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Medical Management of Symptomatic Gallstones: A Narrative Review

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Abstract

Introduction: Fifteen studies, representing over 2,500 patients, have found that up to 40% of patients continue to have abdominal pain and symptoms after cholecystectomy. As a result, there is increasing interest in non-operative approaches for managing patients with symptomatic gallstones. The goal of this study was to summarize the existing evidence and identify remaining evidence gaps for the medical treatment of symptomatic gallstone disease: including synthetic phospholipids, synthetic bile acids, choleretics, cholesterol-lowering medications, and diet.

Methods: A structured search of the literature was conducted to identify clinical cohort studies evaluating medical therapies for the management of symptomatic gallstone disease. Pubmed and Embase were used to extract relevant abstracts using defined search terms. Abstracts were screened for inclusion by two reviewers. The results of included studies were summarized in a standardized table.

Results: Nearly 12,000 articles were identified using the defined search terms. After screening for relevance and removal of duplicates, 243 articles were selected for abstract review. From these, 41 articles were selected for full text review and the results were summarized by the therapy under investigation including: expectant management, synthetic phospholipids, synthetic bile acids, choleretics, cholesterol-lowering agents, and diet and lifestyle modifications.

Conclusions: Medical therapies for gallstones have demonstrated modest success in small, retrospective studies, however, prospective studies are needed to determine their efficacy relative to cholecystectomy. Further refinement of the surgical selection process is needed to ensure maximal benefit and avoid unnecessary surgery in those with symptoms unlikely to respond to cholecystectomy.

Keywords: Gallstones; Gallbladder; Medical Management; Cholecystectomy; Alternatives

Introduction

Since Carl Langenbuch performed the first cholecystectomy in 1882, surgeons have grappled with the indications for gallbladder surgery [1-3]. In the earliest days, owing first to the morbidity of surgery and the risk of anesthesia, cholecystectomy was reserved for patients with severe disease and abscess [4]. Only later in the 20th century did biliary colic become a routine indication for cholecystectomy. The introduction of laparoscopic cholecystectomy in 1985 by Muhe, changed the threshold for surgery dramatically [5]. As laparoscopic cholecystectomy became the standard there was a 20-30% increase in the frequency of cholecystectomy [6] due mostly to the expansion of indications for surgery. Elective procedures for colic surpassed emergency surgery as the most common reason for cholecystectomy. In many cases, surgery is now offered after a single episode of biliary colic or in the absence of gallstones altogether [7].

Cholecystectomy is now the most common abdominal surgery in the US with more than 700,000 cases per year [8]. However, the use of gallbladder surgery varies considerably across geographic areas (Figure 1) and, at least among Medicare beneficiaries, does not appear to be related to the incidence of gallstones [9]. Variability in the use of cholecystectomy for gallstone disease suggests uncertainty about the proper indications for cholecystectomy and raises the question of appropriateness of current practice. As indications for cholecystectomy have expanded, so too has the recognition that a considerable number of patients fail to achieve symptom relief after surgery [10]. Fourteen studies (Table 1), representing over 4,500 patients, have evaluated patient-reported outcomes after cholecystectomy and reported a prevalence of ongoing abdominal symptoms after surgery (e.g. pain, bloating, diarrhea, and food intolerance) ranging from 13-41% [11-26]. In separate systematic reviews exploring persistent symptoms after cholecystectomy, Berger *et al.* determined only 72% of patients experienced symptom relief [27] while Lambert

et al. found abdominal pain persisted in up to 33% [28]. Failure to improve after cholecystectomy further suggests an imperfect surgical selection process [8,10]. While the safety and accessibility of cholecystectomy has made cholecystectomy the standard for people with symptomatic gallstones, non-operative management, which typically includes lifestyle changes and symptomatic management, is associated with a low risk of complications and worsening of disease [23,25].
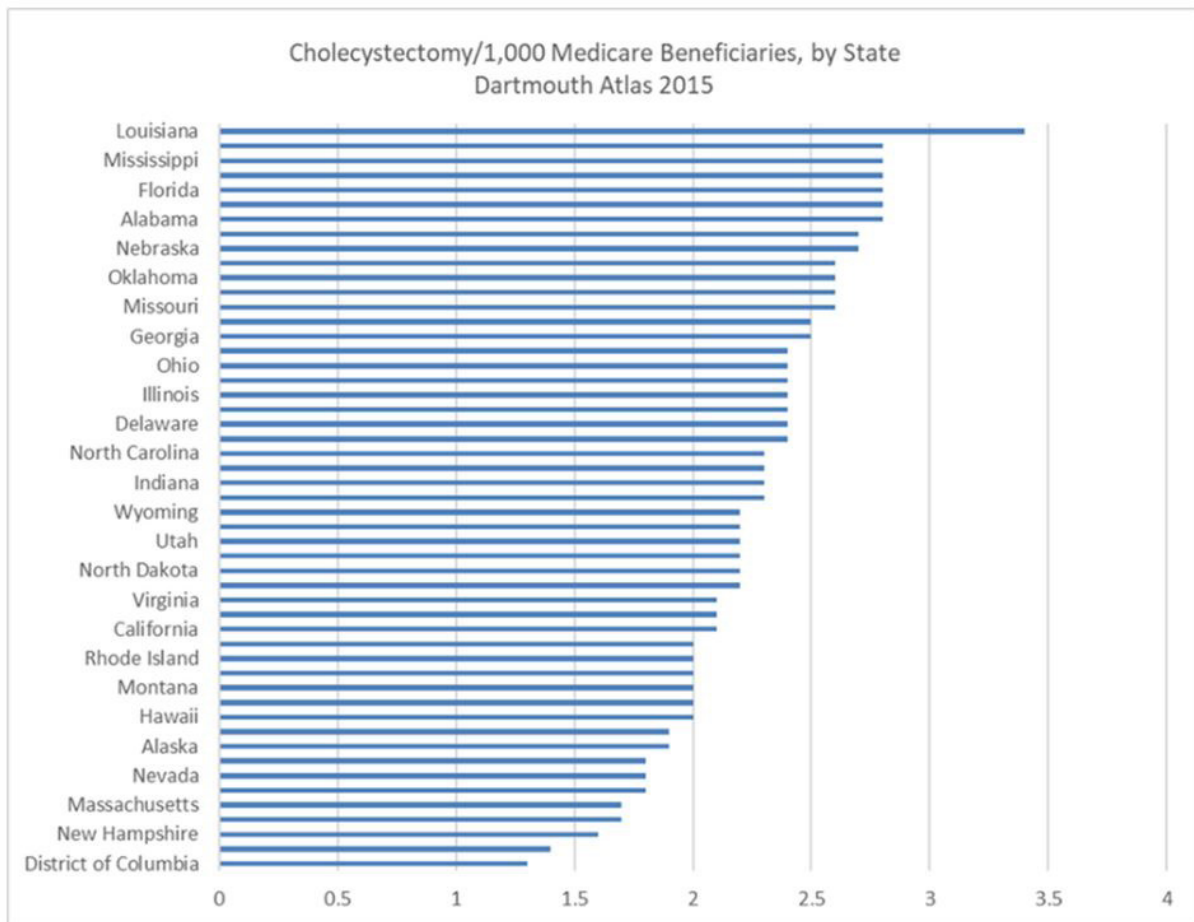

Figure 1: Number of Cholecystectomies Performed in 2015 by State Among Medicare Beneficiaries According to the Dartmouth Atlas of Health Care

Author, Year	Study Size (n)	Follow-up	Outcome Instrument	Outcomes at Follow-up
Qureshi 1993	100	12 months	NSCQ	39% with ongoing abdominal symptoms and pain
Fenster 1995	225	3 months	NSCQ	18% with ongoing abdominal pain 56% with ongoing non-pain symptoms
Ure 1995	468	12-24 months	NSCQ	55.6% with ongoing abdominal symptoms
Luman 1996	100	12 months	NSCQ	13% with ongoing biliary colic symptoms
Gui 1998	93	31 months	NSCQ	30.4% with ongoing abdominal pain
Middlefart 1998	534	60-120 months	VAPS	37% with ongoing abdominal pain
Lublin 2004	573	6-12 months	NSCQ	25% with ongoing abdominal pain 43% with ongoing non-pain symptoms
Vetrhus 2005	124	60 months	VAPS	22% with ongoing abdominal pain after surgery
Finan 2006	55	17 months	GISS	35% with ongoing abdominal pain
Halldestam 2008	198	12 months	NSCQ	17.1% with ongoing abdominal pain
Thistle 2011	1008	12 year	BSQ	41% with ongoing abdominal pain
Lamberts 2014	126	120 months	PESQ, GIQLI	39.7% with ongoing abdominal pain
Wennmacker 2017	360	6 months	GIQLI	40.8% with ongoing abdominal pain
Van Dijk 2019	537	12 months	Izbicki Pain Score, VAPS	40% with ongoing abdominal pain

NSCQ: Non-Standardized Categorical Question; **VAPS:** Visual Analog Pain Scale; **GISS:** Gastrointestinal Symptom Survey; **BSQ:** Biliary Symptom Questionnaire; **PESQ:** Patient Experiences With Surgery Questionnaire; **GIQLI:** Gastrointestinal Quality of Life Index
Table 1: Studies of Patient-Reported Outcomes after Laparoscopic Cholecystectomy

Medical therapies for gallstone disease have been proposed but have been routinely dismissed as alternatives to surgery despite the absence of direct, rigorous comparison [29]. The primary therapeutic approaches include 1) gallstone dissolution therapies that alter the lithogenecity of the bile and 2) therapies that address symptoms associated with gallstones. Bile has three primary components: phosphatidylcholines (phospholipids), cholesterol, and bile acids [30]. Gallstones formation increases as the cholesterol percentage of bile increases and thus it has been postulated that bile solubility can be improved by restoring the normal cholesterol composition of bile [31]. To alter lithogenecity, strategies include supplementation with synthetic phospholipids (e.g. lecithin), synthetic bile acids (e.g. ursodeoxycholic acid), choleretic agents (e.g. rowachol®), cholesterol-lowering agents (e.g. statins), and diet and lifestyle modifications.

In this narrative review, we summarize the current evidence for medical management of symptomatic gallstone disease, identify remaining evidence gaps in the comparison of these strategies to surgical management, and provide guidance to physicians who might consider incorporating these management strategies as part of their practice.

Methods

PubMed (Medline) and Embase were searched using defined search terms (Table 2) in April 2020 to identify prospective and retrospective clinical cohort studies of adult patients evaluating medical therapies for the management of symptomatic gallstone disease limited to the gallbladder without time restrictions. For the purposes of this review, symptomatic gallstone disease was defined as symptomatic cholelithiasis and cholecystitis. Studies of patients with choledocholithiasis, cholangitis, and other complications of gallstone disease were excluded as the higher acuity of these disease processes precludes the use of medical therapies. The search was restricted to English-language studies. Published reviews and meta-analyses were examined to identify additional studies that might not have been identified using our search strategy. After duplicates were removed, article abstracts were screened for inclusion. Primary reasons for exclusion were the lack of a non-surgical comparison group and non-adult populations (e.g. studies comparing early and late cholecystectomy for cholecystitis were considered outside the scope of this study). Selected publications were reviewed by two authors (AL and DF) and available results were extracted from the studies using a standard template (Figure 2).

Pubmed (MEDLINE)	majr: gallbladder diseases/diet therapy; gallbladder diseases/surgery; gallbladder diseases/drug therapy; gallbladder diseases/therapy; cholecystectomy
Pubmed (MEDLINE)	("Gallstones/diet therapy"[Mesh] OR "Gallstones/drug therapy"[Mesh] OR "Gallstones/prevention and control"[Mesh] OR "Gallstones/therapy"[Mesh])
Embase	('gallstones'/mj AND 'drug therapy'/mj OR 'medical therapy'/mj OR 'diet therapy'/mj OR 'lifestyle modifications'/mj OR 'non-operative' OR 'conservative managemetnt' OR 'endoscopic' OR 'ursodiol'/mj OR 'ursodeoxycholic acid'/mj OR 'lecithin'/mj OR 'dissolution'/mj OR 'lithotripsy'/mj OR 'statin'/mj OR 'ezetimibe'/mj) AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [english]/lim AND [adult]/lim AND [humans]/lim AND [clinical study]/lim AND ([embase]/lim OR [medline]/lim) AND [medline]/lim

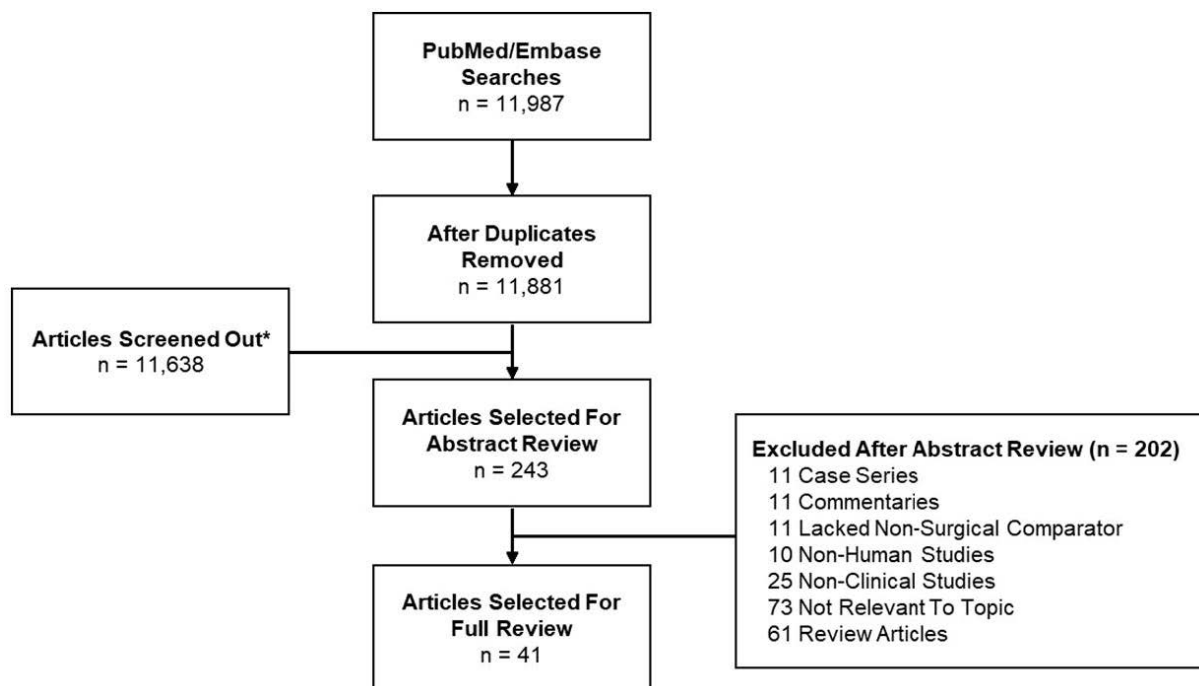**Table 2:** Search Terms Used in PubMed and Embase Searches on April 20th, 2020

Figure 2: Article Selection. *Limited to clinical studies of cholecystitis and uncomplicated cholecystolithaisis. Excluded non-clinical studies, animal studies, studies of complicated gallstone disease (e.g. cholangitis, choledocholithiasis, gallstone pancreatitis), and studies of biliary dyskinesia

A summary of the main outcome measures for each study were compiled. Outcomes of interest were the frequency of recurrent symptoms, frequency of recurrent cholecystitis, and crossover from medical to surgical management. Studies were categorized by the non-surgical comparator being studied. These included restrictive approaches to cholecystectomy, dietary supplementation with lecithin, use of synthetic bile acids (Ursodiol), use of statins for gallstone dissolution, dietary and lifestyle modification, and non-surgical procedural interventions. As our primary focus was to summarize identify evidence gaps in the use of medical therapies for symptomatic gallstone disease that should be addressed with future studies, we additionally reviewed previously published summaries of gallstone disease to determine how previous conclusions highlight the evidence gaps (Table 3).

Author, Year	Study Type	Size (n)	Follow-Up (months)	Comparator	Outcome
Prevention of Gallstone Formation During Rapid Weight Loss					
Shiffman 1995	RCT	1,004	4	UDCA of 1,200mg/day vs 600mg/day vs 300mg/day vs placebo	Gallstone formation 2% vs 3% vs 8% vs 28%, respectively (p<0.01)
Sugerman 1995	RCT	233	6	UDCA of 1,200mg/day vs 600mg/day vs 300mg/day vs placebo	Gallstone formation 6% vs 2% vs 13% vs 32%, respectively (p<0.01)
Miller 2003	RCT	152	24	500mg/day UDCA vs placebo	Gallstone formation 8% vs 30%, respectively (p<0.01)
Adams 2016	RCT	75	12	600mg/day UDCA vs usual care	Gallstone formation 11% vs 40%, respectively (p=0.03)
Nabil 2019	RCT	200	12	500mg/day UDCA vs usual care	Gallstone formation 6% vs 40%, respectively (p<0.01)
Coupaye 2019	Pro	199	12	500mg/day UDCA vs usual care	Gallstone formation 3.5% vs 28%, respectively (p<0.01)
Treatment of Existing Gallstones					
Schoenfield 1984	RCT	916	12	CDCA of 750mg/day vs 375mg/day vs placebo	Complete/partial gallstone dissolution: 54.3% vs 46.0% vs 16.2%, respectively
Leuschner 1988	Pro	33	15	UDCA 11.1mg/kg/day vs UDCA/menthol 4.75mg/kg/day	Complete/partial gallstone dissolution: 75% vs 76%, respectively
Podda 1989	Pro	120	24	10mg/kg/day UDCA vs 5mg/kg/day UDCA and CDCA	Complete/partial gallstone dissolution: 65.1% vs 71.8%
Jazrawi 1992	Pro	58	6	CDCA 12mg/kg/day vs UDCA 12mg/kg/day vs Combination 6mg/kg/day UDCA + CDCA	Complete/partial gallstone dissolution: 48% vs 78% vs 82%, respectively
Tomida 1999	Pro	527	120	600mg/day UDCA vs Usual Care	UDCA associated with lower risk of biliary colic (HR 0.19, 95%CI: 0.10-0.34) and cholecystectomy 0.08 (HR 0.08, 95%CI, 0.03-0.22)
Venneman 2006	RCT	177	3	750mg/day UDCA vs Usual Care	No difference in biliary colic events between groups (26% vs33%, p=0.3)
Hyun 2015	Pro	195	6	750mg/day of combination UDCA + CDCA	Complete or partial gallstone dissolution in 47.2%

RCT: Randomized Clinical Trial; **Pro:** Prospective Cohort Study; **UDCA:** Ursodeoxycholic Acid (Ursodiol); **CDCA:** Chenodexoycholic Acid (Chenodiol)
Table 3: Studies Evaluating Synthetic Bile Acids in the Prevention/Management of Symptomatic Gallstones

Results

Expectant Management of Gallstone Disease and Restrictive Use of Cholecystectomy

Among 1841 patients in 10 RCTS and 14 non-randomized trials, non-operative management was successful in avoiding surgery in 96% with acute cholecystitis [32]. Pooled analyses of 5-year follow-up showed a success rate, defined as no subsequent attacks, of 86% (95 % CI 0.8-0.9), a mortality rate of 0.5% (95 % CI 0.001-0.009) and a cholecystitis recurrence rate of 20% (95 % CI 0.1-0.3) [32]. In the only randomized trial comparing non-operative management with cholecystectomy for acute cholecystitis, Vetrhus and colleagues randomized 64 patients and found no significant difference in gallstone-related events, pain, or quality of life between groups [24,33]. Long-term follow up (median 14 years) of these patients demonstrated that 24% of the non-operative groups experienced recurrent cholecystitis but escalation of disease severity was not observed and patients in both groups reported similar quality of life scores at 5 years [34]. In a similar study of patients with symptomatic gallstones without cholecystitis, 137 patients were randomized to watchful waiting and cholecystectomy and significant improvements in quality of life and pain score were observed in both groups at 5 years regardless of surgical treatment [23,25]. These findings led to the SECURE (Scrutinizing (in)efficient use of cholecystectomy: a randomized trial concerning variation in practice) randomized trial comparing restrictive indications for cholecystectomy to usual care among 1,076 patients with symptomatic gallstones [35]. The restrictive strategy resulted in significantly fewer cholecystectomies (68% vs 75%, p=0.01) with no difference gallstone-related complications (7% vs 8%, p=0.16) or patient satisfaction (8.4 vs 8.4, p=0.976) but with suboptimal pain reduction with 37% of patients in both groups reporting abdominal pain at one year [35].

Medical Management of Gallstones Disease and Symptoms

Synthetic Phospholipids: Lecithin is a plant-based phospholipid has been proposed for secondary prevention for biliary colic by promoting gallstone dissolution through increasing the lipid component of bile. To date, no prospective controlled trials have evaluated the efficacy of lecithin for gallstone dissolution. An uncontrolled case series of eight gallstone patients treated with low dose lecithin for 18-24 months found an increase in biliary phospholipid content and decrease biliary cholesterol [36], yet it is unclear whether these changes in bile composition are of clinical value [31]. Dietary lipid intake does appear to be correlated with biliary lithogenecity as lipid supplementation during rapid weight loss was protective against gallstone development (0% vs 54.5%, p=0.01) [37] however, there remains a paucity of data to support the use of lecithin in the treatment of existing gallstone disease [31].

Synthetic Bile Salts: Synthetic bile salts have been identified as another potential gallstone dissolution therapy. The National Cooperative Gallstone Project, randomized patients with gallstones (symptomatic and asymptomatic identified by cholecystogram) to Chenodiol®, a synthethic bile salt, and placebo [38]. The authors concluded that chenodiol was not successful in reducing stone size or avoiding recurrent symptoms, though the rate of cholecystectomy in the control group was low (2%/year) [38]. More recent studies have focused on another synthetic bile salt, ursodeoxcholic acid (Ursodiol®) given its more favorable side effect profile [39-46]. Ursodiol has been associated with reduced risk of biliary pain (RR 0.19 [95%CI: 0.1-0.34]) and cholecystectomy (RR 0.08 [95%CI: 0.03-0.22]) at 10 years in uncontrolled prospective study of 527 patients [44]. A subsequent 2006 RCT from the Netherlands comparing Ursodiol and placebo in patients awaiting cholecystectomy found no difference in number of colics, non-severe biliary pain, and analgesic intake between groups in the three months prior to surgery [45]. More recently, a 2015 open-label, prospective trial from Korea found a combination tablet of Ursodiol and Chenodiol was associated with gallstone dissolution in 45% of all patients, with highest dissolution rate among patients with stones less than 5mm [46].

Ursodiol has also been shown to be effective as prophylaxis for gallstone formation during periods of rapid weight loss as numerous well-designed RCTs have shown a 3-5 fold reduction in gallstone incidence with Ursodiol® relative to placebo at 6, 12, and 24 months following bariatric surgery [41,43,47-49] and have been well summarized in a 2017 meta-analysis by Magouliotis and colleagues [50]. This protective effects is not unique to surgically-induced weight loss as 600mg Ursodiol daily reduced gallstone incidence compared to placebo amongst patients in a low calorie diet program (3% [95% CI: 1%-7%] vs 28% [95%CI: 22%-35%]) [51]. Ursodiol® has shown promise as an adjunct to expectant management of gallstone disease, however unanswered questions remain as prospective comparison of bile acid therapy and cholecystectomy has yet to be performed [52].

Cholerectics (Rowachol®): Rowachol is a plant-derived choleretic agent found to increase cholesterol solubility in the bile and may potentially act as a cholelitholytic agent [53]. In 2016 study by Han and colleagues compared Rowachol and placebo for prevention of post-cholecystectomy pain [54]. Although underpowered, post-cholecystectomy pain was less frequent among patients in Rowachol group (4.7% vs 14.3%, p=0.08) [54]. To date no randomized controlled trials have compared Rowachol to other therapies for symptomatic gallstones.

Cholesterol-Lowering Agents: Studies of the rate limiting enzymes of hepatic cholesterol and bile synthesis from patients with cholesterol gallstones has shown increased HMGCoA reductase activity [55]. As a result, statins, HMGCoA reductase inhibitors, have been implicated as a potential therapy target. Population-based epidemiologic studies have consistently reported decreased risk of gallstones and cholecystectomy among patients taking statins (OR 0.64-0.88) [56-59]. In clinical studies, simvastatin has been shown to decrease the cholesterol saturation index of bile but has not been effective in gallstone dissolution as monotherapy [60]. The combination of Simvastatin and Ursodiol® was been shown to be more effective than Ursodiol® alone in gallstone dissolution in patients with multiple gallstones (71% vs 25%, p<0.01) [61]. Ezetimibe (Zetia®), a lipid-lowering agent that inhibits absorption of dietary and biliary cholesterol, has also been proposed for gallstone dissolution therapy after promising results in animal studies [62]. Placebo-controlled trials evaluating ezetimibe as means for gallstone dissolution are still pending [63].

Diet and Lifestyle Modifications

Numerous exogenous risk factors for gallstones have been identified including obesity, physical activity, high-calorie intake, low-fiber intake, and weight loss/gain [8,59,64-67]. While various means to address the above risk factors have been proposed for both primary and secondary prevention of complicated gallstone disease; no prospective trials have been conducted to assess the efficacy of these interventions in preventing future biliary colic episodes [45]. This includes the most common recommendation to prevent symptoms related to gallstones, avoiding fatty foods. Biochemical analyses have shown that higher intake of saturated fats is associated with higher incidence of gallstones whereas higher intake of poly or monounsaturated fats is associated with lower risk [30]. Further, population-level epidemiologic studies have shown a decreased risk of cholecystectomy among individuals adhering to a "Mediterranean" diet (HR 0.89, 95%CI: 0.80-0.99) [65]. While knowledge of these associations may be useful for primary prevention, to date no study has demonstrated an association between low-fat diets and reduced incidence of biliary colic events in patients with gallstones. A Cochrane Review has been proposed to assess the benefits and harms of modifying dietary fat intake in the treatment of gallstone disease, however the results have yet to be published [68].

Discussion

This review describes the evidence related to the available medical therapies for symptomatic gallstone disease that have been explored over the last five decades. Of note, this review has focused on non-procedural, medical therapies for gallstone disease. Several non-cholecystectomy, procedural interventions have been proposed for symptomatic gallstones including cholecystostomy, endoscopic therapies, lithotripsy, and percutaneous injection of contact solvents, but these are outside the scope of this review. Perhaps because of a lack of rigorous studies comparing them to cholecystectomy [52], medical therapies are not routinely employed, except in specific subpopulations. More comparative studies may be of value given that a considerable proportion of patients undergoing cholecystectomy fail to achieve lasting benefit [17]. These studies should aim to address several remaining evidence gaps remain to determine the proper role of surgical and medical management of symptomatic gallstones.

Surgical Indications

When evaluating patients referred for possible biliary colic, surgeons must determine if the gallbladder is source of symptoms. Cross-sectional imaging with evidence of gallstones or biliary sludge and gallbladder dysfunction on a dynamic nuclear medicine study can increase suspicion but do not guarantee that the gallbladder is the source of symptoms or that removal of the gallbladder will improve quality of life. The Rome criteria were created to provide a consensus definition of biliary pain in attempt to increase the likelihood of benefit from cholecystectomy [69-71]. The Rome IV criteria specify that epigastric or right upper quadrant pain build to steady level lasting 30 minutes or longer, occur at different intervals, be severe enough to interrupt daily activities, not be related to bowel movements, and not be relieved by postural changes or acid suppression [72]. However, application of these criteria in selecting patients for cholecystectomy has not been associated with improvements in pain at follow-up [35]. Several studies have attempted to determine factors predictive of favorable response to cholecystectomy and found that upper abdominal pain frequency and nocturnal awakening were associated with increased odds of relief after surgery [27,73]. Despite these findings, identifying patients that will achieve full and lasting relief after surgery remains a challenge [74].

Comparative Effectiveness of Medical Management

The same challenges in patient selection present for cholecystectomy are present for the reviewed, medical therapies. As no direct comparisons to surgery have been conducted, it is not known how their efficacy compares to surgery in similar populations. It is not known if the patients that may benefit from non-procedural therapies are the same patients that respond to cholecystectomy or, more importantly, if patients that fail to improve with cholecystectomy would benefit from the discussed adjuncts to expectant management. Regardless, being able to accurately discern patients that would respond to medical therapy for their symptomatic gallstones could potentially avoid many unnecessary surgeries and substantial cost [75,76].

Predicting Response to Treatment

Characterizing patients' gallstone morphology may be means for determining responsiveness to treatment. It is not known if gallstone morphology (size relative to cystic duct, composition, volume) influences the frequency of related symptoms or response to treatment. Given the vast majority of people with gallstones remain asymptomatic for life, it is likely that certain morphologic characteristics are more common in patients that are symptomatic. No relationship between gallstone morphology and likelihood of symptoms has yet been established. However, it has been demonstrated that patients with few, small stones (<20mm) are most likely to respond to both bile acid therapy and fragmentation with lithotripsy [46,77]. Improvements in ultrasound and cholecystography have allowed for increasingly accurate characterization of gallstone morphology and may have a role in guiding treatment selection if gallstone morphology can be confirmed to be predictive of response to medical versus surgical therapies [46].

Benefit of Addressing These Evidence Gaps

Avoidance of surgery in patients with atypical symptoms that are less likely to improve with surgical intervention would benefit patients and health systems alike [78]. Effective medical alternatives to cholecystectomy would also be of great benefit in subpopulations at increased risk for adverse events with surgical intervention and anesthesia. Elderly patients are often at higher risk for surgical complications and it is unclear how often elective surgery provides meaningful quality of life benefit in these patients [79,80]. This is particularly important in the extremes of age where surgical complications may additionally lead to loss of independence. In a retrospective cohort study of adult over age 80 years with biliary disease treated without cholecystectomy, only 11% of patients ended up needing cholecystectomy by 1-year follow-up [81]. Proponents of surgery have cited concern for recurrent disease leading to severe sepsis, however, only 55% of patients required readmission to the hospital for biliary disease [81]. Management with antibiotics and nonsteroidal anti-inflammatory drugs has shown resolution of symptoms in 87% of older adult patients (mean age 79 years) with biliary disease [82]. However, clinical trials in this population have been limited by the lack of specificity in case definitions (e.g., inclusion of acalculous cholecystitis and calculous cholecystitis) making it difficult to identify subpopulations where the risk of surgery may outweigh the risk of recurrent complicated disease or quality-of-life-limiting biliary colic [83]. Importantly, the impact of these treatment decisions on quality of life in elderly patients has not been studied. Additionally, it is not known if adjuncts to this treatment strategy, such as gallstone dissolution therapy, could further reduce the need for subsequent surgical intervention while maintaining quality of life. Other important subpopulations include pregnant patients with symptomatic biliary colic and patients with complicated medical comorbid conditions (e.g., immunosuppression or advanced cardiac disease) for which there is limited evidence to guide shared decision-making conversations between surgeons and patients considering treatment options other than surgery.

Conclusions

In summary, there are many unanswered questions in the management of patients with symptomatic gallstone disease. Several strategies to manage symptomatic gallstones medically have been proposed but, despite the lack of direct comparison to cholecystectomy, concerns about gallstone recurrence and the need for long-term treatment have prevented widespread utilization [78,79]. Comparative studies are needed to better inform discussions between patients and surgeons of the available alternatives to cholecystectomy. Future investigations should also aim to refine the selection process for cholecystectomy to ensure maximal benefit and avoid unnecessary surgery in those unlikely to respond surgical intervention.

Acknowledgements

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