraphy, sphincter of Oddi manometry, and endoscopic retrograde cholangiopancreatography (ERCP). Approximately 50% of patients were found to have a normal gallbladder ejection fraction (GBEF), and within this group, 57% were found to have sphincter of Oddi dysfunction. Of the patients with low GBEF, 50% also were found to have sphincter of Oddi dysfunction. These findings are supported by results from another study that also failed to find a correlation between sphincter of Oddi pressure and GBEF.[21] Thus, it appears abnormalities in GBEF and sphincter of Oddi pressure occur independent of one another.

NATURAL HISTORY

The natural history of functional gallbladder disorder is poorly understood. Information can be gleaned from a recent study by Krishnamurthy and colleagues[22] They found that a low GBEF based on cholecystokinin-cholescintigraphy (CCK-CS) remains low on repeat testing months to years later. The severity of GBEF reduction increased with time. In those with a normal GBEF, about 30% became abnormally low after a mean duration of about 53 months between studies. How these changes correlate with symptoms over time remains poorly defined.

Additional information on the natural history of this disorder can be learned from an assessment of the outcome of the nonsurgical arms of studies conducted on patients with suspected functional gallbladder disorder. Yap and colleagues[23] randomized 21 patients with abnormal GBEF to cholecystectomy versus no surgery and followed the patients for up to 54 months. Of the 10 patients in the no surgery group, all continued to report symptoms of functional gallbladder disorder. A more recent study reported similar findings, with 50% of patients with abnormal GBEF reporting resolution in symptoms up to 4 years after cholecystectomy, compared with only 16% of those with abnormal GBEF who elected not to pursue cholecystectomy ($P = .039$).[24] In contrast, a retrospective study by Ozden and DiBaise[25] found that 50% of patients with an abnormal GBEF who did not undergo cholecystectomy reported clinical remission of symptoms after up to 3 years of follow-up, similar to the 64% of patients with a normal GBEF who reported resolution of their symptoms. Another retrospective study gathered information from 58 patients treated at two community hospitals, 42 of whom had an abnormal GBEF.[26] Of those 42 patients, 12 of 15 who did not undergo cholecystectomy reported lessening or resolution of symptoms. Finally, a study by Gonclaves and colleagues[27] reported 75% of patients with suspected functional gallbladder disorder who did not have cholecystectomy had persistent symptoms, and only 25% had resolution of symptoms without any treatment. Clearly, these results need to be interpreted with caution given the retrospective nature of most of these studies, the variable length of follow-up and criteria of symptom outcome, and the small number of patients evaluated.

DIAGNOSTIC TESTS

In the setting of biliary-like abdominal pain and a normal gallbladder on transcutaneous ultrasound, the diagnosis of functional gallbladder disorder requires a careful evaluation to exclude other causes of the symptoms, and, at a minimum, serologic testing of liver and pancreatic enzymes and upper endoscopy.[6] Several tests have

been developed in an attempt to more objectively implicate the gallbladder as the source of the symptoms. The technique of analyzing aspirated bile from the biliary system or duodenum to assess for microlithiasis has not been widely accepted due to technical issues with the procedure and poor specificity.[28,29] The use of CCK-provocation of abdominal pain when deciding whether to proceed with cholecystectomy is discouraged. Smythe and colleagues[30] evaluated 58 patients with functional biliary pain who underwent CCK provocation test and gallbladder volumetry before cholecystectomy and did not find a significant difference in symptom outcome following cholecystectomy between CCK provocation positive and negative patients. Furthermore, CCK administration, particularly when infused over a few minutes, is known to stimulate not only the gallbladder but also the duodenum and colon. Because small stones (<5 mm) may be missed with traditional transabdominal ultrasonography, three studies[31–33] have prospectively evaluated patients with biliary-type pain and a normal transabdominal ultrasound using endoscopic ultrasound of the gallbladder, finding a significant number of patients with cholecystolithiasis. In one of these studies, 76% of the patients offered cholecystectomy were pain-free at their 1-year follow-up.[33] Despite these encouraging reports, this technique is not yet widely available, and further studies are necessary to determine its clinical utility, cost-effectiveness, and overall place in the evaluation of these patients.

Functional assessment of gallbladder emptying before and after gallbladder stimulation using either a fatty meal or CCK is currently the most common test used to evaluate patients with suspected functional gallbladder disorder. Oral cholecystography, both with and without CCK stimulation,[34] has demonstrated variable results regarding symptom outcome and is considered insufficiently reliable as a measure of gallbladder function. Presently, CCK-CS with measurement of the GBEF is the most commonly used test to aid in the diagnosis of functional gallbladder disorder.[35,36] Although controversial, the use of CCK-CS has been supported by the Rome committee, which has recommended that, in the presence of biliary-like pain, an absence of gallstones on abdominal ultrasound, and normal liver and pancreatic enzymes, CCK-CS should be the next diagnostic step (**Fig. 1**).[7]

CAVEATS RELATING TO THE USE OF CHOLECYSTOKININ–CHOLESCINTIGRAPHY

CCK-CS involves the intravenous administration of [99m]technetium-labeled hepato-iminodiacetic acid, which is taken up by the liver and excreted into the biliary system, where it accumulates in the gallbladder. A GBEF then can be measured reliably after stimulating gallbladder emptying, most commonly with CCK. A low GBEF has been suggested to be indicative of gallbladder dysfunction and supportive of a diagnosis of functional gallbladder disorder; however, its use is not without controversy.[37] This is reflected in clinical practice by the not uncommon scenario of patients with suspected functional biliary pain and a reduced GBEF reporting no or incomplete relief of symptoms or recurrence of symptoms following cholecystectomy.

It is important to recognize that the finding of a low GBEF is not specific for functional gallbladder disorder and may occur in asymptomatic, healthy individuals, in patients with various medical conditions including diabetes, celiac disease, or irritable bowel syndrome,[37] and as a result of a number of medications such as opioid analgesics, calcium channel blockers, oral contraceptive agents, histamine-2 receptor antagonists, and benzodiazepines.[38] It also must be recognized that the gallbladder may not be responsible for a decreased GBEF as, occasionally, outflow obstruction from abnormalities of the cystic duct or sphincter of Oddi may be responsible.[39] Therefore, this test should be considered only when there is a high index of suspicion
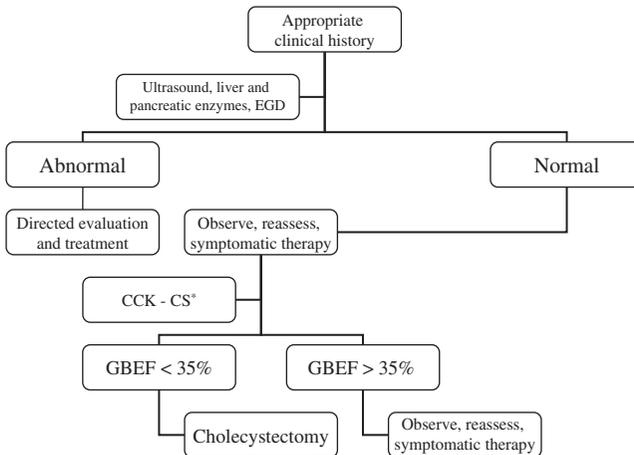
Fig. 1. Suggested algorithm for the diagnosis and treatment of suspected functional biliary pain in patients with a gallbladder. *using slow CCK infusion for at least 30 minutes. CCK-CS, cholecystokinin cholescintigraphy; GBEF, gallbladder ejection fraction. (*Reproduced from DiBaise JK. Evaluation and management of functional biliary pain in patients with an intact gallbladder. Expert Rev Gastroenterol Hepatol 2009;3(3):305–13; with permission.*)

of a gallbladder origin of the symptoms and other diagnoses have been eliminated. Furthermore, when considering whether to perform CCK-CS, it is preferable for it to be performed as an outpatient procedure on a patient who is not having pain at the time given the potential of confounding effects of acute illness in the hospitalized patient who may be receiving multiple medications.[37]

The clinician should be familiar with how the test is performed and interpreted at his or her institution. At present, there is no consensus on the dose, rate, and duration of CCK infusion used in CCK-CS. Many CCK-CS studies are conducted using a rapid infusion of CCK over 2 to 3 minutes, a methodology that has been shown to yield highly variable results.[37] In contrast, the slow infusion of CCK over 30 to 60 minutes results in an overall increase in mean GBEF compared with its rapid infusion and less inter- and intrasubject variability.[40–42] Regarding CCK-CS interpretation, there remains no consensus on the definition of an abnormal GBEF, although most clinicians consider a value of less than 35% as abnormal.[20,38] A multicenter trial is in progress that is attempting to determine the best methodology and establish normal values in a large healthy population.[43]

TREATMENT

The Rome committee also has proposed criteria to confirm successful treatment in long-term follow-up studies.[6] The criteria are threefold and include an abnormal GBEF less than 40% after prolonged CCK infusion; an absence of gallbladder sludge, stones, or microlithiasis; and an absence of recurrent pain for at least 12 months.

Currently, the evidence for medical therapy in functional gallbladder disorder is lacking. Evaluation of psychological conditions and treatment for visceral hyperalgesia have been proposed but not well studied[20] as has the case for prokinetic agents, bile acid composition modifiers, and anti-inflammatory agents. Even though evidence-based recommendations cannot be made, the use of neuromodulators,

similar to their use in other functional GI disorders, seems reasonable to consider in those with suspected functional gallbladder disorder.[44]

EVIDENCE SUPPORTING CHOLECYSTECTOMY FOR PATIENTS WITH FUNCTIONAL GALLBLADDER DISORDER

Many retrospective, generally low-quality, studies have been published that support the performance of cholecystectomy in patients with suspected functional gallbladder disorder, particularly in patients with a GBEF less than 35%.[20] To date, Yap and colleagues[23] have published the only randomized controlled study of cholecystectomy in functional gallbladder disorder. They studied 21 patients with suspected functional biliary pain and a GBEF less than 40% based on a 45-minute infusion of CCK. Eleven patients were randomized to cholecystectomy and 10 to no surgery. Over a 3-year period, 10 patients became asymptomatic after cholecystectomy, and one reported improved symptoms after surgery. In contrast, most patients in the no surgery group reported their symptoms to be unchanged; two of these requested cholecystectomy. Based on these findings, the authors concluded that CCK-CS is useful in identifying a group of patients with acalculous gallbladder disease and biliary-like pain who respond to cholecystectomy. Although encouraging, these results are limited by the small size of the study, lack of concealed allocation to treatment group, and a lack of a sham-control group.

More recently, Paajanen and colleagues[24] completed a prospective, uncontrolled study of patients with presumed functional gallbladder disorder who were categorized into one of three groups based on the results of their CCK-CS. The first group consisted of 32 patients with a GBEF less than 35% who underwent laparoscopic cholecystectomy. The second group included 52 patients with a GBEF less than 35% but who did not undergo surgery. The third group consisted of 38 patients with a normal GBEF. All patients were followed for a mean follow-up of 4 years (range, 1 to 7 years). They found that over 90% of patients in the laparoscopic cholecystectomy group reported their pain had resolved or was substantially improved. In contrast, in the low GBEF and no surgery group, only 16% of patients reported their pain had resolved, and 50% reported no change in symptoms. In the group with a normal GBEF and no surgery, 33% reported their pain had resolved, and 26% reported no change in symptoms. The authors concluded that laparoscopic cholecystectomy is an effective treatment in patients with high clinical suspicion of functional gallbladder disorder and GBEF less than 35%.

Carr and colleagues[45] reported similar findings. They identified 93 patients with suspected functional gallbladder disorder and GBEF less than 35%. Patients were separated into two groups based on symptoms, classical or atypical, and followed for up to 1 year. Sixty of the 61 patients in the classic group underwent cholecystectomy; 58 reported their symptoms resolved. In the atypical group, 23 patients eventually underwent cholecystectomy; 13 reported resolution of their symptoms. The authors concluded that classic biliary symptoms were more predictive of success after cholecystectomy than the GBEF. They also suggested that patients with atypical symptoms such as bloating and upper abdominal fullness should be observed rather than offered surgery.

EVIDENCE AGAINST CHOLECYSTECTOMY FOR PATIENTS WITH FUNCTIONAL GALLBLADDER DISORDER

Despite excellent symptom improvement after cholecystectomy for gallstone disease, the clinical improvement in patients with presumed functional biliary pain

is not as good. Fenster and colleagues[46] prospectively evaluated the effects of cholecystectomy on the presenting symptoms in 225 patients undergoing laparoscopic cholecystectomy. Fifteen percent of the patients were believed to have functional gallbladder disorder, while 48% described atypical pain, and 82% experienced bothersome nonpain symptoms. A key finding was a cure rate for what was described as classic biliary pain of 82% in those with gallstones compared with 52% in those without gallstones. As expected, nonpain symptoms were infrequently completely relieved, in only 46% with gallstones and 38% without gallstones ($P>.05$), emphasizing that these symptoms should not necessarily be attributed to functional gallbladder disease, particularly in the absence of biliary-like abdominal pain. This study demonstrates that while cholecystectomy may relieve classical pain in most patients with cholelithiasis, pain relief in presumed functional gallbladder disorder, even when described as classic biliary pain by the physician, is generally poor.

A recent review on the management of acalculous biliary-type abdominal pain pointed out that the response range for cholecystectomy in patients with biliary-type pain and abnormal GBEF is quite variable between studies, ranging from 38% to greater than 90%.[20] In addition to this wide variation in results, they pointed out that many of the studies are not methodically sound and cautioned of the possibility of publication bias. Therefore, any conclusions drawn from these studies must be interpreted cautiously.

A Cochrane review[47] of the evidence for cholecystectomy in suspected functional gallbladder disorder analyzed randomized clinical trials comparing cholecystectomy versus no cholecystectomy in patients with gallbladder dyskinesia. Only one study was found that met this criteria, but it too was deemed to be at high risk for bias.[23] It was concluded there is a lack of sufficient data to assess the role of cholecystectomy in gallbladder dyskinesia, and randomized clinical trials are necessary.

DOES GBEF PREDICT OUTCOME IN FUNCTIONAL GALLBLADDER DISORDER?

A systematic review and meta-analysis by Delgado-Aros and colleagues[48] of studies dating back to 1966 found only nine articles eligible for inclusion in their study to determine whether patients with suspected functional biliary pain with decreased GBEF have better symptomatic outcome after cholecystectomy than those with normal GBEF. They found that 94% of patients with reduced GBEF had a positive outcome compared with 85% among those with normal GBEF. The odds ratio for positive outcome was 1.37 (95% confidence interval [CI] 0.56 to 3.34; $P = .56$). Thus, based on their pooled analysis, they found no difference in outcomes after cholecystectomy between patients with abnormal GBEF and normal GBEF. In addition, they demonstrated evidence of publication bias, commented on the poor quality of the studies included, and recommended further study be conducted to definitively answer this question.

Similarly, a systematic review assessed the utility of CCK-CS with calculation of the GBEF in predicting symptomatic outcome following cholecystectomy in patients with suspected functional gallbladder disorder and came to the same conclusion.[49] Even though 19 of 23 studies reviewed reported the calculation of GBEF was useful, these authors pointed out there were significant methodological limitations with all of the studies making this conclusion. Therefore, the question as to whether GBEF is useful in predicting symptom outcome remains to be answered.

Box 2
Areas requiring further study in functional gallbladder disorder

Clinical utility of the diagnostic criteria as defined by the Rome committee

Pathogenesis and natural history

Role of endoscopic ultrasound in the diagnosis

Optimization of CCK-CS technique and interpretation

Clinical utility of CCK-CS with calculation of the GBEF

Role of medical therapy

Large, multicenter, randomized, controlled study comparing cholecystectomy to no surgery

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SUMMARY

It is readily apparent that there is a lack of high-quality data to aid in good decision making regarding the role of CCK-CS in the diagnosis and cholecystectomy in the treatment of functional gallbladder disorder. Nevertheless, this does not necessarily negate their utility when used in the patient with a high clinical suspicion of functional gallbladder disorder—suspicion that may be enhanced by using the Rome diagnostic criteria. Several areas have been identified that require further study to have a better understanding of the optimal diagnosis and management of functional gallbladder disorder (**Box 2**). For now, it is recommended that patients with suspected functional gallbladder disorder be carefully evaluated to exclude other causes for their symptoms. As proposed by the Rome committee,[6] initial work-up should include transabdominal ultrasound, liver and pancreatic laboratory studies, and an upper endoscopy (grade B). If these studies are normal, the patient should be observed, provided symptomatic therapy, and reassessed in a few months time. If symptoms warrant further work-up, then CCK-CS with slow infusion over at least 30 minutes is recommended by the Rome group (grade B). If the GBEF is less than 35%, cholecystectomy should be considered; however, if the GBEF is greater than 35%, continued observation and follow-up are advised (grade B). Despite concerns raised about the clinical utility of CCK-CS, with proper patient selection and use of optimal testing technique, on the basis of currently available evidence, this seems to be a reasonable approach. On the other hand, given its limitations and the suggestion of similar results following cholecystectomy in those with reduced and normal GBEF, foregoing CCK-CS testing in a patient with a high index of clinical suspicion after adequate follow-up and exclusion of other disease entities and counseling the patient on postoperative expectations is not entirely unreasonable in the authors' opinion.

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