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Ursodeoxycholic Acid (UDCA) in Symptomatic Patients with Uncomplicated Cholelithiasis Unfit for or Refusing Surgery: A Narrative Review

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Abstract

Background. Cholelithiasis is one of the most prevalent gastrointestinal disorders worldwide, affecting approximately 10–20% of the adult population in developed countries. Although laparoscopic cholecystectomy remains the gold standard treatment for symptomatic gallstones, a significant subset of patients is either unsuitable for surgery due to comorbidities, advanced age, anesthesia-related risks, or declines operative management. In such cases, ursodeoxycholic acid (UDCA) has been proposed as a non-invasive therapeutic alternative.

Aim. This narrative review aims to critically evaluate the current evidence regarding the mechanisms, indications, efficacy, and limitations of UDCA therapy in symptomatic patients with uncomplicated gallstone disease who are not undergoing surgical intervention.

Material and Methods. A narrative review was conducted by integrating data from clinical guidelines, randomized controlled trials, cohort studies, and systematic reviews. Particular emphasis was placed on outcomes such as symptom control, gallstone dissolution, recurrence rates, and patient selection criteria.

Results. UDCA demonstrate beneficial effects in carefully selected patient populations, particularly in terms of gallstone dissolution and symptom relief. However, its clinical utility is

limited by strict eligibility criteria, a slow therapeutic response, and high recurrence rates following treatment discontinuation.

Conclusion. UDCA may represent a valuable non-surgical treatment option in selected high-risk patients when individualized appropriately. Nevertheless, its overall effectiveness remains limited, and careful patient selection is essential to optimize therapeutic outcomes.

Keywords: Ursodeoxycholic acid (UDCA), Cholelithiasis, Gallstones, Gallstone dissolution, Gallstone recurrence, Symptomatic gallstone, Conservative management, Non-surgical treatment, High-risk patients

Content

1. Introduction

Gallstone disease affects approximately 10–20% of adults in developed countries and represents a major burden on healthcare systems (1,2). The clinical presentation varies from asymptomatic gallstones to symptomatic disease characterized by biliary colic and potentially severe complications such as acute cholecystitis, cholangitis, or pancreatitis (3).

Gallstone disease is multifactorial, with risk factors including female sex, increasing age, obesity, rapid weight loss, and genetic predisposition (2). The prevalence varies geographically but remains substantial globally.

While most gallstones are asymptomatic, approximately 1–4% of patients per year develop symptoms such as biliary colic (2). Once symptoms occur, recurrence is common, and the risk of complications—including acute cholecystitis, pancreatitis, and cholangitis—increase significantly (3).

The burden of disease is therefore considerable, both clinically and economically, reinforcing the importance of effective management strategies.

The standard of care for symptomatic cholelithiasis is cholecystectomy, which provides definitive treatment by removing the source of stone formation. However, not all patients are suitable candidates for surgery. Elderly individuals, patients with significant comorbidities, and those with increased perioperative risk often require alternative therapeutic strategies (3,4). Additionally, some patients may refuse surgery due to personal preferences or fear of complications.

Biliary pain is generally attributed to transient obstruction of the cystic duct or common bile duct by gallstones, microlithiasis, or biliary sludge. This mechanical obstruction leads to increased intraluminal pressure and therefore pain (5). Given this mechanism, treatments that modify bile composition and reduce stone formation may theoretically alleviate symptoms.

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, has been used as a pharmacological agent for gallstone dissolution and symptom management. This review focuses on evaluating UDCA effectivnes and limitations in gallstones dissolving, reduction in symptoms and modifying disease progression in symptomatic patients who are not undergoing surgical treatment.

2. Pathophysiology of Gallstone Formation

Gallstone formation is a multifactorial process involving complex interactions between bile composition, gallbladder motility, and nucleation factors. In Western populations, the majority of gallstones are cholesterol stones (2,6). These arise when bile becomes supersaturated with cholesterol, leading to precipitation and crystal formation.

Impaired gallbladder motility plays a crucial role by promoting bile stasis, which facilitates crystal aggregation and stone growth. Nucleation factors further accelerate this process, resulting in clinically significant gallstones.

Metabolic factors strongly influence gallstone formation. Increased body mass index, central obesity, and dyslipidemia—particularly elevated triglycerides—are well-established risk factors (2). These factors persist even after successful stone dissolution and are key contributors to recurrence.

Importantly, symptomatic disease is thought to result from transient obstruction of the cystic duct or common bile duct by gallstones, microlithiasis, or biliary sludge (5). This mechanical process underlies biliary colic and provides a rationale for therapeutic strategies aimed at modifying bile composition and reducing stone burden.

3. Mechanism of Action of UDCA

UDCA exerts multiple biochemical and physiological effects that contribute to its therapeutic potential in gallstone disease. It is a hydrophilic bile acid that modifies bile composition and improves hepatobiliary function through several mechanisms of action that extend beyond simple litholysis (7,8,9):

- Reduction of hepatic cholesterol secretion
- Decreased intestinal absorption of cholesterol
- Increased hydrophilicity of the bile acid pool due to the replacement and displacement of lipophilic, detergent-like, toxic forms
- Promotion of gradual dissolution of cholesterol crystals
- Improvement of gallbladder emptying
- Immodulating and anti-inflammatory effect

At therapeutic doses (8–10 mg/kg/day), UDCA reduces biliary cholesterol saturation by aproxymately 40–60% (7,8,10). This effect is achieved through inhibition of intestinal cholesterol absorption and decreased hepatic secretion of cholesterol into bile.

Additionally, UDCA reduces the toxicity of endogenous hydrophobic bile acids. It does so by inhibiting their intestinal reabsorption, promoting bile flow, and protecting hepatocytes from bile acid-induced injury. These cytoprotective and anti-inflammatory properties may contribute to symptom relief beyond simple stone dissolution.

4. Indications for UDCA Therapy

The use of UDCA is restricted to carefully selected patients due to its limited efficacy in unselected populations. Appropriate candidates typically meet the following criteria (1,3,7,11):

- Symptomatic patients with mild biliary colic
- Presence of radiolucent cholesterol gallstones
- Stone diameter <15mm, preferably ≤5–10 mm
- Functioning gallbladder with preserved motility
- Patent cystic duct
- Patients unfit for surgery or refusing surgical intervention

Despite the fact that approximately 90% of gallstones are cholesterol-based, fewer than 10% of patients meet the criteria for dissolution therapy (7,10). Accurate patient selection is therefore essential and relies on imaging techniques such as ultrasonography and computed tomography.

Ultrasonography allows assessment of stone size, number, and gallbladder motility, while CT imaging helps exclude calcified stones. Stones with density values below 100 Hounsfield Units are more likely to be cholesterol-rich and responsive to UDCA therapy (12).

5. Efficacy of UDCA

5.1 Stone Dissolution

The effectiveness of UDCA in dissolving gallstones depends on multiple factors, including stone size, number, composition, and gallbladder function. Reported dissolution rates range usually from 30% to 60% in appropriately selected patients (13,14). Although some research shows it may even go up to 90% (7,12).

The rate of dissolution is relatively slow, averaging approximately 0.5–1.0 mm reduction in stone diameter per month (12,15). Consequently, treatment duration typically extends from 6 to 24 months.

Smaller stones are significantly more responsive to therapy:

- Stones ≤5 mm: up to 70–90% dissolution rates
- Stones ≤10 mm: approximately 40–60% dissolution
- Stones >10 mm: markedly reduced response (around 29%) (12,13)

These findings emphasize that UDCA is most effective in early-stage disease with small stones. Larger stones and multiple stones significantly reduce the likelihood of success. However, this shows that in some cases there is a good alternative for those for whom cholecystectomy will not be performed.

5.2 Symptoms Control

The effect of UDCA on biliary pain remains one of the most debated aspects of its use. Evidence is conflicting and reflects heterogeneity in study design and patient populations.

One of the best available long-term cohort studies provides by Tomida et al. with up to 18 years follow up demonstrated that UDCA therapy was associated with a reduced risk of biliary pain (62% vs. 92% in untreated patients at 10 years) and acute cholecystitis, even in the absence of complete stone dissolution (5).

The systematic review by Hall et al. reported symptom improvement in a majority of studies (7 out of 8) showing that UDCA may reduce biliary pain, with some reporting symptom improvement in up to 86% of patients (16). However, these findings are limited by variability in study design, follow-up duration (ranging from 14 days to 38 months), and outcome definitions.

On the other hand, the study by Venneman et al. of a randomized, double-blind, placebo-controlled trial in highly symptomatic patients demonstrated no significant benefit of UDCA in reducing biliary pain or complications (17). Notably, the number of prior colic episodes was a stronger predictor of future symptoms than treatment allocation. These findings are supported

by guideline statements indicating a lack of effectiveness in preventing symptoms and complications (1).

Symptom improvement, when present, often occurs within the first 3 months of therapy, whereas stone dissolution requires prolonged treatment (12). Lack of response within 6–12 months is generally considered a poor prognostic indicator.

5.3 Reconciling Conflicting Evidence

The discrepancy between studies may be explained by differences in patient populations. Evidence suggests that UDCA is more effective in early-stage disease with fewer and smaller stones, whereas it is largely ineffective in patients with advanced symptomatic disease. Patients with fewer prior colic episodes are more likely to benefit from therapy, whereas those with highly symptomatic disease derive limited benefits (5,17,16). Relating this to the topic of this work, it shows that with early diagnosis and early treatment, there is a great chance of helping a significant group of people.

6. Limitations and Recurrence

Despite its potential benefits, UDCA therapy has several important limitations:

- Slow onset of action
- Limited efficacy in unselected populations
- Strict eligibility criteria
- Ineffectiveness in calcified or pigment stones
- Requirement for long-term therapy (2)

One of the most significant drawbacks is the high recurrence rate after successful dissolution. This is probably the main reason why this treatment method is relegated to the background in comparison to the effectiveness of cholecystectomy. Reported recurrence rates include (7,8,10,14):

- approximately 12,5% at 1 year
- approximately 30–50% at 5 years
- approximately 50–70% at 12 years

Recurrence is largely attributed to persistence of underlying pathogenic factors such as cholesterol supersaturation and impaired gallbladder motility. Patients with multiple stone prior to treatment are at a particularly high risk of recurrence (12). Although low-dose maintenance therapy may reduce recurrence rates, this approach is not universally effective, especially in older patients who are the main group of patients not eligible for cholecystectomy (14).

7. Safety Profile

UDCA is generally safe and well tolerated. Adverse effects are typically mild and include diarrhea and nausea, with rare cases of hepatotoxicity reported (8,10,11). Its favorable safety profile is a major advantage, particularly in elderly and high-risk patients, where surgical risk may outweigh potential benefits.

8. Discussion

Current clinical guidelines emphasize the limited role of UDCA in the management of gallstone disease. Its use is recommended only in selected patients who are not candidates for surgery.

While laparoscopic cholecystectomy remains highly effective and widely available, it is not without risk, particularly in elderly or frail patients. In such populations, nonsurgical management may offer lower morbidity and mortality. Therefore, the decision between surgical and medical management should be individualized, taking into account both objective clinical criteria and patient preferences.

The evidence regarding UDCA is complex and sometimes contradictory. While some studies demonstrate meaningful symptom reduction and decreased risk of complications, others show minimal or no benefit compared with placebo. This inconsistency highlights the importance of patient selection and suggests that UDCA is not universally effective.

A key challenge in interpreting the literature is the heterogeneity of study designs, including differences in patient populations, treatment duration, and outcome measures. Standardization of clinical trials would be necessary to provide more definitive conclusions.

Despite these limitations, UDCA remains a valuable option in a small group of patients. Its benefits appear to be greatest in individuals with small, radiolucent stones, preserved gallbladder function, and early-stage disease.

9. Conclusion

Ursodeoxycholic acid represents a non-invasive therapeutic option for a highly selected subgroup of patients with symptomatic uncomplicated cholelithiasis who are unfit for or refuse surgery.

Although UDCA can achieve stone dissolution and may reduce biliary symptoms, its overall effectiveness is limited by slow action, strict eligibility criteria, and high recurrence rates. Evidence suggests that its benefits are most pronounced in early-stage disease and in patients with small, cholesterol-rich stones.

In modern clinical practice, UDCA plays a secondary role compared to surgical management. However, in carefully selected patients—particularly those at high surgical risk—it remains a clinically relevant alternative.

Further research is needed to better identify predictors of response, optimize treatment protocols, and clarify its role in symptom management independent of stone dissolution.

10. Disclousure

Supplementary Materials

Not applicable.

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