# The Therapeutic Role of Ursodeoxycholic Acid in Digestive Diseases

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## ABSTRACT

Ursodeoxycholic acid (UDCA) makes up a small portion of the naturally occurring bile acid pool in humans, and the drug is effective in several diseases. The mechanism of action involves the displacement of more toxic endogenous bile acids, direct protection of hepatocytes against apoptosis, and stimulation of endogenous secretion of bile to alleviate cholestasis. The use of UDCA has been studied extensively in primary biliary cirrhosis and cholelithiasis and there is evidence for its use in both diseases. There is also evidence against the use of UDCA in primary sclerosing cholangitis (PSC). Several potential uses of UDCA warrant further investigation after initial studies have shown promise including treatment for microlithiasis, intrahepatic cholestasis of pregnancy, total parenteral nutrition, chemoprophylaxis of colorectal cancer in patients with ulcerative colitis and PSC, viral hepatitis, and in bone marrow transplantation. Ursodeoxycholic acid is generally well tolerated with few adverse events, though minor weight gain is a common side effect.

Keywords: Ursodeoxycholic acid, primary biliary cirrhosis, primary sclerosing cholangitis, cholelithiasis, microlithiasis

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## INTRODUCTION

Ursodeoxycholic acid (UDCA) constitutes around 3% of the total bile acid pool in humans. Bacteria modify another naturally occurring bile acid, chenodeoxycholic acid, in the gut to form UDCA. The UDCA is a primary bile acid found in bears, and it was discovered in polar bears by Swedish and Danish explorers in Greenland in the early 1900s. Later UDCA was isolated from the black bear and given its current name for being an isomer of deoxycholic acid.[1]

The mechanism of action for UDCA is multifactorial. First, UDCA is hydrophilic whereas many other bile acids are hydrophobic and therefore more cytotoxic to hepatocytes. The UDCA competes with dominant endogenous bile acids for absorption in the terminal ileum, making the bile acid pool more hydrophilic.[2,3] Second, UDCA has a direct protective effect on hepatocytes against bile acid-induced apoptosis.[3] Third, in cholestatic diseases, the retention of toxic bile acids leads to cell injury. The UDCA counters this effect by stimulating hepatocytes and bile duct epithelial cells to secrete bile (Figure 1).[4] The UDCA is generally a well-tolerated drug, but weight gain is a well-documented side effect. Patients gain on average 2.2 kg in the first year of treatment and their weight stabilizes thereafter.[5]

## PRIMARY BILIARY CIRRHOSIS

In primary biliary cirrhosis (PBC), an immune reaction targets bile duct epithelium and destroys intrahepatic ducts. Subsequent cholestasis leads to damage to hepatocytes and can eventually result in cirrhosis in up to 25% of patients.[2] The UDCA at 13–15 mg/kg/day is approved for treatment of PBC by the United States Food and Drug Administration, and UDCA is the only disease-modifying agent recommended by the American Association for the Study of Liver Disease (AASLD) for PBC.[6] Several trials show that UDCA improves transplant-free survival, delays histologic progression of liver disease, and improves biochemical markers of the disease.[6,7]

Patients in early histologic stage of PBC (I or II) on liver biopsy who are treated with UDCA have the best outcomes and have been shown to have survival rates similar to control populations without PBC.[8,9] In treated patients, survival rates are better than rates predicted by the Mayo model.[8–10]

When treating a PBC patient with UDCA, improvement in transaminases and bilirubin levels is a favorable prognostic factor. Transplant-free survival is best predicted biochemically by lower levels of alkaline phosphatase, aspartate aminotransferase (AST), and bilirubin. Patients with lower biochemical markers had a 10-year transplant-free survival rate of 90% compared to 51% in patients with higher levels in one study.[11] Despite an increase in the total number of liver transplants over a 12-year period ending in 2006, the number of transplants for PBC patients declined over the same time period. This finding suggests that UDCA has been successful as the primary treatment for PBC.[12]

Ursodeoxycholic acid may also decrease the risk of developing esophageal varices in PBC patients. A prospective trial following 180 patients with PBC for 4 years showed that 16% of patients treated with UDCA developed esophageal varices versus 58% of those given placebo.[13] This effect may be due to delayed progression of advancing liver disease, as opposed to a protective effect against portal hypertension.

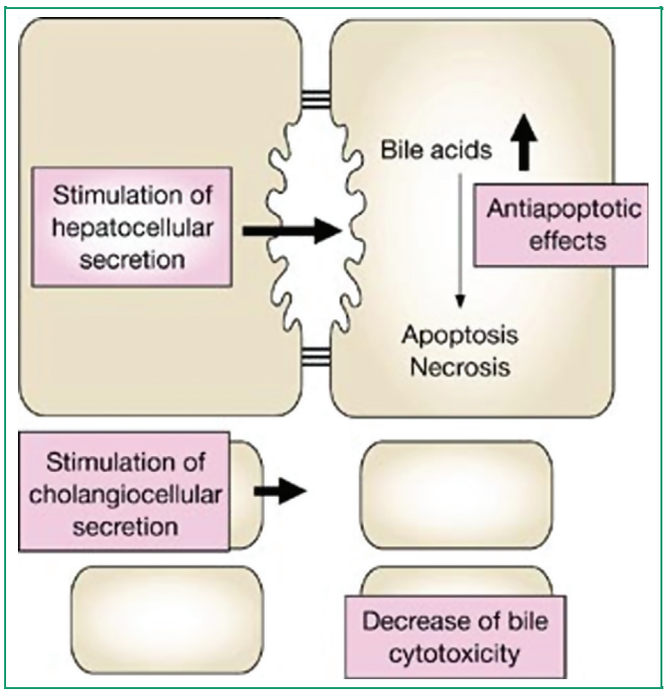


**Figure 1.** Mechanisms of action of UDCA. Ursodeoxycholic acid decreases the cytotoxicity of bile by making the bile acid pool more hydrophilic. The UDCA also directly inhibits apoptosis induced by hydrophobic bile acids. Finally, UDCA stimulates secretion of bile, decreasing the retention of toxic bile acids. Reprinted by permission from MacMillan Publishers Ltd: Beuers U. Drug insight: mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol.* 2006;3(6):318–328.

Several meta-analyses have shown conflicting results regarding outcomes in PBC patients treated with UDCA. Two meta-analyses showed no benefit on mortality or liver transplant rates.[14,15] Common criticisms of these analyses are that they included studies with inadequate follow-up times and small doses of UDCA.[2,6] Two other meta-analyses demonstrated an improvement in survival with no liver transplant.[16,17] A 2006 meta-analysis requiring at least a mid-dose of UDCA (10 mg/kg/day or more) and long-term follow-up of at least 2 years showed an odds ratio of 0.65 for liver transplant and 0.75 for death or liver transplant in patients receiving UDCA versus placebo or no treatment.[16]

Current AASLD guidelines recommend a dose of 13–15 mg/kg/day for PBC in patients with abnormal liver markers with a cholestatic pattern, regardless of histological stage. Patients with PBC but no elevation of liver markers are not advised to use UDCA.[6] Patients discontinuing UDCA tend to have liver biochemical markers return to pretreatment values, therefore treatment is continued indefinitely.[2] Patients awaiting transplant may be treated with UDCA as well.[18]

The recommended dose of 13–15 mg/kg/day is based on a study comparing low dose (5–7 mg/kg/day), standard dose (13–15 mg/kg/day), and high dose (23–25 mg/kg/day) UDCA. Maximum improvement in alkaline phosphatase, AST, the amount of UDCA in bile, and Mayo risk score were seen with the standard dose. There were no additional side effects with this dose. The high dose did not have additional side effects but also was not shown to be of any additional benefit.[19]

The use of UDCA in combination with other medications has been considered. A recent study suggests that patients with suboptimal biochemical response to UDCA after 1 year may derive benefit from a combination of UDCA, budesonide (6 mg/day) and mycophenolate mofetil (1.5 g/day).[20] Finally, there is also evidence that UDCA is effective when combined with corticosteroids in lowering serum biochemistries in patients with PBC and autoimmune hepatitis overlap syndrome.[21]

## PRIMARY SCLEROSING CHOLANGITIS

Initial studies of UDCA in primary sclerosing cholangitis (PSC) showed improvement in biochemical markers, histological features, and clinical symptoms of pruritis and fatigue.[22–25] However, in 1997 there was a larger randomized, double-blind trial comparing UDCA with placebo in treating PSC. The dose was 13–15 mg/kg/day with a median follow-up of 2.2 years. There was no difference between the treatment and the placebo groups when examining the combined outcome of death, need for transplant, histological progression, development of varices, ascites, encephalopathy, fatigue, or pruritis.[26]

Later smaller studies suggested that higher doses may be of more benefit. In three studies, doses ranging from 17 to 30 mg/kg/day improved serum biochemistries, cholangiographic appearance, rate of liver fibrosis, or Mayo risk score.[27–29] Finally, a trial compared 10, 20, and 30 mg/kg/day doses and the Mayo risk score was significantly better in the high dose group.[30]

Despite these successes with high dose UDCA, a randomized, double-blind placebo-controlled trial of high dose UDCA by Lindor et al looking at 150 patients with PSC showed poorer outcomes among patients treated with UDCA. Patients were given 28–30 mg/kg/day of UDCA. The study included long-term follow-up and measured the following primary outcomes: development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, and death. Thirty nine percent of patients in the UDCA group reached one of the above endpoints by the end of the study versus 26% in the placebo group. The UDCA group had lower serum liver tests.[31] The authors offered several explanations for the results. Higher doses may have allowed more drugs to reach the colon with subsequent conversion into hepatotoxic bile acids. High dose UDCA may also inhibit the apoptosis of activated stellate cells, allowing for more fibrinogenesis and liver disease. Finally, UDCA may exacerbate hepatocyte necrosis in the setting of biliary obstruction and PSC.[31]

The AASLD gives a 1A recommendation (strong recommendation with high quality evidence) against the use of UDCA in patients with PSC.[32] As an editorial on the negative study above points out, the role of UDCA for PSC remains unclear. Low or medium dose UDCA for PSC could be further evaluated in large trials with longer durations of treatment.[33]

## CHOLELITHIASIS

Cholecystectomy is the treatment of choice for patients with symptomatic cholelithiasis. However, in certain cases of uncomplicated cholelithiasis, UDCA may be useful. A randomized, double-blind placebo-controlled trial of 177 patients with highly symptomatic gallstones awaiting cholecystectomy showed that the rate of biliary colic, nonsevere biliary pain, and analgesic intake were similar between the UDCA and placebo groups over a 90-day follow-up period. This indicates that UDCA does not have a role in alleviating biliary pain in the short-term among patients awaiting cholecystectomy.[34]

The UDCA may however be useful in longer-term treatment of gallstones in patients not undergoing cholecystectomy. In a nonrandomized cohort of 527 patients with uncomplicated gallstones, UDCA was associated with decreased need for cholecystectomy and decreased biliary pain. This was independent of the analysis of gallstone dissolution.[35]

Among patients with an intact gallbladder, recurrent acute pancreatitis may occur less frequently when UDCA is used, especially if microlithiasis may be playing a role.[36] In patients with recurrent pancreatitis who will not undergo cholecystectomy, performing a sphincterotomy is advised as well.[37]

In certain populations, UDCA may effectively dissolve cholesterol gallstones by solubilizing cholesterol in bile. A meta-analysis showed that UDCA successfully dissolved radiolucent stones in 37% of patients. The efficacy increased with decreasing size of the stones.[38] Other analyses have shown dissolution rates of 30%–50%.[39] However, stones frequently return after dissolution with UDCA. Single stones have the lowest rate of recurrence.[40,41] Recurrence rates have been shown to be 12.5% in the first year and 61% by 11 years in one study.[41]

Patient selection is very important for successful dissolution of gallstones with UDCA. Ideal candidates for UDCA therapy should have a functioning gallbladder, their largest stone should be ideally less than 5 mm and certainly less than 10 mm, and the stones should be of the cholesterol variety and thus radiolucent.[35,42,43]

Ursodeoxycholic acid has been shown to reduce the incidence of rapid weight loss induced gallstone formation in patients undergoing gastric bypass. A randomized placebo-controlled study using 600 mg daily for 6 months reduced the incidence of gallstone formation over 6 years following gastric bypass from 32% with placebo to 2% with UDCA.[44]

## MICROLITHIASIS

Treatment of microlithiasis may include cholecystectomy, endoscopic sphincterotomy, or UDCA. The UDCA can prevent recurrence of acute ''idiopathic'' pancreatitis, which is often caused by biliary sludge and microlithiasis in patients with an intact gallbladder.[36,45] In a study of patients with recurrent pancreatitis and cholesterol monohydrate crystals in their bile, UDCA eliminated biliary microlithiasis and prevented recurrence of pancreatitis over a 44-month period.[36] In another small study, 4 out of 5 patients with biliary sludge and microlithiasis treated with UDCA achieved long-term relief from recurrent pancreatitis.[45,46] Because of the risk of recurrence, however, cholecystectomy is routinely recommended in patients with biliary sludge who have had acute pancreatitis.

Many patients who undergo cholecystectomy for symptomatic gallstones continue to experience pain. Approximately one-third of all patients undergoing cholecystectomy will experience this postcholecystectomy syndrome. The pathophysiology of postcholecystectomy syndrome has not been clearly delineated, though several mechanisms have been proposed including sphincter of Oddi dysfunction.[47]

Microlithiasis has been identified in some patients who have undergone cholecystectomy, and one study demonstrates that it may be a cause of postcholecystectomy pain. The UDCA may be useful for treatment in these cases. The study looked at 118 patients with postcholecystectomy syndrome, and 12 (10%) were found to have microlithiasis on examination of their bile. These 12 patients were further studied. In the first phase of the study, 6 patients received UDCA and had a significant reduction in pain compared to the untreated 6 patients. In the second phase, the other 6 patients were treated with UDCA and also experienced a significant reduction in pain. The UDCA may be of benefit in patients with postcholecystectomy pain and microlithiasis.[47]

This study was limited by several factors including the small sample size of 12 and the lack of placebo control. Bile analysis was not performed after treatment to confirm the resolution of microlithiasis as the reason for pain relief. Also, the appropriate duration of treatment is not known. It is not known whether endoscopic sphincterotomy is an effective therapy in patients with microlithiasis and postcholecystectomy syndrome.[47]

## MISCELLANEOUS CHOLESTATIC DISEASES

Intrahepatic cholestasis of pregnancy (ICP) manifests as pruritis with elevated serum bile acids in the second half of pregnancy. It generally resolves after pregnancy with only rare complications for the mother. Fetal complications are more common and are associated with elevated maternal serum bile acid concentrations. The mechanism of disease involves improper biliary transport across the canalicular membrane.[48]

Recent trials have evaluated the utility of UDCA in treating ICP. In one study, patients received either UDCA at a dose of 8–10 mg/kg of body weight daily or cholestyramine. The UDCA group had a decrease in serum aminotransferases, serum bile acid levels, and pruritis. Babies in the UDCA group were delivered significantly closer to term without adverse events from UDCA.[49] In another trial comparing UDCA at 1 gm daily to dexamethasone, patients receiving UDCA showed a decrease in serum alanine transaminase (ALT) and bilirubin. In the women with the highest initial serum bile acid levels, UDCA also decreased pruritis and serum bile acid levels. There was no significant effect on fetal complications.[50] There have been no reports of fetal complications

with maternal use of UDCA, but no study has been powered to detect such events.[51]

Patients on long-term total parenteral nutrition (TPN) are at risk for hepatobiliary complications including cholestasis.[52,53] A study of nine patients with cholestasis due to TPN who were treated with UDCA at 10.6–12 mg/kg/day showed a significant reduction in gamma-glutamyltransferase (GGT) and ALT during treatment periods compared to nontreatment periods. There was no significant difference in bilirubin, AST, or alkaline phosphatase.[54] Three small retrospective studies examining UDCA in pediatric populations receiving TPN showed improvements in liver biochemistries as well.[55–57]

There is no evidence regarding the use of UDCA in the treatment of hepatotoxic drug reactions. However, given the benefit of UDCA in other cholestatic diseases, it is a reasonable assumption that UDCA may be of benefit in cholestatic drug hepatotoxicity with minimal risk to the patient. A dose of 13–15 mg/kg/day has been suggested.[58]

## BONE MARROW TRANSPLANTATION

Various hepatic complications are associated with hematopoietic cell transplantation including veno-occlusive disease, hepatic graft-versus-host disease (GVHD), and liver failure.[59,60] A prospective randomized trial examining prevention of hepatic complications after allogeneic stem cell transplantation suggests a role for UDCA. Patients received either UDCA or placebo from the day preceding conditioning until day 90 after transplantation. The UDCA group had significantly lower serum bilirubin and ALT levels, a significantly lower incidence of grade III or IV acute GVHD, and improved overall survival at 1 year (71 vs 55%). There was no difference in the incidence of veno-occlusive disease.[61]

A small study examined the use of UDCA for the treatment of hepatic GVHD. Twelve allogeneic bone marrow transplant patients received 6 to 12 weeks of UDCA for treatment of refractory GVHD. Results showed improvement in AST, bilirubin, and alkaline phosphatase with approximately a one-third decline in each. However, there is no evidence for long-term use.[62]

## VIRAL HEPATITIS

Ursodeoxycholic acid has been associated with improved serum transaminases in patients with chronic hepatitis C despite having no influence on the viral load. The mechanism likely involves the cytoprotective effect of UDCA.[63] A trial in 1994 demonstrated that UDCA at a dose of 600 or 900 mg/day for 16 weeks was associated with a 26% reduction in ALT and a 50% reduction in GGT.[64] A recent large, double-blind trial evaluated serum biochemical response to UDCA at either 150, 600, or 900 mg/day for 24 weeks in 596 patients with chronic hepatitis C. This trial confirmed that 600 mg/day was the preferred dose for maximal response in transaminases, but serum GGT decreased significantly more in the 900 mg/day group. This may be a reflection of the choleretic effect of UDCA. There was no difference in adverse events among the groups.[65]

Progression of fibrosis in chronic hepatitis C has been linked to serum transaminase levels.[66] However, trials of UDCA have failed to show benefit in histological progression. This may be due to the relatively short duration of follow-up of the studies to date, which have been 6 to 12 months.[63,67,68]

A recent Cochrane review of UDCA in viral hepatitis showed an improvement in liver biochemistries for Hepatitis B and C. The UDCA did not affect clearance of virus, and there was no evidence to indicate improvement in outcomes such as progression to cirrhosis or incidence of hepatocellular carcinoma.[69]

## NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) includes hepatic steatosis and nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and hepatocellular carcinoma.[70] A pilot study suggested a role for UDCA in treating NASH.[71] However, a randomized controlled trial of 166 patients who received either 13–15 mg/kg/day of UDCA or placebo for 2 years showed no significant difference in serum liver biochemistries or histology.[72] The authors of this study suggest that perhaps the dose of UDCA used was not high enough to detect a benefit. Another study using a fixed dose of 1200 mg/day of UDCA versus placebo also failed to show a benefit for serum transaminases.[73] Finally, a Cochrane review with meta-analysis examined four randomized trials of UDCA for NAFLD and was unable to detect a significant benefit for mortality or biochemistries with UDCA.[70]

## CHEMOPROPHYLAXIS OF COLORECTAL CANCER

The use of UDCA in patients with ulcerative colitis (UC) and PSC for chemoprevention of colorectal cancer has also been investigated. A cross-sectional study of 59 patients with UC and PSC revealed an odds ratio of 0.18 for the development of colonic dysplasia in patients taking UDCA versus patients not taking UDCA.[74] In another study, 52 patients with UC and PSC received either UDCA for a median of 42 months or placebo for a median of 40 months. The relative risk of developing dysplasia or cancer was 0.26 for the UDCA group compared to the placebo group.[75]

Finally, a retrospective analysis compared 28 patients with UC and PSC who were treated with UDCA for at least 6 months to 92 patients who did not receive UDCA. There was no significant difference in the incidence of dysplasia or cancer.[76] Given the potential adverse outcomes in PSC patients taking UDCA and the inconclusive evidence, the AASLD recommends against the use of UDCA for chemoprophylaxis.[32]

## CYSTIC FIBROSIS

In cystic fibrosis patients with evidence of hepatic involvement, UDCA was shown in an observational study to be

**Table 1.** Potential Uses of UDCA

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| *Conditions with evidence supporting use* |
| Primary biliary cirrhosis |
| Cholelithiasis |
| *Conditions with some evidence supporting use requiring further investigation* |
| Microlithiasis and pancreatitis |
| Microlithiasis and postcholecystectomy syndrome |
| Intrahepatic cholestasis of pregnancy |
| TPN-induced liver injury |
| Bone marrow transplantation and GVHD |
| Viral hepatitis |
| Nonalcoholic fatty liver disease |
| Chemoprophylaxis of colorectal cancer for UC and PSC |
| Cystic fibrosis |
| *Conditions with evidence against use* |
| Primary sclerosing cholangitis |
| *Conditions with theoretical benefit but no evidence* |
| Drug-induced hepatotoxicity |

associated with a delay in the progression of liver disease. No solid evidence for its use in cystic fibrosis is available in the form of randomized controlled trials.[77]

## CONCLUSION

Ursodeoxycholic acid is a well-tolerated and safe drug with a wide range of potential clinical uses (Table 1). In PBC, the evidence favors the use of UDCA as a disease-modifying agent that improves transplant-free survival. The UDCA is useful for dissolving gallstones and preventing symptoms in carefully selected patients with cholelithiasis; namely, in patients with small gallstones and a functioning gallbladder who are not undergoing cholecystectomy. The UDCA is effective in preventing cholelithiasis in patients who have undergone gastric bypass surgery.

In PSC, the evidence is equivocal but suggests potential harm from high-dose UDCA use. Finally, there is promise for the potential use of UDCA in microlithiasis, cholestatic diseases such as ICP and liver injury from TPN, as well as in chronic viral hepatitis, bone marrow transplantation, chemoprophylaxis in UC and PSC, and cystic fibrosis. More research is warranted in these areas.

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