Review Article

The Chronic Acalculous Symptomatic Hyperkinetic (CASPER) Gallbladder or "*The Excitable Gallbladder*"

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Abstract

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In this Invited Review, we provide an update on "Gallbladder Hyperkinesia" for medical and lay audiences. The Chronic Acalulous Symptomatic hyPERkinetic (CASPER) gallbladder can be considered the opposite of the Chronic Acalulous Symptomatic hyPOkinetic (CASPO) gallbladder. Just as the CASPO gallbladder could be typified as "*the lazy gallbladder*," the CASPER gallbladder would correspond to "*the excitable gallbladder*." Symptomatic gallbladder hyperkinesia has three essential features: a) biliary symptoms, b) no gallstones on ultrasound (acalculous), and c) an unusually elevated gallbladder ejection fraction on HIDA scan. Although gallbladder hyperkinesia is recognized in standard medical textbooks, gallbladder hyperkinesia garnered over the past five years after we independently identified gallbladder hyperkinesia as a novel entity at the University of lowa Gallbladder hyperkinesia garnered over the past five years after we independently identified gallbladder hyperkinesia as a novel entity at the University of lowa Gallbladder hyperkinesia, and emphasize that it is a diagnosis of exclusion. We present a 12-point checklist for the symptoms and signs of CASPER gallbladders. We explain the deviations of this 12-point checklist for the Rome IV Criteria for functional gallbladder disorders. We review the literature written on gallbladder hyperkinesia over the past two decades and summarize observations of several clinicians from various geographical regions. We underline the problems associated with trying to complete a prospective, randomized, controlled study to validate the indication for cholecystectomy in patients experiencing substantial symptoms from gallbladder hyperkinesia. We point out the role played by internet-based social medical platforms in bringing together patients with gallbladder hyperkinesia and surgeons that recognize the condition.

TOPIC

We were invited to review *The Hyperkinetic Gallbladder* for this Special Issue on *"Biliary Tract Disease"* as we recently published the first statistically analyzed study to show that gallbladder removal surgery has substantially greater odds in relieving symptoms of gallbladder hyperkinesia than in controls where the gallbladder is not removed [1]. In addition to using a control group and performing detailed statistical analyses, another novel aspect of our study included meticulous histological analyses and morphometric studies of the resected gallbladder specimens by a pathologist [1].

PURPOSE

The purpose of this publication is to provide an update on *Gallbladder Hyperkinesia* not only for the medical community but also for a lay audience. Therefore, difficult medical terminology is either avoided or explained. Removal of the gallbladder (cholecystectomy) for chronic cholecystitis (long-term inflammation of the gallbladder) resulting from acalculous* symptomatic gallbladder hyperkinesia is not yet a widely

recognized treatment (*calculus: *Latin* "small stone"; "acalculous" in the present context: in the absence of gallstone formation).

GENERAL INTRODUCTION

Symptomatic gallbladder hyperkinesia, a chronic malady that presents with biliary symptoms even in the absence of gallstones but where the gallbladder empties too quickly, is not yet an established clinical diagnosis as it has only recently been noticed [1-7]. Within recent years, several publications from different geographical regions suggest that hyperkinetic gallbladders cause biliary symptoms, and the topic is gaining momentum [1-22]. We independently identified symptomatic gallbladder hyperkinesia at the University of Iowa Gallbladder Dysfunction Clinic in 2018 when two severe cases of acalculous biliary pain associated with high gallbladder ejection fractions (92% & 100%) responded impressively to cholecystectomy [1]. The unique focus of our Gallbladder Dysfunction Clinic on diseases of the gallbladder helped us identify these initial patients and to continue our work on the topic. We then published a retrospective study of patients with symptomatic gallbladder hyperkinesia from 2013 to 2018 at our institution where we compared patients who had cholecystectomy (Study Group, n = 21) to those

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who did not have cholecystectomy (Control Group, n = 25) [1]. Evidence of long-term follow-up with the referring clinician (e.g., gastroenterologist, primary care physician) averaged 3.5 years in the Study Group (range 1 – 76 months) and 3 years in the Control Group (range 10 –120 months). In our study, we found that the odds of the cholecystectomy group showing symptom resolution (18/21 or 86% of patients) were 19.7 times that of the non-cholecystectomy group (only 5/25 or 20% patients showed spontaneous resolution of symptoms over time) [1]. This indicates that 80% of patients will continue to suffer symptoms indefinitely if they do not undergo cholecystectomy. Over the past 5 years, we have gained experience in the clinical presentation, investigation, diagnosis, and treatment of patients with symptomatic gallbladder hyperkinesia.

What is gallbladder hyperkinesia?

The <u>Chronic</u> <u>A</u>calculous <u>Symptomatic</u> hy<u>PER</u>kinetic (CASPER) gallbladder, or "the excitable gallbladder," can be explained as the opposite of the Chronic Acalculous Symptomatic hyPOkinetic (CASPO) gallbladder, or "the lazy gallbladder." Symptomatic hypokinesia of the gallbladder was investigated with a randomized study in 1991, showing cholecystectomy was better than no operation [23], that justified its entry into medical textbooks. In contrast, the condition of symptomatic gallbladder hyperkinesia is a recently described condition that has not yet reached general acceptance as a recognized clinical condition [1-22]. Simply put, symptomatic gallbladder hyperkinesia consists of a triad of a) biliary symptoms, b) a gallbladder without stones ("acalculous"), and c) a high gallbladder Ejection Fraction on cholescintigraphy (Hepatobiliary Imino-Diacetic Acid scan or HIDA scan) [1]. The HIDA scan is a nuclear medicine scan used to measure gallbladder emptying (Ejection Fraction) after hormonal stimulation or a fatty meal [24-26]. In normal physiology, the gallbladder stores and concentrates bile between meals, and when a meal is eaten the duodenum secretes cholecystokinin (CCK) hormone into the bloodstream making the gallbladder contract and the bile duct sphincter relax, allowing concentrated bile to reach the duodenum and mix with the meal [25]. This explains why biliary pain is typically exacerbated by a meal.

Why is Gallbladder Hyperkinesia not in the standard medical textbooks?

Although gallbladder hypokinesia (often called gallbladder dyskinesia) [27] has been in the textbooks of surgery for several decades, gallbladder hyperkinesia in adults has not yet made its entry into the standard medical textbooks for several reasons. Gallbladder hyperkinesia is also not currently found in the question databases for surgical trainees such as SESAP [Surgical Education & Self-Assessment Program (American College of Surgeons)], the ABS (American Board of Surgery) Certification Examination, and the ABSITE (ABS Inservice Training Examination), while gallbladder hypokinesia is included. Similarly, the Rome IV Diagnostic Criteria for Functional Gallbladder Disorders (see below) recognizes gallbladder hypokinesia as a gallbladder motility disorder but not gallbladder hyperkinesia [28]. Many clinicians may not accept the formalization of a new clinical condition until and unless a randomized controlled clinical trial is conducted. This would require a prospective study where patients with symptomatic

gallbladder hyperkinesia are randomly allocated to a cholecystectomy group or a non-cholecystectomy group (diet and analgesia only) and are then evaluated by blinded independent observers for at least one to two years. However, obtaining research funding could be a hurdle. Also, if a randomized study is attempted, most patients needing surgery could be in so much agony that they may refuse randomization and avoid entering the study by choosing early surgical intervention. Furthermore, even if a successful randomized study is completed, the inherent bias amongst many clinicians against motility disorders of the gallbladder may be difficult to overcome [29]. Therefore, it could take many years for this condition to be recognized by the medical community and enter standard medical textbooks. In the meantime, continued publications, as exemplified in the present review [1-22], would help to inform healthcare providers about symptomatic gallbladder hyperkinesia and the favorable effects of cholecystectomy in well-selected patients.

Is a prospective, randomized, controlled study essential to justify cholecystectomy for symptomatic gallbladder hyperkinesia?

Not every treatment for every medical condition has undergone a prospective randomized study with a control group prior to general acceptance. In fact, gastric bypass surgery for severe obesity was performed internationally from the 1960s onwards [30] for almost half a century based entirely upon retrospective studies [31-34] until the first prospective randomized study in 2012 showed that surgery was better than medical treatment for diabetes associated with obesity [34-36]. Before 2012, most published bariatric surgery studies were observational (retrospective) and only a limited number of them had nonsurgical control groups [34]. Ethical considerations may have inhibited performing randomized control trials and so the central hypothesis that bariatric surgery is more effective than medical treatment for weight loss in the severely obese remained untested for half a century. But even then, bariatric surgery continued a relentless expansion for almost 50 years despite the lack of randomized studies [31-34].

Interestingly, in 1926 the legendary American surgeon Dr. Allen O. Whipple published a series of 217 consecutive cholecystectomies with post-operative follow-up of up to 10 years [37]. Of these, 170 (78%) were for calculous disease and 47 (22%) were for acalculous disease showing 89.4% and 76.6% symptom relief, respectively [37]. It is reasonable to suggest that some of these 47 patients with acalculous biliary symptoms had either gallbladder hypokinesia or hyperkinesia.

If gastric bypass for severe obesity and cholecystectomy for acalculous biliary pain were performed in the 20^{th} century without randomized studies, then is a randomized study essential to justify cholecystectomy for symptomatic gallbladder hyperkinesia in the 21^{st} century?

What is the current definition of gallbladder hyperkinesia?

The essential features of symptomatic gallbladder hyperkinesia are [1-2]:

Clinical presentation suggestive of biliary symptoms,

No gallstones on radiologic imaging, and

High gallbladder Ejection Fraction on HIDA scan.

Clinical presentation suggestive of biliary a) symptoms: This is a clinical diagnosis and is quite dependent on the person taking the history, as history taking is a science and an art. Unfortunately, recent reliance on innovative technology has blunted classical attention to detail of a well-taken history. Modern clinicians often prefer to look at a radiological image or read a report rather than listen to the patient and ask probing questions. To help guide a useful clinical history-taking in the evaluation of gallbladder hyperkinesia, we provide a detailed list (see below) garnered during 5 years of experience at our Gallbladder Dysfunction Clinic. The most common symptoms suggestive of a biliary cause are nonspecific: upper abdominal pain, nausea and vomiting, and gaseous symptoms such as bloating [1-22,28].

b) No gallstones on radiologic imaging: If an ultrasound shows gallbladder stones, it will support a diagnosis of *calculous* chronic cholecystitis and additional studies of gallbladder motility (HIDA scan) may not be needed. If only a small amount of gallbladder sludge is seen on ultrasound in a symptomatic patient, a HIDA scan could provide additional justification to consider cholecystectomy if it shows either gallbladder hypokinesia or hyperkinesia — as then, the odds of cholecystectomy relieving the presenting symptoms are increased. It is important to remember that ultrasound is the gold standard for the diagnosis of gallbladder stones as diagnostic modalities using X-rays (e.g., plain X-ray or CT scan) may miss up to 80-90% of gallstones as only about 10-20% of gallstones contain sufficient calcium to show up on X-ray images [38].

High Ejection Fraction of the gallbladder on HIDA c) scan: When radioisotope cholescintigraphy was introduced in the 1950s, ¹³¹Iodine-Rose Bengal dye given intravenously was taken up by the liver, secreted into the biliary tract, and then reached the duodenal lumen while also filling the gallbladder [39]. Its initial use was to test hepatobiliary function, identify non-filling gallbladders to confirm acute cholecystitis, or to investigate biliary leaks. In 1981, the first gallbladder Ejection Fractions were calculated when gallbladders that filled after ⁹⁹Technitium-HIDA radioisotope administration were IV stimulated with a CCK analog, and gallbladder emptying was recorded [24]. This technological advancement led to the first functional evaluations of gallbladder motility. Therefore, from the early 1900s until 1981, surgeons were removing acalculous symptomatic gallbladders based entirely on symptoms and signs without any information about gallbladder ejection efficiency [37]. From 1981, after gallbladder ejection fraction data became available, the focus for many years was the slowly emptying gallbladder (hypokinesia) causing biliary symptoms [23,40]. Now, several studies emphasize a new-found interest in the rapidly emptying gallbladder (hyperkinesia) that was generally considered to be normal until recent reports [1-22]. Currently, most clinicians use the 80% Ejection Fraction as the cut-off level to define gallbladder hyperkinesia, but there is no scientific justification yet for the selection of this percentage number.

What should be the cut-off Ejection Fraction level for a diagnosis of gallbladder hyperkinesia?

Although gallbladder Ejection Fractions above 80% are widely considered as the diagnostic criterion for gallbladder hyperkinesia, this cut-off level has been arbitrarily chosen without scientific investigations [1-22]. The 80% Ejection Fraction level seems to have taken root in the scientific literature by mere repetition in several papers. At our Gallbladder Dysfunction Clinic, using our clinical judgement in select patients, we have gone down to Ejection Fractions of 74% based upon clinical necessity and found a good response to biliary pain with cholecystectomy. There is one paper that reported a range of 71% to 99% in a series of patients with gallbladder hyperkinesia that responded well to cholecystectomy, where they used an arbitrary cut-off of 65% for their definition of hyperkinesia [10]. Therefore, until and unless extensive detailed clinical studies are undertaken, patients with Ejection Fractions in the borderline gray area between 70% and 80% will have to be considered on a case-by-case basis. If clinically indicated (intolerable symptoms), cholecystectomy in patients with Ejection Fractions between 65% and 80% can be justified by referencing the publication that offered surgery to symptomatic adults with Ejection Fractions above 65% [10]. There are some studies that used a 75% Ejection Fraction as their cut-off [7,12].

Is gallbladder hyperkinesia a new disease entity or merely a marker of disease?

Clinicians opposing the belief that symptomatic gallbladder hyperkinesia is a real entity cite evidence that a certain percentage of normal people that go through their daily lives without any symptoms will have a high gallbladder ejection fraction if a HIDA scan is done. The counter-argument would be that a good percentage of normal people that go through their daily lives without any symptoms will have gallstones in their gallbladder if an ultrasound is done [38]. Therefore, if gallstone formation is a pathologic entity even if the person is asymptomatic, then gallbladder hyperkinesia can also be an asymptomatic pathologic entity and symptoms could develop over time in a certain percentage of individuals, just as up to 30% of patients with gallstones can become symptomatic over time but as many as 70% may go through life without any symptoms [41]. On the other hand, it is quite possible that hyperkinesia of the gallbladder is not in itself a disease entity but only a marker of an underlying poorly understood disease.

What is the pathogenesis of gallbladder hyperkinesia?

At the present time, the pathogenesis of how gallbladder hyperkinesia develops and progresses to becoming symptomatic is not known. As gallbladder hyperkinesia has not yet gained acknowledgment as a recognized disease entity, investigations into its pathogenesis are still pending. Most studies of symptomatic gallbladder hyperkinesia show a female preponderance, [1-22] similar to that of gallstone disease [41]. Therefore, one can only speculate that the pathogenesis of symptomatic gallbladder hyperkinesia may have some correlation to the female hormones and their effect on the biliary tract. For example, the increased incidence of cholesterol gallstones in females is thought to be related to the effect of female hormones on the liver metabolism

of cholesterol [41]. In our recent study, we presented novel data where a pathologist studied the surgically resected gallbladder histology in 21 patients with symptomatic gallbladder hyperkinesia and found a prominent increase in the thickness of the smooth muscle layer within the gallbladder wall in many of these patients [1]. The reasons as to why this smooth muscle hypertrophy occurs, and its relevance to the pathogenesis of gallbladder hyperkinesia, remain unknown. In our study, we showed fibrosis and lymphocytes in the submucosal area of the gallbladder wall suggestive of mild to moderate chronic cholecystitis that indicates a long-term inflammatory process [1].

What are the non-surgical treatment options for the CASPER gallbladder?

At the present time, the only non-surgical management for symptomatic gallbladder hyperkinesia is a low-fat diet with appropriate painkillers used on an "as per need" basis. At our Gallbladder Dysfunction Clinic, non-surgical management has been used in a small number of patients who had mild symptoms not affecting their quality of life and therefore opted to defer surgery unless exacerbations developed. If symptoms are mild and the patient is compliant with diet, surgery could be postponed or even avoided. In our retrospective study, we showed that only 20% of patients with symptomatic gallbladder hyperkinesia who did not receive cholecystectomy improved spontaneously over a period of years.

Other treatments may exist but have not been researched to provide proof of benefit for symptomatic gallbladder hyperkinesia [1-22]. Most pharmacological agents tried are those usually used for irritable bowel syndrome [antispasmodic dicyclomine (can cause giddiness) and peppermint oil (IBgard)].

What are the various investigations that patients undergo before a diagnosis of gallbladder hyperkinesia is entertained?

Most patients coming to our Gallbladder Dysfunction Clinic to evaluate symptomatic gallbladder hyperkinesia have been referred by gastroenterologists or primary care physicians and have already undergone various investigations. In effect, at the present time, symptomatic gallbladder hyperkinesia is generally considered a diagnosis of exclusion. Such an approach is clinically sound as diseases of the gastrointestinal tract have much overlap in symptoms and signs and differentiating between them based on history and examination alone can be challenging. Hepatic function panel and pancreatic enzymes have usually been already evaluated and are normal (except transaminase elevations related to a fatty liver), and should be a basic part of the evaluation in all these patients to exclude bile duct obstruction and pancreatic disease.

The following is a list of most common investigations done on symptomatic gallbladder hyperkinesia patients before they come to our Gallbladder Dysfunction Clinic, but we do not mean to imply that every patient needs to undergo each and every one of these studies as the choice would be left to the clinical judgement of the healthcare provider evaluating the patient:

1. Esophagogastroduodenoscopy (EGD)

- 2. CT scan of abdomen and pelvis
- 3. Colonoscopy
- 4. Radioisotope gastric emptying study

5. Hydrogen & methane breath test for small intestinal bacterial overgrowth (using glucose, lactulose, or fructose) or lactose intolerance (using lactose).

- 6. Esophageal manometry and pH studies
- 7. Helicobacter pylori tests
- 8. Tests for celiac disease

9. Trial of anti-acid treatment such as several months of proton pump inhibitor treatment

10. Psychological or psychiatric assessments.

What are some conditions that patients with undiagnosed gallbladder hyperkinesia are labelled with?

As HIDA scans reporting high gallbladder ejection fractions are at present mostly reported as "normal" at many institutions, and as visceral symptoms are poorly localized, symptomatic gallbladder hyperkinesia patients are often given a variety of different diagnoses:

- Irritable bowel syndrome (IBS)
- Acid peptic disease (APD)
- Gastroesophageal reflux disease (GERD)
- Gastroparesis (Slow gastric emptying),
- Small intestinal bacterial overgrowth (SIBO)
- Constipation
- Cardiac or rib causes for chest pain
- Psychiatric disorder
- Malingering

• Or, they are simply told, "We do not know what is wrong with you."

What are the symptoms and signs of gallbladder hyperkinesia?

Over the past five years, we have evaluated several patients with gallbladder hyperkinesia and have distilled a list of signs and symptoms that patients present with. Often, patients have at least half of the signs or symptoms listed here, but occasionally — in an atypical presentation — only one or two.

1. Pain: right upper quadrant, epigastric, or upper abdominal.

2. Onset of pain after a meal (post-prandial pain), varying from a short time to a few hours after a meal. However, although abdominal pain is typically post-prandial in gallstone-biliary colic, it may not always follow a meal in gallbladder hyperkinesia patients, as it can sometimes come on randomly, or even become constant with occasional or frequent waves of exacerbation.

3. Certain foods especially are known to initiate the pain: deep fried food, whole milk, milk products (cheese, cream, butter), or fatty meats. Also, large meals.

4. Pain radiates to the flank, back, shoulder blade, or shoulder, most often to the back, occasionally travelling along the left side or upwards to the chest or neck.

5. Post-prandial nausea with or without overt vomiting.

6. Post-prandial gaseous symptoms such as bloating, with burping, belching, or flatulence.

7. Waking up at night with pain, especially after a late meal or a large meal.

8. An unusual sensation in the right upper quadrant, likened to a "tense balloon about to burst," a "clenching fist," or a "cramping pain," located over the gallbladder region.

9. Exacerbation of pain in the right upper quadrant with postural movements that increase intra-abdominal pressure, such as bending down to pick something from the ground or rising from the sitting position.

10. Post-prandial urgency for a bowel movement, most often within a few to 60 minutes.

11. Diarrhea, after a meal, but often even between meals.

12. Localized tenderness directly over the anatomical location of the gallbladder.

Regarding the 12 symptoms and signs listed above, not all 12 needs to be present in any patient as occasionally only a few symptoms or even only one symptom may be present. Although abdominal pain is the most common presenting symptom, some patients do not experience pain but only have uncomfortable abdominal bloating, intolerable nausea, or mainly urgency for a bowel movement with diarrhea after eating. The post-prandial temporal relation of symptoms such as abdominal pain, nausea and vomiting, gaseous symptoms, or diarrhea, is not always present and the symptoms can occur at any time even without a meal and can even exacerbate to reach a state that is continuous. Additional complaints that we have heard occasionally from patients that reversed after cholecystectomy include weight loss due to insufficient nutrition (excess pain and vomiting with attempted meals), sporadic fainting, tachycardia, and fatigue. Patients should always be cautioned that not all their symptoms might be improved with cholecystectomy as there can be overlap of symptoms with different upper gastrointestinal diseases. Occasionally, some patients may have no benefit at all from cholecystectomy if they had asymptomatic gallbladder hyperkinesia with symptoms from other undiagnosed conditions. In difficult-to-diagnose cases, the only way to find out is by performing cholecystectomy and seeing what happens (an interrogative cholecystectomy). Such difficulties in diagnosis arise as the visceral symptoms of upper gastrointestinal diseases are often vaguely demarcated and various investigations can turn out to be negative. Therefore, most cases-series of cholecystectomy for the CASPER gallbladder can be expected to have a certain percentage of failure of surgical treatment, [1-22] just as in the case of the CASPO gallbladder.

The Rome Foundation [42] is a private not-for-profit organization that supports international collaboration to understand functional disorders of the gastrointestinal tract (Disorders of Gut-Brain Interaction or DGBIs). The Rome IV Criteria of 2016 for "Gallbladder and Sphincter of Oddi Disorders" focus on symptoms of acalculous biliary disease and only mention gallbladder hypokinesia (and sphincter of Oddi dysfunction) and have not yet recognized gallbladder hyperkinesia as a clinical condition [42]. The 12 symptoms and signs that we have associated with gallbladder hyperkinesia and have listed above show several differences when compared to the Rome IV Diagnostic Criteria for "Functional Gallbladder Disorders" or "Biliary Pain" [42]. Notably, the Rome IV Criteria document only four symptoms: biliary pain as the main symptom, with three supportive criteria – a) nausea and vomiting, b) radiation of pain to the back and/or right infra-subscapular region, and c) waking from sleep due to pain. The presence of biliary pain is an essential requirement to satisfy the Rome IV criteria, and the pain: a) reaches a steady level lasting at least 30 minutes, b) is not daily, c) is severe enough to interrupt daily activities or need an emergency department visit, d) is not significantly related to bowel movement, and e) is not significantly relieved by postural change or acid suppression.

As we independently identified symptomatic gallbladder hyperkinesia in 2018 at the University of Iowa Gallbladder Dysfunction Clinic, and over the past five years saw several referrals for assessment for cholecystectomy, we intentionally deviated from the Rome IV Criteria for Functional Gallbladder Disorder to autonomously characterize the symptoms and signs of this novel clinical condition. Such an autonomous approach was justified as the Rome IV Criteria for Functional Gallbladder Disorders do not acknowledge symptomatic gallbladder hyperkinesia as a clinical disorder [42].

Exacerbation of abdominal pain during the HIDA scan after the administration of CCK analog is commonly considered a positive indicator of gallbladder disease by many clinicians [43] but this topic is controversial as CCK administered intravenously to anyone can potentially cause pain and nausea [44]. Therefore, we have not included CCK-induced reproduction of symptoms in our current list of symptoms of the CASPER gallbladder.

Post-operatively, most patients appreciate the impact of cholecystectomy on their gallbladder hyperkinesia symptoms within 1 to 5 days, as the laparoscopic incisional pain, carbon-dioxide gas-related referred shoulder pain, and anesthetic effects fade away. Some patients need a few weeks, as each patient reacts differently to cholecystectomy. Patients are best advised to remain on broth the first night after laparoscopic cholecystectomy, and to then advance steadily onto a low-fat diet such as the BRAT diet (Bananas, Rice, Applesauce, Toast). Adventurous consumption of a cheeseburger few days after surgery can result in an Emergency Department visit with abdominal pain. Tolerance of a general diet and resolution of post-cholecystectomy diarrhea happen in a few weeks as the body acclimatizes to the lack of a gallbladder.

Summary of literature published on symptomatic gallbladder hyperkinesia

We have identified a total of 29 scientific works, including

7 peer-reviewed national conference abstract presentations (Table 1) [45-51] and 22 peer-reviewed papers (Table 2) [1-22] published in the literature on the topic of symptomatic gallbladder hyperkinesia. Conference abstract presentations that were published later as full-length papers are excluded from Table 1, but are included in Table 2. Historically, to our knowledge, the first description of gallbladder hyperkinesia was only in abstract form in 1999 (Table 1), and we could not identify the same study published as a full manuscript. The first full-length article publishing a study on the topic was in 2012, [7] and the total number of papers have presently reached 22 (Table 2). In effect, symptomatic gallbladder hyperkinesia is a condition brought into focus only in the 21st Century, especially in the past decade [1-22].

Except for one paper from the UK, [4] which was a metaanalysis of 13 previous studies, all the other 28 publications were from the USA (Tables 1&2). Invariably, the 22 published articles were all studies led by surgeons that performed cholecystectomy for gallbladder hyperkinesia showing evidence that cholecystectomy is useful in mitigating the associated biliary symptoms in a substantial percentage of patients. When data was provided, there was female gender predominance in adults (Table 2). Success of cholecystectomy for relief of symptoms with symptomatic gallbladder hyperkinesia ranged from 65% to 100% in adults (Table 2). The meta-analysis from 13 previous studies involved data from 332 patients and concluded that cholecystectomy was successful in ameliorating symptoms in more than 90% of patients with the hyperkinetic gallbladder [4]. Some of these publications mentioned the histology report findings, but did not present a detailed descriptive characterization of all the histology slides performed by a single pathologist.

Our study was the only one that showed statistical data indicating that the odds of symptom improvement were substantially higher (19.7 times greater) with cholecystectomy than without. Such a sizeable Odds Ratio advantage of cholecystectomy over nonsurgical treatment suggests that it

TABLE 1: Abstracts on gallbladder hyperkinesia presented at conferences and published online									
	Year	Authors/Region	Patients (n), EF, Type of paper	Controls	Histology	Statistics	Improvement	Reference	
1	1999	Cook CH, Kisner J, Melvin WS, Olsen J, Pozderac R, Martin LC. Ohio State Univ. MC, Columbus, OH	n = 7 (EF>80%) Retrospective study	Yes (n = 7 nonsurgical controls)	No	Yes; but Odds Ratio not calculated (descriptive only)	7/7 (100%) (Controls 0/7 = 0%)	Society for Surgery of the Alimentary Tract (SSAT) Annual Meeting 1999.	
2	2009	Holes-Lewis K, Hakim S, Rehman F, Nabi H, Uhde T. MUSC, Charleston, SC; Mercy & SUNY, Buffalo, NY	n = 28 EF > 80% Retrospective study	No	No	No	27/28 (97%)	Society of Nuclear Medicine (SNMMI) Annual Meeting 2009. J Nucl Med. 2009;50(suppl 2): 1312.	
3	2014	Law JK, Antoniou A, Kalloo AN, Shin EJ. USA	n = 26 EF > 80% Retrospective study	No	No	No	18/26 (69%)	American Gastroenterological Association (AGA) Annual Meeting 2014. Gastroenterology, vol. 146, no. 5, pp. S–880, 2014.	
4	2015	Diarra C, Ho S, Lynsue J, Pauli EM, Rogers AM. Penn State Hershey Medical Center, Hershey, PA	n = 24 EF > 65% Retrospective study	No	Yes (insufficient details)	No	24/24 (100%)	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Annual Meeting 2015.	
5	2016	Cetrulo LN, Joshi A, Trang A. Einstein Healthcare Network, Norriton, PA	n = 4 EF: Ejection Fraction > 80% Retrospective case series	No	No	No	4/4 (100%)	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Annual Meeting 2016.	
6	2017	Melvin JC, Ibendahl E, Perna M, Rawlings AL. Univ. of Missouri, Columbia, MO	n = 23 EF > 80% Retrospective study	No	19/21 (90%) showed chronic cholecystitis	No	21/23 (91%)	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Annual Meeting 2017.	
7	2017	Pallapothu R, Protas M, Prier T, Brustein J, Anne N. Binghamton, NY	n = 41 EF > 80% Prospective study	No	32/41 (78%) showed chronic cholecystitis	No	40/41 (97%)	Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Annual Meeting 2017.	

A total of 7 peer-reviewed abstract presentations at national academic conferences describing data on symptomatic gallbladder hyperkinesia are listed in chronological order. Abstracts where the material was followed up with a full manuscript publication are excluded in Table 1 but included in Table 2, to avoid duplication. A link to the PDF copy of the published Abstract is available under the individual item in the Reference section. EF: Ejection Fraction

Table 2: Articles published on gallbladder hyperkinesia								
	Year	Authors/Region	Patients (n), EF, Type of paper	Controls	Histology	Statistics	Improvement	Reference
1	2012	DuCoin C, Faber R, Ilagan M, Ruderman W, Wier D. Orlando Health, Orlando, FL	n = 19 adults Females 15/19 (79%) EF mean 75% Retrospective study	No	Yes 19/19 (100%) showed chronic cholecystitis	No	18/19 (95%)	Normokinetic biliary dyskinesia: a novel diagnosis. Surg Endosc. 2012; 26: 3088-3093
2	2013	Lindholm EB, Alberty JB, Hansbourgh F, Upp JR, Lopoo J. LSU, Baton Rouge & New Orleans, LA	n = 12 All 12 <i>pediatric</i> age 4/12 females (33%) EF > 80% Retrospective study	No	Yes 12/12 (100%)	No	11/12 (92%)	Hyperkinetic gallbladder: an indication for cholecystectomy? Am Surg. 2013;79(9):882- 884
3	2013	Huckaby L, Timmapuri S, Prasad R. Temple Univ. & Drexel Univ. Philadelphia, PA	n = 3 females All 3 <i>pediatric</i> age EF > 65% (72% was lowest) Case -Series of 3	No	Yes 2/3 (68%) showed chronic cholecystitis	No	3/3 (100%)	Biliary hyperkinesia: A potentially surgically correctable disorder in adolescents. Journal of Pediatric Surgery Case Reports. 2013; vol. 1, no. 9, pp. 314–316.
4	2014	Steele J, Wayne M, Iskandar M, Wolmer T, Bratcher J, Cooperman A. Beth Israel MC, NY	n = 2 adults Females 2/2 (100%) EF > 80% Case-Series of 2	No	No	No	2/2 (100%)	Biliary pain, no gallstones– remove the gallbladder, anyway? J Fam Pract. 2014;63:421–3.
5	2017	Alexida L, Tiesenga FM. Elmwood Park, IL	n = 17 adults Females (insufficient data) EF > 75% Retrospective study	No	No	No	11/17 (65%)	Laparoscopic cholecystectomy for biliary dyskinesia in patient with an extended spectrum of ejection fraction on hepatobiliary iminodiacetic acid scan. International Archives of Integrated Medicine. 2017; 4(11): 14- 17.
6	2018	Greenberg JJ. Mercy Walworth Hosp. & MC, Lake Geneva, WI	n = 13 (11 adults, 2 pediatrics) Females 8/11 (73%) adults EF > 65% (Lowest EF 71%) Retrospective study	No	Yes 11/13 (85%) showed chronic cholecystitis	No	13/13 (100%)	What is Biliary Hyperkinesia? Global Surgery, 2018; Volume 4(1): 1-3
7	2018	Pihl KD, Jones MW, Deppen JG, Ferguson TM, Hanses SM. Lansing, MI	n = 18 adults Females (insufficient data) EF > 80% Retrospective study	No	No	No	16/18 (88%)	Effects of laparoscopic cholecystectomy in normokinetic biliary dyskinesia. The American Journal of Surgery 215 (2018) 116-119
8	2019	Gazzetta J, Fan B, Bonner P, Galante J. Ohio Health Doctors Hospital, Columbus, OH, USA	$\label{eq:n=77} \begin{array}{l} n=77\\ \mbox{Adults Vs pediatric not}\\ \mbox{defined}\\ \mbox{Females} \mbox{(insufficient}\\ \mbox{data})\\ \mbox{EF} \geq 80\%\\ \mbox{Retrospective study} \end{array}$	No	Yes 60/70 (86%) showed chronic cholecystitis	No	70/77 (91%)	Cholecystectomy for Biliary Hyperkinesia. Am Surg. 2019;85(2):219- 222.
9	2019	Saurabh S, Green B. Mercy Medical Center, Iowa City, IA, USA	n = 32 adults Females 27/32 (84%) EF > 80% Retrospective study	No	Yes 29/32 (90%) showed chronic cholecystitis	No	28/32 (88%)	Is hyperkinetic gallbladder an indication for cholecystectomy? Surg Endosc. 2019;33(5):1613-1617

10	2019	Bates JA, Dinnan K, Sharp V. Beaumont Health Farmington Hills, MI, USA	n = 1 female <i>Pediatric</i> EF > 80% Case Report	No	Yes 0/1 (0%) showed changes	No	1/1 (100%)	Biliary hyperkinesia, a new diagnosis or misunderstood pathophysiology of dyskinesia: A case report. International Journal of Surgery Case Reports 2019 Vol. 55 Pages 80-83
11	2019	Wright RC, Thach N, Peffer H, Robles R, Wright RJ. Meridian Surgery Center, Puyallup, WA	n = 40 adults Females 22 (55%) EF > 80% Retrospective study	No (no non- operated controls)	Yes 40/40 (100%) had chronic cholecystitis	Yes: But, no analytic statistics versus non- operated control group	36/40 (90%)	Surgical outcome in patients with biliary colic and atypical workup findings. Am J Surg 2019 Vol. 217 Issue 5 Pages 986-989
12	2020	Pillenahalli Maheshwarappa R, Menda Y, Graham M, Boukhar S, Zamba G, Samuel I. University of Iowa, Iowa City, IA*	n = 21 adults Females 18/21 (86%) EF > 80% Retrospective- Controlled study	Yes (n = 25 nonsurgical controls)	Yes 21/21 (100%) showed chronic cholecys- titis. Also, histo- logic char- acterization by patholo- gist.	Yes: Analytic statistics showed 19.7 Odds that surgery is superior to no surgery*	18/21 (86%)	Association of gallbladder hyperkinesia with acalculous chronic cholecystitis: A case- control study. Surgery. 2020 Nov;168(5):800-808
13	2020	Dekonenko C, Sujka JA, Dorman RM, Oyetunji TA, St. Peter SD. Children's Mercy, Kansas City, MO, USA	n = 13 All 13 <i>pediatric</i> age Females 9/13 (69%) EF > 80% Retrospective study	No	No	No	6/13 (50%)	Self-reported Outcomes After Cholecystectomy for Pediatric Hyperkinetic Biliary Dyskinesia. Journal of Surgical Research. Volume 246, February 2020, Pages 73-77
14	2020	Falco GM, Condon FJ, Yheulon CG. Tripler Army Medical Center, Honolulu, HI, USA	n = 3 adults Females 3/3 (100%) EF > 80% Retrospective study (bariatrics, status post RYGB surgery)	No	3/3 (100%)	No	3/3 (100%)	Biliary Hyperkinesia: A Potentially Overlooked Source of Abdominal Pain Following Bariatric Surgery. Am Surg. 2020:3134820973736
15	2021	Williford ML, Fay KT, Simpson FJ, Defnet A M, Schuster DM, Sethi I. Lin E, Davis SS Jr. Emory University, Atlanta, GA	n = 18 adults Females 11/18 (61%) EF > 80% Retrospective- Controlled study	Yes (n=50)	No	Yes: But, no analytic statistics, Odds Ratio not calculated (descriptive only)	16/18 (89%)	Optimal Management of the Hyperkinetic Gallbladder: A Comparison of Outcomes Between Operative and Nonoperative Approaches. Am Surg. 2021, Vol. 87(6) 903–909
16	2021	Bosley ME, Jacobson J, Gaffley MWG, Beckwith MA, Pandya SR, Davis JS, Neff LP. Wake Forest Baptist MC, Winston-Salem, NC. UTSMC, Dallas, TX. U of Alabama, Birmingham, AL.	n = 17 All 17 <i>pediatric</i> age Females 14/17 (83%) EF > 80% Retrospective study	No	Yes 14/17 (82%) showed chronic cholecystitis or choles- terolosis	No	14/17 (82%)	Biliary hyperkinesia in adolescents-it isn't all hype! Transl Gastroenterol Hepatol 2021;6:36
17	2021	Singh J. Oswego Hospital, Oswego, NY	n = 3 adults Females 3/3 (100%) EF > 80% Case-Series of 3	No	3/3 chronic cholecystitis (100%)	No	3/3 (100%)	Role of Cholecystectomy in Symptomatic Hyperkinetic Gallbladder Patients. Case Reports in Surgery 2021, 5569850

18	2021	Nasri B, Glass T, Singh K, Saxe J. St. Vincent Indianapolis, Indianapolis, IN	n = 59 adults Females 49/58 (83%) EF > 80% Retrospective study	No	Yes 41/59 (70%) showed chronic cholecystitis	No	45/59 (76%)	Biliary hyperkinesia: an indication for cholecystectomy? Surgical Endoscopy (2021) 35:3244–3248.	
19	2021	Eltyeb HA, Al- Leswas D, Abdalla MO, Wayman J. Newcastle, Manchester, & Carlisle, United Kingdom	Meta-analysis of 13 studies n = 332 Females (Not applicable) EF = 80%	Not applicable	Not applicable	See meta- analysis	303/332 (91%)	Systematic review and meta- analyses of cholecystectomy as a treatment of biliary hyperkinesia. Clin J Gastroenterol. 2021, 14:1308-17.	
20	2021	Sadek AA, Higgins RM. USA	n = 2 adults Females 2/2 (100%) EF > 80% Case-Series of 2	No	No	No	2/2 (100%)	Hyperkinetic Biliary Dyskinesia in Adults: Cholecystectomy as a Treatment Option. ACS Case Reviews in Surgery 2021.	
21	2022	Hart R, Senapathi H, Satchell EK, Mandal S, McAndrew M, Scharf M, Cagir B, Miner J. Guthrie Robert Packer Hospital, Sayre, PA	n = 48 adults Females 40/48 (83%) EF > 80% Retrospective study	No	33/48 (68.8%) had chronic cholecystitis	No	46/48 (96%)	The Role of Cholecystectomy in Hyperkinetic Gallbladder: A Retrospective Cohort Study in a Rural Hospital. Cureus 14(9): e29778.	
22	2022	Whitaker LF, Bosley ME, Refugia JM, Powell MS, McNatt SS, Westcott CJ, Koch KL, Bennett P, Rigdon J, Fernandez AZ. Wake Forest School of Medicine, Winston Salem, NC	n = 91 adults Females 75/98 (77%) EF > 80% Retrospective study	No	73/91 (80%)	No	84/91 (92%)	Outcomes after laparoscopic cholecystectomy in hyperkinetic biliary dyskinesia. Am Surg. 2022, 88:1983-7.	
A to	A total of 22 articles or full-length papers published on symptomatic gallbladder hyperkinesia that are available via PubMed or on the web are								

A total of 22 articles or full-length papers published on symptomatic gallbladder hyperkinesia that are available via PubMed or on the web are presented in chronological order. Single case reports and small case series are included. Articles in rows 2, 3, 10, 13, & 16 included only *pediatric* cases. The full reference to each of these publications is in the References section. EF: Ejection Fraction (of gallbladder on HIDA scan). RYGB: Rouxen-Y Gastric Bypass. *Study No. 12 was the only study that performed analytic statistics versus non-operated controls to provide an Odds Ratio comparing cholecystectomy to no cholecystectomy.

could be unethical not to offer surgery to a patient suffering intolerably with symptoms from gallbladder hyperkinesia.

Nomenclature

Many publications have referred to gallbladder motility disorders associated with a low ejection fraction as "gallbladder" (27,29]. However, now that gallbladder hyperkinesia has entered the scene, labelling low Ejection Fraction gallbladders as "gallbladder dyskinesia" would be a misnomer, and the term "gallbladder hypokinesia" would be more appropriate as "gallbladder hyperkinesia" is also "dyskinesia" of the gallbladder. Similarly, the term "biliary dyskinesia" [12,13,16,29,40] should not be used synonymously with "gallbladder hypokinesia" or "gallbladder hyperkinesia" as the term "biliary" can refer to anatomical areas outside the gallbladder such as the sphincter of Oddi (sphincter of Oddi dysfunction) or any segment of the biliary tract.

Social media engagement

Modern technology has brought to the forefront world-wideweb sites and services such as social media internet platforms where patients seeking information, help, or emotional peer support have been able to connect and interact. A Facebook. com private group called "Hyperkinetic Gallbladders" was started in 2017, collected 500 members by 2020, and surpassed 1300 members by early 2023 [52]. Patients discuss their symptoms, diagnosis, and experiences, and assist each other. An experience mentioned regularly is of patients being diagnosed with gallbladder hyperkinesia but being refused surgery by consultant surgeons due to nonrecognition of the condition. In response, this Facebook Group has accumulated a list of surgeons that recognize and offer cholecystectomy for symptomatic gallbladder hyperkinesia from Canada, the United Kingdom, New Zealand, Turkey, and the United States, and the list of surgeons and countries continually grows. Twitter.com shows 16 tweets about "gallbladder hyperkinesia" from 2020 onwards, 4 of them from surgeons posting our 2020 Surgery journal article [1] and the remaining from symptomatic patients [53]. Twitter.com also shows 25 tweets about the "hyperkinetic gallbladder" from 2012 onwards that includes a discussion between surgeons, and has several tweets from symptomatic patients seeking advice or help [54]. Therefore, social media internet platforms serve as an interface to facilitate interactions between patients, between surgeons, and between patients and surgeons. The momentous global reach of the internet and its ubiquity are strengths that

aid the exchange of new information and that initiate unexpected collaborations.

Potential future directions for the CASPER Gallbladder

Clinicians from different specialties and geographical regions should publish their experience regarding the diagnosis and treatment of the CASPER Gallbladder. Ideally, retrospective studies should include patients that did not have cholecystectomy as a control group and include statistical odds ratios for chances of improvement with cholecystectomy versus no cholecystectomy, as in our recent study [1].

If possible, well-designed prospective studies should be conducted where patients with the CASPER Gallbladder are randomized into a cholecystectomy group and a diet-andanalgesia group and followed for one to two years by blinded observers. However, ethical considerations may imply that withholding surgical options for the Control Group patients that may be in agony cannot be justified.

Standardization of cholescintigraphy methodology and evaluations of reproducibility should continue [26,55]. A gallbladder Ejection Fraction cut-off level to define gallbladder hyperkinesia needs well-executed statistical interrogations.

Detailed studies of pathological changes of the CASPER Gallbladder by gastrointestinal pathologists need to be undertaken [1].

Basic science research into motility disorders of the gallbladder — both the CASPER Gallbladder and the CASPO Gallbladder — need to be initiated. Contractility studies of the gallbladder smooth muscle, inquiries into the possible activation of inflammatory pathways in the gallbladder wall, and autonomic neuromuscular responses of the gallbladder smooth muscle would be reasonable areas to begin bench-top investigations using fresh cholecystectomy specimens from patients with symptomatic gallbladder motility disorders. This may potentially open avenues for pharmacological therapeutic options useful for the amelioration of symptoms.

Engagement of the patient population suffering from symptomatic gallbladder hyperkinesia via social media networks to help them understand their condition, assist them to find surgeons that will offer surgery to deserving patients, and make available to them publications on the topic that will facilitate health insurance coverage and surgeon involvement for their surgical treatment [52-54].

Taken together, these wide-ranging initiatives could result in *symptomatic gallbladder hyperkinesia* being introduced into the Rome V Criteria for Functional Gallbladder Disorders targeted for 2026 [56], serving as a first step in the potential formal recognition of this novel clinical entity.

SUMMARY CONCLUSION

Symptomatic gallbladder hyperkinesia is a new clinical condition, either a disease or a marker for disease, that is steadily gaining validation among patients and clinicians as a new clinical indication for cholecystectomy in well-selected patients.

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