Ursodeoxycholic Acid in Liver Cirrhosis: An Evidence-Based Review

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Abstract

Ursodeoxycholic acid (UDCA) is a drug with multiple hepatoprotectant and anticholestatic properties. It is used extensively for the dissolution of gallstones and for the treatment of various cholestatic liver diseases. UDCA modifies the constituents of the bile acid pool, stimulates hepatobiliary secretion, exerts cytoprotective effects, inhibits bile acid absorption by cholangiocytes, and exerts immunomodulatory action. These cytoprotective effects alleviate hepatic inflammation and provide potential anti-fibrotic property of this compound. The mechanism involved in the direct inhibitory fibrogenetic effects is unclear, and the data concerning it is extremely limited. In clinical studies, UDCA has been shown to delay the progression of fibrosis, stabilize portal pressure, and delay development of varices and clinical decompensation in patients with primary biliary cholangitis. The effects of UDCA on liver fibrosis and cirrhosis in other chronic cholestatic disorders show heterogeneous results. In non-cholestatic disorders, UDCA demonstrated limited clinical benefits, and currently, there is insufficient evidence to support its use in these conditions. It should be emphasized that there is a possibility that the treatment duration in the studies may not be of sufficient length for the drug to show the effects, as the fibrosis may progress slowly. Future studies are required to elucidate long-term clinical benefits in conditions, such as cirrhosis, and also to investigate any potential cirrhosis-related complications.

Keywords

Liver Fibrosis · Liver Cirrhosis, Biliary · Deoxycholic Acid · Polycyclic Compound · Cholestasis, Intrahepatic

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5.1 Introduction

Ursodeoxycholic acid (UDCA; 3α,7β-dihydroxy-5β-cholanic acid), also known as ursodiol, is a secondary bile acid occurring in human bile. It is a hydrophilic bile acid accounting for a small proportion (1–3%) of the human bile acid pool [1]. It is the predominant bile acid of the bile of black bears. UDCA was first utilized for the dissolution of gallstones in the 1970s. This utilization was followed up by a lot of studies into various liver diseases, especially cholestatic liver diseases. There is abundant data supporting its use in patients with primary biliary cholangitis (PBC), and it is currently approved for first-line treatment of this condition. However, there are limited data regarding the effect of UDCA treatment on liver fibrosis, liver cirrhosis outcomes, and cirrhosis-related portal hypertension. This chapter will summarize current evidence pertinent to the mechanism of the action and effects of UDCA on liver fibrosis and portal hemodynamics, clinical evidence of UDCA use on hepatic fibrosis and potential cirrhosis-related complications in patients with chronic liver diseases, and clinical outcomes in patients with cirrhosis.

5.2 UDCA Mechanism of Action and its Effects on Liver Fibrosis

Many mechanisms have been proposed as being responsible for the hepatoprotective effects of UDCA. It is unclear, however, about which mechanism provides the major beneficial effects and the predominant mechanism may vary depending on the nature and severity of the liver disease. The mechanisms mainly considered to be responsible are summarized below [1–3].

5.2.1 Alteration of the Bile Acid Pool and Protection of Injured Cholangiocytes from Toxic Bile Acids

The magnitude of hydrophobicity of human bile acids in order should be lithocholic acid > deoxycholic acid > chenodeoxycholic acid > cholic acid > ursodeoxycholic acid [4]. The accumulation of hydrophobic bile acids is known to cause damage to cell membranes and also extracellular cytotoxicity especially when in excess. Therefore, in patients with cholestasis, bile retention promotes cholangiolar injury and inflammation. UDCA is a hydrophilic bile acid, and continuous therapeutic use can cause it to become the major bile acid in the bile pool (40–50% of total bile acid by continuous use of UDCA at a standard dose of 13–15 mg/kg per day). Hence, replacing hydrophobic bile acids with more hydrophilic UDCA lessens the toxicity of bile that may aggravate the activity of primary bile duct disease. This mechanism is thought to be the main mechanism of action of UDCA in patients with early cholestatic disorders when the bile excretory function is still reserved.

5.2.2 Stimulation of Impaired Hepatobiliary Secretion

UDCA causes biliary secretion of bile acids and other organic compounds in experimental models. This effect is also demonstrated in patients with PBC and primary sclerosing cholangitis (PSC) resulting in a decrease in endogenous, hydrophobic bile acid, chenodeoxycholic acid, and bilirubin. UDCA stimulates the elimination of toxic compounds from hepatocytes by stimulating the expression of transporter proteins that are needed for biliary secretion. It also stimulates HCO_3^- secretion by cholangiocytes and increases cytosolic free Ca^{2+} in cholangiocytes, resulting in increasing activity of Cl^- channels and promoting bicarbonate movement into the bile ducts. The stimulation of cholangiocellular calcium-dependent chloride/bicarbonate anion secretion is considered to be the mechanism responsible for the anticholestatic effect of UDCA in the diseases in which HCO_3^- secretion is impaired.

5.2.3 Hepatocytes and Cholangiocyte Cytoprotection

A variety of pathways involving the stabilization of plasma membranes and mitochondria and induction of subcellular anti-apoptotic pathways by UDCA offer cytoprotective effects against bile acid-induced apoptosis.

5.2.4 Inhibition of Absorption of Toxic, Hydrophobic, Endogenous Bile Salts

Under cholestatic conditions, UDCA use is associated with impaired apical uptake of hydrophobic bile acid by cholangiocytes, thus reducing the toxic bile acids within the cell.

5.2.5 Potential Immunomodulatory Effects

Modulation of cell-mediated immunity by UDCA has been observed. Human leukocyte antigen (HLA) class I and class II molecules are overexpressed by hepatocytes and cholangiocytes under chronic cholestasis conditions. This aberrant expression of HLA class I may induce recognition and subsequent destruction by cytotoxic T lymphocytes. UDCA reversal of aberrant HLA class I molecules has been demonstrated; however, this effect might be secondary to the anticholestatic properties of UDCA.

5.2.6 Mechanisms Involved in the Anti-Fibrosis Effects of UDCA

Protection of hepatic tissues against hepatic fibrogenesis by UDCA in a cholestatic-induced hepatic fibrosis rat model has been demonstrated [5]. Aforementioned

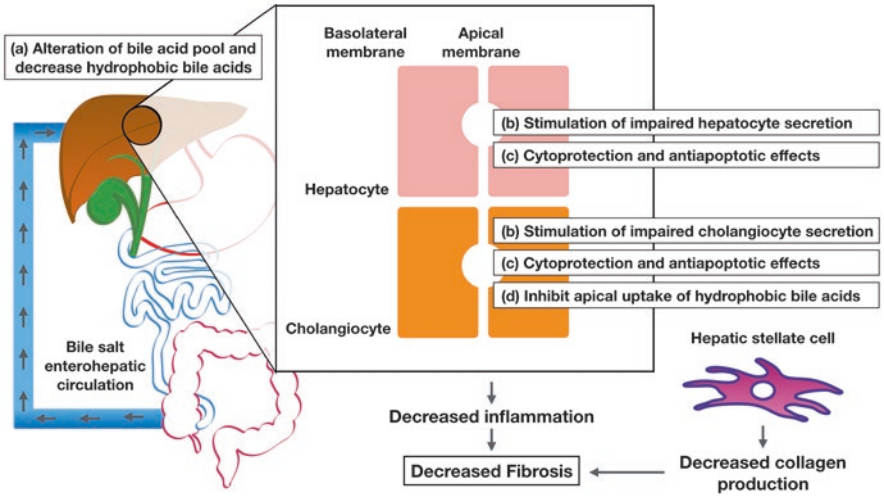

Fig. 5.1 Potential mechanisms of the action and anti-fibrosis effects of UDCA. (**a**) Alteration of the bile acid pool by replacing toxic, hydrophobic bile acids with non-toxic, more hydrophilic UDCA; (**b**) Stimulation of impaired hepatocyte and cholangiocyte secretion; (**c**) Cytoprotection and anti-apoptotic effects; (**d**) Inhibition of cholangiocyte apical uptake of hydrophobic bile acids. The mechanisms listed as A-D illustrate the anticholestatic effect of UDCA resulting in the decrease in hepatic inflammation and decrease in hepatic fibrosis in cholestatic liver disease. UDCA may also cause a decrease in the production of collagen by hepatic stellate cells, therefore, providing primary anti-fibrosis activity

multiple mechanisms involving the inhibitory pathogenic process of cholestatic liver disease and alleviation of cholangiocellular injury and inflammation by UDCA are considered to be responsible for its anti-fibrotic activity in cholestatic liver diseases. Data from an experimental study also shows that UDCA displays anti-fibrotic activity by decreasing collagen production by hepatic stellate cell (HSC) and cell survival [6]. Less severe liver fibrosis and lower hepatic expression of type I and type III collagens proteins were observed in a UDCA-treated rat model of liver fibrosis [7]. The mechanism underlying its direct anti-fibrotic activity is currently unclear, and data are scarce. The autophagy process was found to facilitate HSC activation, and inhibition of autophagy by UDCA has been proposed as demonstrated in a preclinical study [6]. This primary anti-fibrotic property of UDCA still needs to be confirmed, and further investigation is necessary. The potential mechanisms involved in the action of UDCA and the effects on liver fibrosis are summarized in Fig. 5.1.

5.3 The Effect of UDCA on Portal System Hemodynamics

UDCA affects systemic hemodynamics by decreasing diastolic blood pressure without significant alteration of splanchnic hemodynamics in healthy subjects [8]. A study using the nitric oxide (NO)-releasing derivatives of UDCA (NX-1000; 2

(acetyloxy) benzoic acid-3 (nitroxymethyl) phenyl ester) in patients with cirrhosis and portal hypertension also demonstrated changes in systolic blood pressure and hepatic blood flow without any reduction in portal pressure [9]. Therefore, based on current evidence, UDCA has no direct effect on portal hemodynamics.

5.4 The Effects of UDCA on Liver Fibrosis, Cirrhosis-Related Complications, and Cirrhosis Outcomes in Patients with Chronic Liver Diseases (Table 5.1)

5.4.1 Cholestatic Liver Diseases

5.4.1.1 Primary Biliary Cholangitis (PBC)

The use of UDCA showed remarkable beneficial effects on disease progression in patients with PBC. A dose-finding study showed that UDCA in a dosage of 13–15 mg/kg/day is the effective and preferred dose in patients with PBC [10]. UDCA therapy was found to significantly delay the progression of liver fibrosis and is associated with five-fold lower yearly fibrosis progression rate from early stage of the disease to extensive fibrosis or cirrhosis [11]. In earlier analysis, the effects on the development of portal hypertension complications were not demonstrated [12]. The likely explanation of this result might be because the disease progression is slow in PBC patients and the 2-year UDCA treatment used in clinical trials is probably not long enough to detect the difference from placebo. Reports of UDCA treatment with adequate duration of drug exposure showed that its use prevents the progression of portal hypertension in most patients receiving treatment [13]. Lower risk of the development of varices was observed in patients treated with UDCA for 4 years compared to placebo [14]. This is likely due to the improvement in liver architecture resulting in a decrease in portal venous outflow resistance in patients receiving UDCA. UDCA use is also associated with a reduction in the rate of liver transplantation or death in patients with PBC. The number needed to treat to prevent one liver transplantation or death within 5 years in patients with and without cirrhosis was 4 and 20, respectively [15].

It is estimated that 30–50% of patients receiving UDCA do not have a satisfactory response to the treatment. Multiple prognostic models have been proposed to evaluate the response [16, 17]. The Toronto criteria proposed by Kumagi et al. in 2010 demonstrated that histologic progression of fibrosis was associated with the lack of biochemical response after 2 years of treatment [18]. An alkaline phosphatase (ALP) of >1.67 × ULN (upper limit of normal) was associated with an increase in 1 stage of fibrosis progression at 2 years, and ALP of >1.76 × ULN was associated with an increase in 2 stage of fibrosis progression at 2 years [18]. The UDCA non-responders defined by other biochemical response criteria were related to significant development of liver cirrhosis and higher mortality than those who responded to treatment [19]. A recent study showed that UDCA use in PBC patients with compensated cirrhosis reduced clinical decompensation in patients who

Table 5.1 Summary of clinical evidences regarding the effects of UDCA use in liver fibrosis, cirrhosis-related complications, and cirrhosis outcomes in patients with chronic liver diseases

Liver diseases	UDCA doses	Effects	Results
Primary biliary cholangitis (UDCA responder)	13–15 mg/kg/day	Fibrosis/cirrhosis progression	Delayed
		Portal hypertension	Stabilized
		Development of varices	Reduced risk
		Liver transplantation and death	Reduced risk
Primary biliary cholangitis and compensated cirrhosis (UDCA responder)	13–14 mg/kg/day	Clinical decompensation	Reduced risk
Primary sclerosing cholangitis	13–15 mg/kg/day	Disease progression	No improvement
	17–23 mg/kg/day	Liver transplantation	No improvement
	28–30 mg/kg/day	Development of varices	Increased risk
Cystic fibrosis	10–20 mg/kg/day	Fibrosis improvement	Potential improvement in patients without cirrhosis
	20–25 mg/kg/day	Development of portal hypertension	No risk reduction
Cystic fibrosis and cirrhosis	10–20 mg/kg/day	Overall survival	No improvement
Progressive familial intrahepatic cholestasis (complete responder)	20–30 mg/kg/day	Fibrosis/cirrhosis improvement	Improved
Non-alcoholic steatohepatitis	13–15 mg/kg/day	Fibrosis improvement (histology)	No improvement
	23–28 mg/kg/day	Fibrosis improvement (histology)	No improvement
	28–35 mg/kg/day	Fibrosis improvement (serum fibrosis markers)	Improved
Autoimmune hepatitis	13–15 mg/kg/day	Fibrosis improvement	No improvement
Alcoholic cirrhosis (advanced disease with jaundice)	13–15 mg/kg/day	6-month survival	No improvement
Hepatitis C infection	600 mg/day	Fibrosis improvement	No improvement

responded to the treatment compared to those who showed partial response [20]. Therefore, in patients with PBC, UDCA exerts stabilization or delayed progression of fibrosis and reduction of cirrhosis-related complications in those who responded to treatment. The drug has therefore been described as safe and is recommended as the first-line therapy in patients with PBC. Patients treated with UDCA should be evaluated for biochemical response at 12 months after the initiation of treatment to

identify those who are non-responders and who might not benefit from UDCA, and the introduction of second-line therapy is necessary.

5.4.1.2 Primary Sclerosing Cholangitis (PSC)

Standard dose UDCA treatment in patients with PSC is associated with improvement of liver biochemistries without demonstrating any delay in disease progression [21]. Treatment with UDCA at 17–23 mg/kg/day provided no significant benefit with regard to death or transplantation [22]. Despite considered as being an extremely safe therapy, a higher dosage of 28–30 mg/kg/day of UDCA use in patients with PSC was related to higher rates of adverse events, including the development of varices, death, or becoming eligible for liver transplantation in a treated group in comparison to placebo [23]. This study was terminated after 6 years due to the futility of the outcomes. The possible explanation of this result might be due to the toxic bile acids being produced from unabsorbed UDCA. It has been shown in animal models that UDCA aggravates bile infarcts and hepatocyte necrosis in the case of biliary obstruction, which is found in patients with PSC [23]. To date, there is no recommended pharmacological treatment for patients with PSC and the clinical benefits of taking UDCA are limited. High dose UDCA use in this condition increases adverse effects and should not be used.

5.4.1.3 Cystic Fibrosis (CF)

Cholestasis in the case of this genetic disease is caused by defective secretion of cholangiocellular bicarbonate. Thick biliary secretions in CF patients lead to biliary obstruction. Two-year treatment with UDCA is associated with a trend toward less fibrosis compared to baseline prior to treatment initiation in patients with CF [24]. Improvement of liver stiffness in patients treated with UDCA is demonstrated only in patients initiated onto UDCA based on Colombo criteria without liver cirrhosis [25]. A longitudinal population-based cohort study including over 3000 CF patients showed that UDCA improved overall survival only in patients without cirrhosis, but not in those with cirrhosis [26]. However, another large cohort demonstrated conflicting result showing that earlier use of UDCA did not change the incidence of severe liver disease defined as cirrhosis or portal hypertension development [27]. Furthermore, a recent study demonstrated that CF patients followed up in UDCA prescribing centers (41% of patients receiving UDCA) did not show a lower incidence of portal hypertension as compared to those followed in centers not prescribing UDCA (2.5% of patients receiving UDCA) [28]. The role of UDCA in CF patients has been controversial as the outcomes from the studies are inconsistent. The effect of UDCA in reducing the risk of severe liver disease with portal hypertension was not established, and the potential prevention of the progression of fibrosis when administered early before apparent liver damage is controversial. The data from several studies implies that this drug might have limited effects on liver fibrosis, and survival outcomes in patients with CF and liver cirrhosis.

5.4.1.4 Progressive Familial Intrahepatic Cholestasis (PFIC)

Pediatric patients with PFIC treated with UDCA at a dose of 20–30 mg/kg/day had a 42–46% chance of complete response to treatment with normalization of transaminases, gamma glutamyl transferase (GGT), and direct bilirubin [29]. In patients who had a complete response, decreased liver fibrosis was observed in all 4 patients with baseline fibrosis or cirrhosis who underwent a paired liver biopsy [29]. After 4.5 years of UDCA administration, a patient with PFIC type 3, an inherited disease characterized by a multidrug resistance protein 3 (MDR3) deficiency, exhibited the reversal of advanced fibrosis from METAVIR fibrosis stage 4 to stage 1 [30]. The use of UDCA in patients with PFIC results in fibrosis regression in patients who respond to treatment.

5.4.2 Other Liver Diseases

5.4.2.1 Non-alcoholic Steatohepatitis (NASH)

One of the proposed mechanisms involved in the development of NASH involves inflammatory processes and the administration of non-toxic UDCA might provide cytoprotective effects. UDCA use in an animal model of NASH showed anti-apoptotic and mitochondrial protective effects and reduction of pro-inflammatory cytokines [31]. The effects of UDCA use in NASH patients were evaluated in several clinical trials. The use of 13–15 mg/kg/day of UDCA for 2 years was not associated with any improvement of liver fibrosis in patients with biopsy-proven NASH [32]. The use of a higher dosage of 23–28 mg/kg/day of UDCA for 18 months also demonstrated negative improvement of liver fibrosis evaluated by liver histology compared to placebo [33]. Meanwhile, another study evaluated the effect of 28–35 mg/kg/day of UDCA for 12 months on liver fibrosis. The outcome was assessed by the changes in the serum marker associated with fibrosis (Fibrotest®), and improvement was shown in the surrogate marker of fibrosis with an excellent safety profile [34]. Therefore, current evidence shows no significant benefit of the use of UDCA up to 28 mg/kg/day dosage on liver fibrosis in patients with NASH. It is important to note that NASH has a slow progression disease and inadequate duration of treatment in these studies might cause negative results. A higher dosage of UDCA may result in the improvement of fibrosis, but to date this outcome has not been confirmed by histology, the reference standard for the evaluation of fibrosis in patients with NASH. Further study is needed to confirm this finding.

5.4.2.2 Autoimmune Hepatitis (AIH)

A small case series in 1998 demonstrated improvement of liver biochemistries, reduction of immunoglobulin G and anti-nuclear antibodies titer in 8 patients with AIH type 1 after 2 years of treatment with UDCA [35]. In 4 patients with baseline bridging fibrosis who had follow-up liver biopsy, histological improvement was seen in all cases without any changes in liver fibrosis. A study in patients with a suboptimal response to prednisolone or a combination treatment of prednisolone

and azathioprine revealed unchanged liver fibrosis in patients treated with UDCA compared to placebo [36].

5.4.2.3 Cirrhosis Due to Alcohol-Related Liver Disease (ALD Cirrhosis)

UDCA use in patients with ALD cirrhosis and jaundice was evaluated in a randomized controlled trial, and no beneficial effect of UDCA on 6-month survival was observed [37]. Most of the participants in this study had advanced liver cirrhosis with a mean Child–Pugh score of 10, and approximately half of the patients in this study resumed their alcoholism, which might contribute to the poorer prognosis of patients in the study. Therefore, UDCA does not appear to provide any survival benefit in advanced alcoholic cirrhosis; however, the effects in patients with early cirrhosis and those abstaining from alcohol remained to be elucidated.

5.4.2.4 Viral Hepatitis C

UDCA use in combination with interferon therapy in patients with hepatitis C did not change the degree of portal fibrosis at the end of treatment compared to interferon monotherapy [38]. A study in hepatitis C cirrhosis patients showed a decrease in hepatic transaminases and GGT [39]. However, no data regarding the progression of liver fibrosis or long-term outcomes are available. These studies were all conducted prior to the era of direct acting antiviral agents treatment, which significantly improve liver-related outcomes. Therefore, the role of UDCA at present, especially in patients with fibrosis or cirrhosis after sustained virological response (SVR), should be further evaluated.

5.5 Conclusion

UDCA has multiple beneficial mechanisms for the treatment of cholestatic liver diseases. Reduction of hepatic inflammation may in turn decrease hepatic fibrogenesis. Few experimental studies suggest direct anti-fibrotic effects of UDCA, and further studies are required to expand current knowledge. UDCA has significant benefits in PBC patients who respond to treatment by delaying the progression of fibrosis, stabilizing portal pressure, decreasing the risk of the development of varices and liver decompensation. Induction of fibrosis regression was seen in patients with PFIC. In CF patients, data from observational studies suggested that UDCA does not prevent the development of portal hypertension. Based on current evidence, UDCA has no benefit in those with PSC, AIH, alcoholic cirrhosis, and hepatitis C infection. The result of using high dose UDCA in patients with NASH indicates the potential improvement of fibrosis, which needs to be confirmed in future studies. It is worth noting that the progression of fibrogenesis and cirrhosis is a slow process; therefore, adequate duration of UDCA treatment is important to evaluate the outcomes. The data regarding long-term effects of UDCA use in various liver diseases are lacking and more studies are warranted.

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