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Enteronephrohepatic circulation of bile acids and therapeutic potential of systemic bile acid transporter inhibitors

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Authors' contributions

AG, JGH, PAD: conceptualized and wrote the article, and prepared the figures. MM, GST, JG, EL, TL, S van der M, JRA, HS, SJK, PF, MT: contributed to the writing and critically revised the manuscript. MM: contributed to figure preparation. All authors approved the final version of the manuscript for submission.

Conflict of interest

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Summary

Together with carriers in the liver and small intestine, kidney transporters function to conserve and compartmentalise bile acids in the enteronephrohepatic circulation. In patients with liver disease, systemic bile acid levels are elevated, undergo increased renal glomerular filtration, and contribute to the pathogenesis of cholemic nephropathy and acute kidney injury. In this review, we describe mechanisms for renal bile acid transport and highlight very recent discoveries that challenge current paradigms on the pathogenesis of cholemic nephropathy and renal tubule cast formation. We also discuss the therapeutic potential of inhibiting the kidney apical sodium-dependent bile acid transporter to redirect bile acids into urine for elimination, reduce hepatobiliary accumulation and systemic levels of bile acids, and treat cholemic nephropathy. In conclusion, a deeper understanding of the enteronephrohepatic bile acid axis is providing insights into novel strategies to protect both the liver and kidney in patients with liver disease.

Keywords

Enterohepatic circulation; bile acid transporters; cholestasis; cholemic nephropathy; bile cast nephropathy; ASBT

Introduction

The enterohepatic circulation of bile acids and its interruption in cholestasis has been the subject of considerable study.[1–3] Comparatively less is known about kidney-liver (nephrohepatic) cycling of bile acids and its relationship to the progression of liver injury or damage to extrahepatic tissues such as the kidney in cholestasis. Under normal physiological conditions, systemic bile acid concentrations are low, which limits renal bile acid exposure. However, in cholestatic liver diseases, nephrohepatic cycling of bile acids becomes critical as bile acid concentrations rise in the systemic circulation and consequently the glomerular filtrate. This leads to two significant consequences. First, exposure to elevated concentrations of bile acids in the primary urine can lead to injury or death of bile acid-transporting epithelial cells in the proximal tubule. Second, persistent tubular bile acid reabsorption impedes renal clearance of bile acids and subverts effective shunting of

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cytotoxic bile acids from an already compromised cholestatic liver into urine for elimination. Intriguingly, both complications have the potential to be addressed by approaches that target the kidney apical sodium-dependent bile acid transporter (ASBT/*SLC10A2*; also called ileal bile acid transporter, IBAT), such as systemic ASBT inhibitors, which would block the renal reabsorption of bile acids and enhance their urinary excretion. For a thorough discussion of the underlying mechanisms, we first introduce the key transporters that mediate bile acid cycling and discuss the enterohepatic and nephrohepatic arms of bile acid circulation.

Enteronephrohepatic bile acid cycling and renal bile acid transport

The major transporters that function to maintain bile acid cycling have been identified[4,5] and are summarised in Fig. 1. The major bile acid transporters in humans are shown, with rodent models expressing a similar complement of transporters.[6] In the liver, absorbed bile acids delivered from the portal vein are taken up across the hepatocyte sinusoidal membrane by the Na^+-taurocholate cotransporting polypeptide (NTCP/*SLC10A1*) and members of the organic anion transporting polypeptide (OATP) family (OATP1B1/*SLCO1B1* and OATP1B3/*SLCO1B3* in humans) and exported across the canalicular membrane by the bile salt export pump (BSEP/*ABCB11*) into bile. Epithelial cells lining the biliary tract (cholangiocytes) and gallbladder epithelial cells express the ASBT and heteromeric organic solute transporter, OSTα/β (*SLC51A/SLC51B*), which may function to facilitate the absorption and cholehepatic or cholecystohepatic shunting of a small fraction of the taurine- and glycine-conjugated (amidated) bile acids in bile.[7–9] Bile acids ultimately pass from the liver into the small intestine and are taken up across the apical brush border membrane of ileal enterocytes by the ASBT and are exported across the basolateral membrane into the portal circulation by OSTα/β.[10–13] Under normal physiological conditions, a portion of the bile acids entering the small intestine escape absorption and their loss in the faeces is the major route for bile acid elimination.[14] In addition to the liver and intestine, the kidneys also actively reabsorb bile acids.[15] Indeed, our understanding of the kidney's role in bile acid excretion is steeped in Hepatology, arising in part from seminal research conducted in the Liver Unit established by Dame Sheila Sherlock at the Royal Free Hospital in London. There, Stephen Barnes, John Gollan, and colleagues working with Barbara Heap Billing studied renal tubule bile acid reabsorption, metabolism, and secretion in rat models and in patients with cholestasis.[16–18]

First pass hepatic extraction of bile acids from the portal circulation in healthy humans is efficient but varies depending on bile acid structure and conjugation, ranging from ~90% for cholic acid, to ~70–80% for chenodeoxycholic acid and deoxycholic acid, to ~50% for ursodeoxycholic acid.[19,20] Bile acids that escape first pass hepatic clearance spill over into the systemic circulation where they travel in protein-bound or free forms. Binding to plasma proteins (primarily albumin) varies for different bile acid species (ranging from ~45 to 98%)[21] with the unbound bile acid fraction being free to undergo glomerular filtration.[21] In healthy humans, it is estimated that the kidney filters approximately 100 μmoles of bile acids each day, but only 1 to 2 μmoles of bile acids are lost in urine since renal tubular reabsorption is highly efficient.[22] As such, under normal physiological conditions, renal excretion in urine plays only a very minor role in daily bile acid loss, while faecal elimination represents the major route.[23] However, in patients with cholestatic liver

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disease, hepatic bile acid clearance and canalicular secretion are reduced, and plasma bile acid levels are significantly elevated.[21,24] The increase in plasma bile acid levels includes conjugated bile acids and bile acid metabolites, such as polyhydroxylated, sulfated and glucuronidated species,[25] which are synthesised by hepatocytes and exported across the sinusoidal membrane as a critical part of the liver's adaptive response in cholestasis.[26] Hepatocyte expression of enzymes involved in bile acid detoxification pathways (*i.e.* hepatic phase I hydroxylation, and phase II sulfation and glucuronidation) is induced to render bile acids less cytotoxic, more hydrophilic, and more amenable to excretion. This adaptation in cholestatic liver disease includes increasing expression of CYP3A4, SULT2A1 and UGT (UDP-glucuronosyltransferase) isoforms and is mediated by the master regulators farnesoid X receptor (FXR), pregnane X receptor and constitutive androstane receptor,[26,27] with induction of UGT1A1, 1A3, 1A4 and 2B4 being mediated by peroxisome proliferator-activated receptor (PPAR).[28] Like the liver,[29] the kidney also possesses bile acid glucuronidation capacity[30] and may directly metabolise bile acids to promote their urinary excretion.

The 24-hour urinary excretion of non-sulfated/non-glucuronidated conjugated bile acids (*i.e.* bile acids that are amidated to taurine or glycine) remains significantly lower than the quantity estimated to undergo glomerular filtration.[31] In contrast, urinary clearance of bile acid metabolites (sulfated and glucuronidated bile acids) in patients with cholestasis can be 100-fold higher than for the unmodified bile acid species,[31,32] with the increase in urinary bile acid excretion overwhelming in the sulfated *vs.* non-sulfated bile acid fraction[33] (Fig. 2). This increased urinary excretion cannot be explained by reduced protein binding by sulfated and glucuronidated bile acids (and a resultant higher free circulating fraction).[34,35] Subsequent studies suggested that the urinary excretion of conjugated bile acids may be lower than that of their phase I and phase II metabolites because of their active reabsorption from the renal proximal tubules.[15,36] The renal proximal tubule epithelium expresses ASBT[37,38] and OSTα/β,[8] providing a circuit for uptake and transport of conjugated bile acids from the kidney tubule lumen back into the systemic circulation for reuptake by the liver. In contrast to amidated (taurine- and glycine-conjugated) bile acids, sulfated and glucuronidated bile acids are not efficiently transported by the ASBT.[38–40] Mechanistically, the observed renal bile acid flux and selective loss of sulfated and glucuronidated bile acids[17,18] partly reflects this preferential ASBT-mediated reabsorption of amidated *vs.* sulfated or glucuronidated bile acids from the lumen of renal proximal tubules.[8,37,38,41] Notably, ASBT expression is restricted to the proximal tubular epithelial cells (TECs) and absent from other cells in the nephron[42–45] (Fig. 2). In addition to tubular bile acid absorption, there is also evidence for direct tubular secretion of sulfated bile acids from blood into the lumen of the renal tubules.[18] Although the details of the mechanism(s) and their quantitative significance have not been fully elucidated, renal sulfated bile acid secretion potentially involves uptake from the blood by the major anion carrier OAT3/*SLC22A8* on TECs,[46–49] and export across the TEC apical membrane by ABC transporters such as MRP2 (*ABCC2*) and MRP4 (*ABCC4*) for elimination in the urine.[16,18,50] In addition to glucuronidation, there is also evidence that the kidney expresses bile acid sulfotransferase activity, raising the prospect that in addition to the liver, renal

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synthesis of bile acid sulfates in TECs may have a role in bile acid urinary excretion.[51] A model of our current understanding of renal bile acid transport is provided in Fig. 2.

Renal bile acid elimination in patients with cholestatic liver disease

In addition to increases in phase I and phase II enzymes, hepatocyte expression of sinusoidal membrane transporters, including MRP3 (*ABCC3*),[52] MRP4,[53] and OSTα/β,[54,55] is induced in response to a block in normal hepatocyte canalicular secretion, obstruction or damage to the biliary system, and cholestasis. This promotes efflux of bile acids and bile acid metabolites into the space of Disse, thereby reducing hepatocellular bile acid accretion and increasing levels of conjugated bile acids and bile acid metabolites in the systemic circulation[54,56,57] (Fig. 3). For many years, the accepted dogma has been that kidney ASBT expression or function is significantly reduced as an adaptive response to cholestatic conditions.[58] However, that dogma has been challenged by closer scrutiny of the evidence, as well as recent findings from animal models and patients with liver disease and cholemic nephropathy (CN). As mentioned above, the preferential urinary loss of bile acid metabolites *vs*. conjugated bile acids in patients with cholestasis does not reflect their relative abundance in plasma[31,59,60] and is consistent with ongoing ASBT-mediated tubular reabsorption of non-sulfated bile acids. In the kidneys of bile duct-ligated rats and mice, ASBT expression was found to be significantly decreased in some[50,58,61] but not all studies,[62,63] whereas renal OAT3 expression is induced.[64,65] Moreover, a recent longitudinal study in mice that underwent bile duct ligation (BDL) found only minor reductions in kidney ASBT expression and *in vivo* activity (as assessed by intravital microscopy),[66] and pharmacological inhibition of kidney ASBT in cholestatic rodent models significantly increases urinary excretion of non-sulfated bile acids.[66,67] Of translational importance, immunohistochemical analysis of kidney biopsies from humans revealed that kidney ASBT protein expression is preserved in patients with CN at both early and advanced stages.[66] Overall, the findings support the concept that ASBT expression is partially reduced in cholestasis, with possible interspecies differences. However, substantial ASBT function appears to be preserved, allowing persistent renal tubular reabsorption of bile acids and limiting the urinary elimination of non-sulfated conjugated bile acids. A model of our current understanding of the hepatorenal bile acid flux under cholestatic conditions is provided in Fig. 3.

Liver disease, acute kidney injury and cholemic nephropathy

Individuals with acute liver failure, alcohol-related hepatitis, as well as decompensated cirrhosis, in particular those with acute-on-chronic liver failure, are at high risk of developing acute kidney injury (AKI),[68–70] and renal failure in patients with advanced chronic liver disease is associated with poor outcomes and high hospitalisation costs[71] (Fig. 4). Although portal hypertension-related and splanchnic systemic haemodynamic alterations are thought to play a major role in the development of renal dysfunction associated with liver disease,[72] non-haemodynamic mechanisms of injury, such as CN, have also been implicated in its pathogenesis.[73] The umbrella term CN describes compromised renal function together with histological features, such as renal tubule epithelial cell injury and intratubular cast formation,[74] and is thought to be a cause of AKI in cholestasis.[74–77] Indeed,

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the presence of intrarenal “bile casts” may be a more common pathological finding in patients with liver disease than is generally appreciated.[74,78] Clinically, AKI in patients with liver disease is currently defined and detected by indicators of kidney dysfunction (*i.e.* primarily increased serum creatinine), although there is increasing recognition that damage detected by biomarkers may precede the development of dysfunction. Prerenal AKI is exclusively functional and not accompanied by relevant damage (*i.e.* tubular injury), and it does not overlap with CN. Thus, damage markers such as urinary neutrophil gelatinase-associated lipocalin (NGAL) are usually low and this condition is highly reversible upon volume resuscitation. Hepatorenal syndrome-AKI (HRS-AKI) is primarily a consequence of vasodilatation and may respond to treatment with vasoconstrictors plus albumin. However, biomarkers may indicate limited tubular injury in a subset of HRS-AKI. Importantly, a considerable rate of non-response is observed, accompanied by extremely high short-term mortality. High bilirubin, as a surrogate of cholestasis, and high NGAL, as a biomarker of tubular damage, are major risk factors for non-response. These findings suggest that CN could play a role in HRS-AKI. Finally, acute tubular necrosis (ATN) is the most severe form of kidney damage and is characterised by elevated levels of kidney injury molecule-1 (KIM-1) and NGAL, resembling observations in rodents shortly after BDL.[66] As suggested by published series of deeply jaundiced patients with kidney dysfunction or histological proof of CN, patients with ATN may be the main population in which CN is encountered in the clinic. While obstructive jaundice/mechanical cholestasis (*i.e.* the human equivalent of BDL) can usually be relieved by endoscopic or surgical interventions, this is not the case for patients with severe alcohol-related hepatitis and/or acute-on-chronic liver failure or ductopenic liver diseases who may present with HRS-AKI/ATN and in whom kidney dysfunction remains a key driver of mortality.

The frequency of CN is currently underestimated. After review of the literature to seek insights into the incidence/prevalence of CN, the following important limitations of the available evidence were identified: (i) the diagnosis of CN may require a considerable level of suspicion, since microscopic examination of urine sediment for bile casts is not systematically performed in clinical practice at many centres, and diagnosis of CN may be restricted to patients showing evidence of renal dysfunction, thereby missing patients with kidney damage without overt dysfunction. Without attempts to raise awareness of CN, urine analysis may be even less commonly performed in the future. For instance, while patients with ascites and (renal) dysfunction (*i.e.* AKI) have a predisposition to CN, the ADQI (Acute Disease Quality Initiative) and ICA (International Club of Ascites) joint multidisciplinary consensus meeting recently proposed a positive definition of hepatorenal syndrome,[70] thereby potentially decreasing utilisation of urine analysis to rule out alternative causes such as CN. (ii) There is no generally accepted definition of CN in humans. It is unclear whether (renal) dysfunction is a *sine qua non* for diagnosing CN, or whether renal dysfunction should rather serve as a delineator between a subclinical (kidney damage without dysfunction) and a clinically evident form, which would be more in line with the current understanding of AKI in general. Although there are numerous reports on renal dysfunction due to CN in the literature,[79] large series are much rarer than for other aetiologies of (renal) dysfunction in patients with liver/biliary disease. However, evidence of tubular damage (*i.e.* high KIM-1) is nearly ubiquitous in patients with advanced liver

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disease and a serum bilirubin level ≥6 mg/dl, even in the absence of (renal) dysfunction.[66] This suggests that CN is underdiagnosed/underreported but also indicates that its incidence/prevalence critically depends on the definition applied (*i.e.* whether it includes subclinical CN). (iii) Although the systematic assessment of biomarkers of tubular damage and microscopic examination of urine sediment for bile casts would be desirable to gain insights into the incidence/prevalence of CN, some authors demand a kidney biopsy to establish the diagnosis of CN.[2] However, kidney biopsies do not seem to be justified and may be contraindicated in several clinical contexts in which CN may occur, due to a high procedural bleeding risk. However, when biopsies are performed *postmortem*, histological evidence of CN is found in the majority of individuals who had acute-on-chronic liver failure and stage 3 AKI,[80] further strengthening the previous point that any estimate of the incidence/prevalence of CN is likely profoundly impacted by underdiagnosis/underreporting. Thus, firm conclusions on the overall incidence/prevalence of CN cannot be drawn from the current evidence, and this applies even more to comparisons thereof in the specific clinical contexts in which CN may occur.

Although the recognition of CN as a clinical entity is experiencing a resurgence, the concept of a causal relationship between liver-derived metabolites “cholephiles” and CN or AKI has been controversial.[81,82] In addition to bile acids, plasma bilirubin concentrations are elevated in patients with cholestasis and cirrhosis,[78] and bile pigment staining is a classical feature of renal casts in CN.[73] Moreover, the relative contribution of bile acids, bilirubin or other liver-derived cholephiles *vs.* other mechanisms in the pathogenesis of kidney injury is difficult to decipher and may show profound interindividual variability.[73,83] In particular, gut-derived pathogen-associated molecular patterns and damage-associated molecular patterns are important drivers of systemic inflammation in liver disease, which may lead to kidney injury both via direct (*e.g.* via TEC damage[84]) and indirect (*e.g.* arterial vasodilation in patients with ascites) mechanisms.[85] However, recent findings (as described below) support a prominent role for bile acids in the pathogenesis of CN and suggest that ASBT inhibition could play a role in preventing/treating kidney dysfunction in these conditions for which there is a high unmet medical need.

Evolving concepts on the pathogenesis of cholemic nephropathy and acute kidney injury

To study the pathological mechanisms of CN, mice subjected to BDL have been used as a model system, because the kidney is particularly susceptible to the high systemic bile acid concentrations caused by ligation of the common bile duct and develops several features seen in patients with CN.[74,86] An earlier landmark study demonstrated renal tubular epithelial injury as early as 3 days after BDL[86] and suggested that renal-excreted bile acids play an important pathophysiological role.[76,86] Those studies gave rise to a model where elevated levels of bile acids acting at the distal collecting ducts damage the epithelial cell barrier and increase leakage of urine into the surrounding kidney parenchyma. This event is followed by cast formation, collecting duct obstruction and ultimately progressive tubular dilatation, tubulointerstitial nephritis and fibrosis.[74,86] Importantly, the model suggested that

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diverting more bile acids from blood into the lumen of renal distal tubules and collecting ducts would be expected to promote CN and kidney injury.

Recently, the temporal and spatial order of events for BDL-induced CN in mice was re-examined using new higher resolution techniques, including functional intravital 2-photon microscopy imaging, which provided important new mechanistic insights. Using these approaches, the study yielded evidence supporting the following temporal sequence of events in CN development[66] (Fig. 5). (1) Systemic bile acid levels increase due to cholestatic liver disease, leading to elevated bile acid concentrations in the glomerular filtrate and lumen of the renal tubules; (2) bile acids accumulate in proximal TECs due to persistent ASBT activity, leading to (3) oxidative stress, cell death, and release of cell debris from a subset of proximal TECs. (4) The released cell debris floats downstream in the tubule lumen, becomes concentrated as water is absorbed in the distal collecting tubules, and forms casts (obstructions) that cause tubule dilatation upstream of the obstruction. (5) Concurrently, surviving proximal TECs continue transporting bile acids from the tubule lumen into the interstitium. (6) This increases bile acid concentrations in the interstitial space and may act to compromise peritubular capillary endothelial cell barrier function and increase the leakiness of those vessels. (7) Progressive kidney fibrosis is triggered by the cell death events of proximal TECs, increased tubule pressure, and leakage of blood and primary urine into the interstitium. (8) A late event in the progression of CN is the formation of glomerular cysts. These glomeruli maintain their blood supply by afferent and efferent arterioles but are connected to obstructed and leaky tubules, thereby releasing primary urine into the interstitium.

Intravital microscopy enabled direct visualisation of the release of cell debris into the tubule lumen and helped to resolve the conundrum of how early cell death events in bile acid-transporting proximal TECs could lead to formation of tubular casts, which are found primarily in distal nephron segments.[74] These early events are followed by histological evidence of endothelial cell damage and functional changes in peritubular renal capillaries, as demonstrated by strong leakage of Evans blue dye from capillaries into the interstitium at 3 weeks after BDL.[66] In advanced stages after BDL, glomerular cysts – evident as dilatation of Bowman's space[66] – may represent a response to tubular constriction due to progressive fibrosis or complete tubule obstruction by casts, occurring while glomerular filtration remains active. The spatial and temporal order for the proposed sequence of events for BDL-induced CN were also supported by observed changes in the kidney injury markers KIM-1 (a proximal tubular epithelial cell death marker), NGAL (a proximal and distal tubular epithelial cell death marker) and cystatin C (a biomarker of glomerular filtration rate).[66]

The findings described above suggested that enrichment of bile acids in proximal TECs is an early initiating event that precedes later features of CN. Strong evidence supporting this hypothesis comes from preclinical experiments with a systemically bioavailable ASBT inhibitor AS0369.[66] In mice after BDL, AS0369 significantly increased urinary excretion of bile acids. Administration of AS0369 almost completely blocked bile acid enrichment, oxidative stress and cell death events in proximal TECs and strongly ameliorated all hallmarks (dilated tubules, glomerular cysts, tubular casts, capillary damage, and fibrosis)

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of CN (Fig. 6). This ASBT inhibitor-associated protection was also evident after BDL in *Cyp2c70* knockout mice, a mouse model with a humanised and hydrophobic bile acid composition.[66] Of particular importance, blocking ASBT in the proximal TECs dissociated the effects of increasing urinary elimination of conjugated bile acids from the development of CN and suggested that cells in the distal nephron, which lack bile acid transporters, are relatively resistant to conjugated bile acid-induced injury.

Pressing questions regarding the pathological mechanisms of CN

1. A major question that remains to be answered is whether bile acids or other cholestatic liver-derived molecules act as the primary causative factor of CN. In a 6-week study in BDL mice, total bile acid concentrations in blood were reduced by a factor of approximately 10 with two daily oral doses of 60 mg/kg AS0369.[66] However, bilirubin concentrations were simultaneously reduced by a factor of approximately two, and it remains to be determined if systemic inflammatory cytokines and other cholephiles were also reduced by the systemic ASBT inhibitor. Therefore, further studies that increase only bile acids or only bilirubin and consider the possible role of additional cholephiles are required to finally clarify the long-standing question of causality.

Regarding the relationship between bilirubin levels and CN or AKI, Dubin-Johnson syndrome and Rotor syndrome are rare inherited defects in bilirubin transport that present with a conjugated (direct) hyperbilirubinemia or mixed unconjugated (indirect)/conjugated hyperbilirubinemia, respectively. Despite significantly elevated circulating bilirubin levels, subjects with Dubin-Johnson syndrome or Rotor syndrome are generally asymptomatic, and CN or renal injury has not been associated with either disorder.[87,88] Regarding elevated bile acid levels and CN, cases of hypercholanemia (elevated serum bile acids) due to NTCP mutations have been described in individuals without any known kidney phenotype.[89] In the original index case, the NTCP-deficient patient exhibited extreme hypercholanemia and total bile acid levels as high as 1,500 μM. Clinically, this patient exhibited mild hypotonia, growth retardation and delayed motor milestones, but nephropathy was not reported.[89] Later reports of more individuals with NTCP deficiency did not mention any kidney phenotype.[90–92] Another relevant observation to be considered when discussing the pathological mechanisms of CN is that nephrotoxic effects have not been reported in patients receiving the NTCP inhibitor bulevirtide. Mean serum C_{max} of total bile acids was 178 μM after the first bulevirtide dose and 209 μM at steady state when 10 mg of bulevirtide was administered subcutaneously for six consecutive days together with tenofovir.[93] A general limitation of these studies of individuals with hyperbilirubinemia or hypercholanemia is that systematic screening for kidney damage, including measurements of early injury biomarkers, *e.g.* KIM-1, is lacking. As such, future studies that include measurements of biomarkers will be required to determine whether increased bile acids alone (acting as a proximal tubule nephrotoxin) are sufficient to cause kidney tubule injury and CN, or whether additional factors, such as other cholephiles (*e.g.* bilirubin), damage-associated molecular patterns, or inflammatory cytokines released from inflamed liver tissue are also required.

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2. Another question is what mechanisms are responsible for the renal endothelial cell damage. A possible mechanism is that the previously described enhanced export of bile acids by MRP3 and OSTα/β on the basolateral side of proximal TECs increases extracellular bile acid concentrations near endothelial cells lining the peritubular capillaries. This hypothesis is supported by the observation that both MRP3 and OSTα/β are upregulated in the kidneys after BDL.[66] Although this mechanism may appear plausible, it has not yet been formally proven, which could be achieved, for example by inhibition or knockout of the basolateral export carriers MRP3 and OSTα/β.

3. An open question is whether the mechanisms observed in mice are relevant to humans. Analysis of kidney biopsies from patients without CN demonstrated that ASBT is expressed on the luminal side of proximal TECs, as observed in mice.[66] Moreover, ASBT expression is preserved in patients with early as well as later stage CN, suggesting that the proximal TECs lack the ability to protect themselves from bile acid overload by downregulation of the responsible uptake carrier. This contrasts with hepatocytes, where downregulation of NTCP represents a well-documented adaptive mechanism to cholestasis.[94–96] Moreover, serum analysis of patients with acute and chronic cholestatic liver disease showed that total bile acid concentration was an explanatory variable in a multiple linear regression model with the proximal TEC injury marker KIM-1 as the dependent variable, although confirmatory studies with higher numbers of patients are still required.[66]

Different transport efficacy of ASBT on biliary and gallbladder epithelial cells and renal tubular epithelial cells

Uncertainties remain concerning ASBT's role in cholangiocytes and the function of cholehepatic or cholecystohepatic bile acid shunting in health and disease.[7,9] Expression of ASBT and OSTα/β on the cholangiocyte apical and basolateral membranes, respectively, provides a conduit to transport conjugated bile acids from the bile duct lumen into the interstitial space from where they enter the peribiliary plexus of bile ducts and pass into portal vein radicles in the portal tract.[97,98] However, the quantitative contribution of ASBT to this cholehepatic shunt remains to be elucidated, as indicated by the question marks in Figs 1 and 3. Under pathological conditions, namely cystic duct ligation in mouse models of cystic fibrosis (*Cftr*$^{-/-}$), shunting from the gallbladder to portal vein blood has also been reported.[9,99] This was studied by injecting a fluorescent bile acid into the gallbladder and analysing its appearance within bile canaliculi within 20 min. However, it should be noted that total bile acid concentrations in the gallbladder bile in healthy mice are ~100–130 mM[66] compared to only ~70 μM in the portal vein and <2 μM in the systemic circulation.[95] Therefore, under normal conditions, cholangiocytes and gallbladder epithelial cells form an efficient barrier with little evidence of ASBT-mediated transport of significant quantities of bile acids from the biliary tract or gallbladder into the blood. This framework is very different from that in hepatocytes, where NTCP facilitates the efficient uptake of bile acids from sinusoidal blood, enabling their subsequent secretion across the bile canaliculi. It is

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also different from that in ileal enterocytes or renal proximal tubule cells, where ASBT functions in the quantitative reclamation of bile acids. Nevertheless, evidence in favour of an ASBT-mediated cholehepatic shunt comes from experiments with a systemic ASBT inhibitor after BDL.[66] After BDL, under conditions where the ligation was performed downstream of the gallbladder without cholecystectomy to allow for analysis of gallbladder bile, total bile acids in the gallbladder increased from ~3 mM in untreated mice to ~22 mM after 6 weeks of administration of a systemic ASBT inhibitor[66] (in the chronic phase after BDL, concentrations of bile acids in gallbladder bile are much lower than in healthy mice). In urine, total bile acids increased from <0.1 mM in untreated bile duct ligated mice to >5 mM after ASBT inhibitor treatment. Considering that bile excretion is blocked due to ligation, while urine continues to flow, this scenario demonstrates that ASBT on cholangiocytes or gallbladder epithelial cells shunts only a very small fraction of luminal bile acids, while ASBT on renal proximal TECs seems to efficiently transport bile acids. Possible explanations for ASBT's low transport efficiency/capacity in bile duct/gallbladder epithelial cells *vs.* renal proximal TECs may be that i) bile acids are packed into micelles in bile (but not in urine) and are thus less accessible and/or ii) post-translational modifications reduce ASBT transport activity.[97,98,100,101] However, direct experimental proof of these hypotheses is not yet available.

ASBT as a potential therapeutic target for liver disease-associated acute kidney injury

Inhibition of ileal bile acid reabsorption by intestine-restricted ASBT inhibitors represents a well-established therapeutic principle that has been reviewed previously.[102–105] Intestine-restricted ASBT inhibitors interrupt enterohepatic cycling of bile acids, thereby increasing faecal excretion and reducing systemic pools. Approved intestine-restricted ASBT inhibitors include maralixibat and odevixibat, which have been shown to ameliorate cholestatic pruritus in Alagille syndrome and PFIC (progressive familial intrahepatic cholestasis).[103,106] In contrast to intestine-restricted compounds, systemic ASBT inhibitors that are absorbed into the systemic circulation have not yet been approved, but a successful phase I study has recently been completed with A3907, also known as ritivixibat[67] (ISRCTN17748514). Based on our current understanding of the pathological mechanisms of CN, systemic ASBT inhibitors may be effective, because they act via two independent mechanisms. The primary effect is ***target cell protection*** by inhibition of ASBT-driven bile acid enrichment in proximal TECs, a key early event in CN (Fig. 6). It should be considered that ASBT is the only transporter that mediates this effect in proximal TECs, which represents a favourable situation for a pharmacologic intervention. A secondary favourable effect of systemic ASBT inhibition in CN is the ***reduction of the systemic bile acid load***. In mice with cholestasis, systemic ASBT inhibition causes a strong increase in urinary bile acid excretion.[66] Moreover, it can be expected that – similar to intestine-restricted ASBT inhibitors – orally administered systemic ASBT inhibitors will block ileal reabsorption of bile acids.[107]

CN occurs as a severe complication in patients with end-stage liver disease, acute liver failure or alcohol-related hepatitis. It presents as AKI that is caused by haemodynamic and

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inflammatory mechanisms.[70,108–110] The efficacy of the vasoconstrictor terlipressin (plus albumin) for the treatment of HRS-AKI has been demonstrated in numerous studies.[111–115] However, only 64–76% of patients show a response (complete or partial), while a complete response is seen in only 46–56%.[109] The relatively high fraction of terlipressin non-responders suggests that besides haemodynamic factors, infection or inflammation, the above-described bile acid-mediated CN is an independent disease-driving factor or part of the clinical spectrum of HRS-AKI.[73,85,116,117] Histological features of CN – besides tubular cell injury – are Hall's stain-positive bilirubin casts.[74] Kidney autopsy studies of patients with acute-on-chronic liver failure and AKI, as well as those with decompensated cirrhosis, showed histologically proven CN with Hall's stain-positive bilirubin casts in 25–75% of all samples, demonstrating that the frequency of a bile acid-mediated contribution to HRS-AKI may currently be underestimated.[118] Terlipressin non-responders with HRS-AKI and high serum bile acid levels represent a potential target population for future clinical studies evaluating the potential of systemic ASBT inhibitors to ameliorate CN.

Therapeutic significance outside the kidney box

Reducing the hepatic bile acid burden in patients with cholestasis is one of the postulated mechanisms of action for FXR agonists,[119] PPAR agonists,[120–122] the gut-restricted ASBT/IBAT inhibitors,[123–125] and NTCP inhibitors in clinical development.[126] Systemic ASBT inhibitors represent an approach to specifically prevent or ameliorate CN. Moreover, systemic ASBT inhibition reduces the total bile acid burden by increasing urinary bile acid excretion, thereby reducing the exposure of tissues whose functions are compromised by increased levels of bile acids[17,18] (Fig. 7). It is not our intention to give a complete account of all secondary diseases of cholestasis, but we would like to discuss the potential indications of systemic ASBT inhibitors for some examples. Thus far, CN appears as a unique scenario, since the target cells of this disease, proximal TECs, actively enrich bile acids via ASBT and the resulting cell death events and all consequences can be prevented by ASBT inhibitors, thus representing an ideal situation for target protection (category 1, Fig. 7). The high efficacy of systemic ASBT inhibitors in CN in preclinical mouse models is because the enrichment of bile acids in proximal TECs can be blocked almost completely.[66]

A different scenario can be expected for bile acid-mediated complications, where the bile acids are believed to act via cell surface receptors or enter the target cells through passive diffusion (category 2, Fig. 7). An example is the anorexigenic effect of bile acids that reach the hypothalamus[127,128] and activate TGR5 (Takeda G protein coupled receptor), leading to reduced food intake[128] and activation of the sympathetic nervous system.[129] In an early landmark study, bile acids administered to mice were shown to increase energy expenditure in brown adipose tissue, probably via type 2 iodothyronine deiodinase and TGR5.[130] Conjugated bile acids regulate steroidogenic factor 1 in adrenocortical cells[131] and increase steroidogenesis in cholemic mice,[132] while patients with cholestasis show hypercortisolism.[133] Other cholestatic complications where bile acids probably reach their target cells by diffusion are cardiomyopathy,[134–138] sarcopenia,[139] and cognitive dysfunction.[140] Systemic ASBT inhibition may also be useful for the treatment of these complications, by decreasing bile acid concentrations in the blood and consequently in the target tissues. However, the threshold bile acid concentration in blood needed to avoid

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complications in the individual tissues listed as category 2 remains to be investigated (Fig. 7). It should be considered that twice daily administration of the systemic ASBT inhibitor AS0369 to mice (60 mg/kg b.w.; gavage) reduced total bile acids from ~2,000 μM to ~200 μM over a 6-week period, which represents an effect of remarkable size.[66] Nevertheless, the resulting total bile acid concentration of ~200 μM is still clearly above normal concentrations that range below 3 μM in mice. Higher or more frequent doses of AS0369 are unlikely to further reduce blood bile acids. Similarly, a further systemic ASBT inhibitor, A3907, was effective at reducing serum bile acids in mice after BDL at doses up to 30 mg/kg (50), but serum bile acid levels were still far above normal. In fact, even ASBT knockout mice had elevated serum bile acids after BDL, though they were significantly lower than in wild-type mice after BDL.[141] This limitation may be due to low bile acid concentrations in the intestine and induction of hepatic bile acid synthesis, with newly synthesised bile acids being secreted via the upregulated hepatocellular basolateral export transporters MRP3, MRP4, and OSTα/β into the sinusoidal blood[96] (Fig. 3). In this case, an option in the future may be to combine systemic ASBT blockers with inhibitors of bile acid synthesis, for example synthetic FXR agonists, although possible adverse effects due to increased choleresis in cases with obstructions of the biliary tract should be carefully studied.[142–144] It should be considered that reducing systemic bile acid levels represents only one of the therapeutic mechanisms of FXR agonists. For example, FXR has also been demonstrated to protect kidney and liver tissue via its anti-inflammatory and antifibrotic effects.[145,146] Moreover, PPAR agonists may help to further reduce bile acids.[147] A promising possibility for future studies may be the combination of norucholic acid (NCA; formerly referred to as norUDCA) with ASBT inhibitors, since the effects of NCA may be ASBT independent,[148] enabling targeting of both liver and kidney injury in cholestasis.[76] It will be important to determine the threshold concentrations of bile acids at which complications in the aforementioned tissues can be avoided, as will determining whether these thresholds can be reached with ASBT inhibitors and/or other therapeutic strategies. Besides bile acid pool size, bile acid pool composition may be of critical importance. The above discussed complications of cholestasis should be differentiated from those that are due to malabsorption, such as compromised mineral density of bones or compromised growth (category 3, Fig. 7). The latter are caused by a lack of intestinal bile acids due to obstructions of the biliary tract and are of course not candidates for therapy with systemic ASBT inhibitors.

Conclusions and future directions

Systemic ASBT inhibitors represent a new approach to avoid bile acid overloading of proximal TECs in cholestasis, thereby preventing or ameliorating CN. Moreover, these agents decrease the systemic bile acid burden by increasing urinary bile acid excretion, which protects all tissues that are susceptible to increased bile acid exposure, including the cholestatic liver. An important step in the future will be a proof-of-concept phase II study, since all indications from preclinical studies suggest that the mechanisms originally discovered in mice are likely applicable to humans. The most promising applications will be (i) CN with the goal of preventing or ameliorating AKI; and (ii) obstructive cholestasis with the primary goal of reducing bile acid concentrations in the systemic circulation.

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Supplementary Material

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Abbreviations

AKI	acute kidney injury
ASBT	apical sodium-dependent bile acid transporter
ATN	acute tubular necrosis
BDL	bile duct ligation
BSEP	bile salt export pump
CN	cholemic nephropathy
FXR	farnesoid X receptor
HRS-AKI	hepatorenal syndrome-acute kidney injury
KIM-1	kidney injury molecule
MRP	multidrug resistance protein
NGAL	neutrophil gelatinase-associated lipocalin
NTCP	sodium-taurocholate cotransporting polypeptide
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OSTα/β	organic solute transporter α/β
PAMPs	pathogen-associated molecular patterns
PPAR	peroxisome proliferator-activated receptor
TECs	tubular epithelial cells
UGT	UDP-glucuronosyltransferase

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Keypoints

- Transporters in the small intestine, kidney and liver function to conserve and recycle bile acids within the enteronephrohepatic circulation.
- Urinary bile acid excretion is increased in cholestasis, but the quantity of bile acids that are excreted is substantially lower than the quantity estimated to undergo renal glomerular filtration.
- Kidney exposure to liver-derived molecules such as bile acids contributes to the development of cholemic nephropathy and acute kidney injury.
- Expression of the renal apical sodium-dependent bile acid transporter (ASBT) is preserved in cholestatic liver diseases.
- Inhibition of the renal ASBT in cholestasis enhances the urinary excretion of bile acids and thereby reduces the hepatobiliary accumulation and systemic levels of bile acids.
- Inhibition of the renal ASBT represents a specific therapeutic target for cholemic nephropathy and may also protect all tissues whose functions are compromised by increased levels of bile acids.

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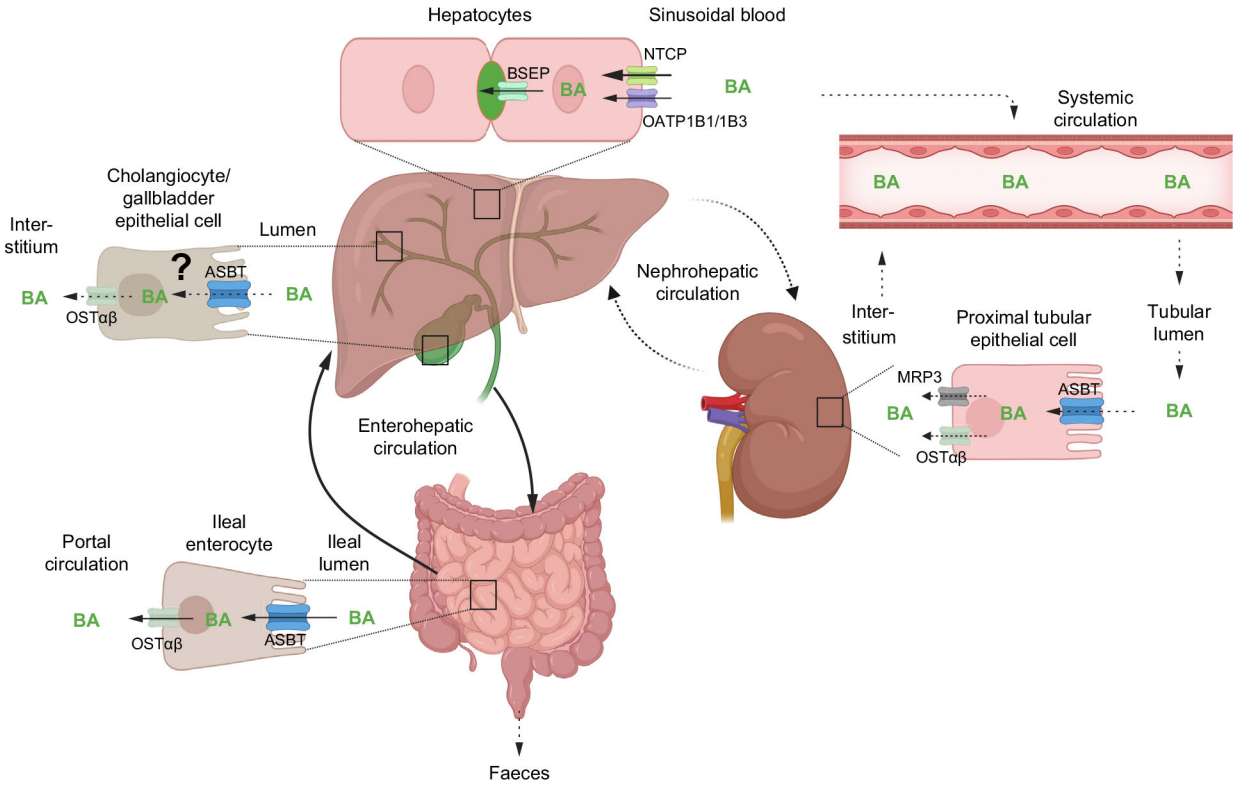


Fig. 1. Model for the enteronephrohepatic circulation of BAs in health.

BAs are secreted in an ATP-dependent fashion by BSEP into the canalicular space, travel down the biliary tract, enter the gallbladder and eventually empty into the small intestine. Most conjugated BAs are then reclaimed by ASBT on the ileal enterocyte, transported across the basolateral membrane by the heteromeric transporter OSTα/β and carried back in the portal circulation to the sinusoidal membrane of the hepatocyte, where they are taken up by NTCP and members of the OATP family. BAs that escape hepatic first pass clearance spill over into the systemic circulation. Free BAs can undergo glomerular filtrations and are reabsorbed in the proximal tubules by the combination of ASBT and OSTα/β and sent back to the liver for uptake and re-secretion into bile. ASBT and OSTα/β are also expressed by cholangiocytes and gallbladder epithelial cells, where they may participate in cholehepatic or cholecystohepatic shunting of conjugated BAs. The model displays the major BA transporters in humans. ASBT, apical sodium-dependent bile acid transporter; BAs, bile acids; OSTα/β, organic solute transporter α/β. Created in https://BioRender.com

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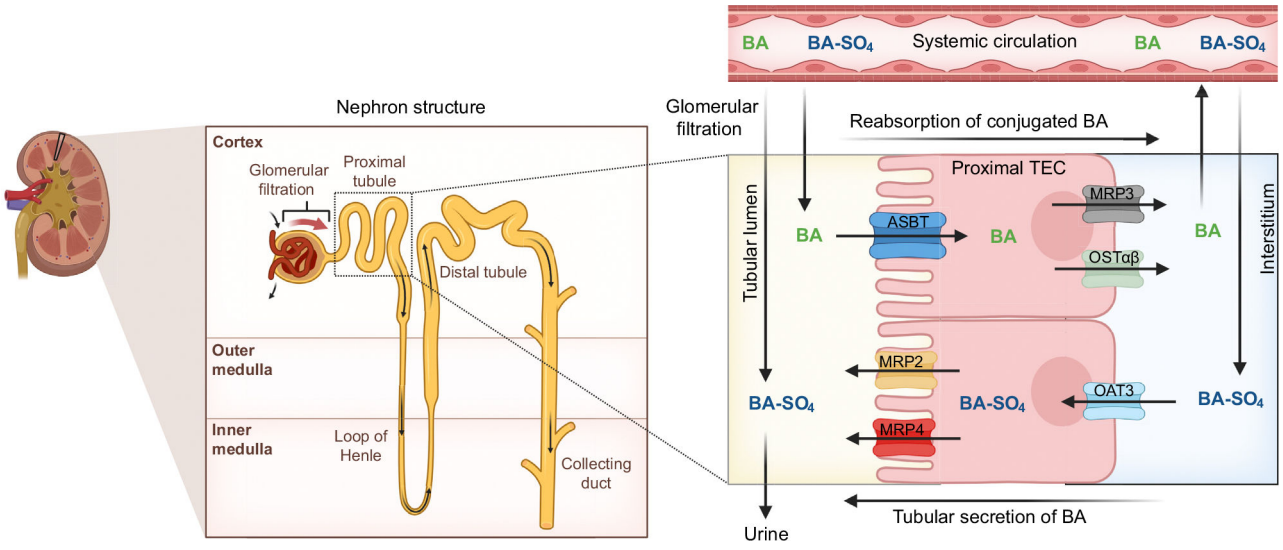


Fig. 2. BA transport in the kidney.

The unbound BAs in blood undergo glomerular filtration and enter the lumen of the renal tubules. The conjugated BAs are efficiently reabsorbed from tubule lumen by ASBT on the apical brush border membrane of the proximal tubules and transported by OSTα/β or potentially MRP3 (*ABCC3*) across the basolateral membrane back into the systemic circulation. In addition to their glomerular filtration, sulfated BAs may undergo direct tubular secretion from blood into the tubule lumen in a mechanism involving basolateral membrane uptake by OAT3 and apical secretion via MRP2 (*ABCC2*) or MRP4 (*ABCC4*), whereas sulfated BAs are not transported via ASBT. The model illustrated is applicable to humans and rodents. ASBT, apical sodium-dependent bile acid transporter; BAs, bile acids; BA-SO_4, sulfated bile acids; MRP, multidrug resistance protein; OAT, organic anion transporter; OSTα/β, organic solute transporter α/β. Created in https://BioRender.com.

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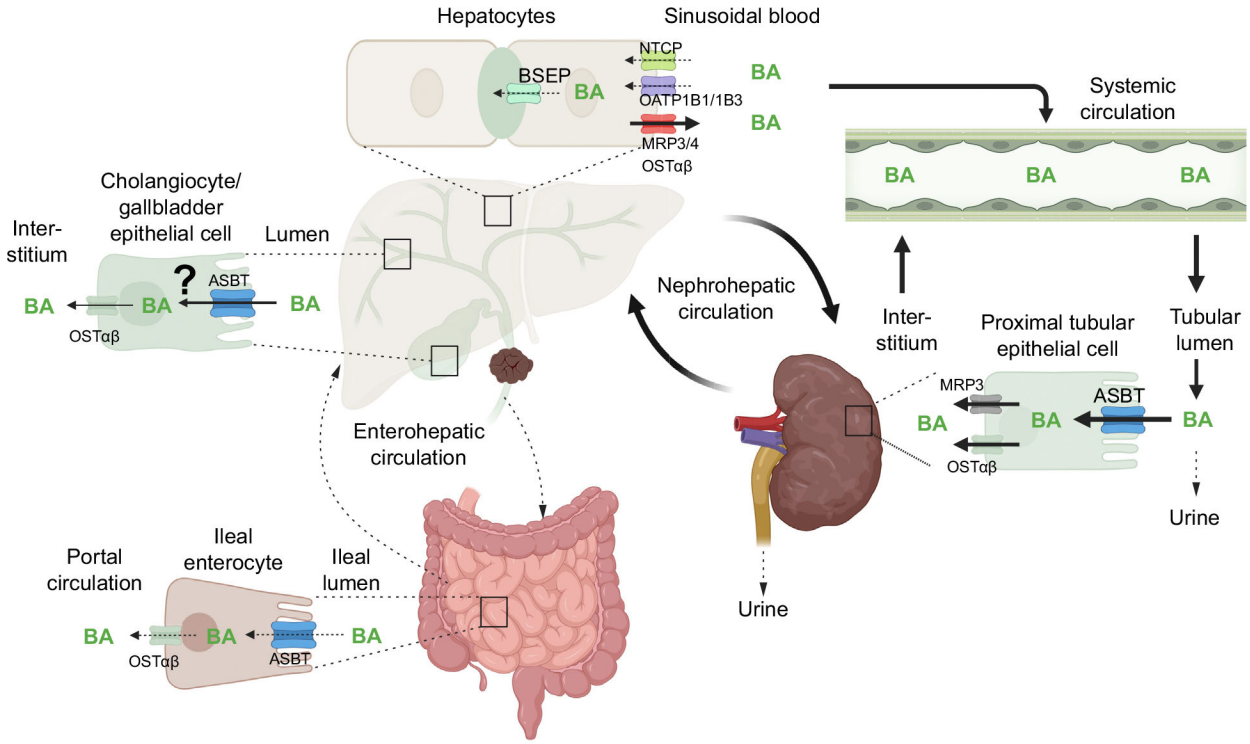


Fig. 3. Model for the enteronephrohepatic circulation of BAs in disease.

Changes in the enteronephrohepatic circulation in cholestasis. As part of the adaptive response to cholestasis, hepatocyte BA uptake via NTCP decreases and BA export via MRP3, MRP4 and OSTα/β increases, thereby elevating BA concentrations in the systemic circulation. In the kidney, BA levels are increased in the renal filtrate and primary urine, with a resultant increased transcellular transport of BAs across the proximal tubule cell via ASBT and OSTα/β and other carriers such as MRP3. The model illustrated is applicable to humans and rodents. ASBT, apical sodium-dependent bile acid transporter; BAs, bile acids; MRP, multidrug resistance protein; NTCP, Na^+-taurocholate cotransporting polypeptide; OSTα/β, organic solute transporter α/β. Created in https://BioRender.com.

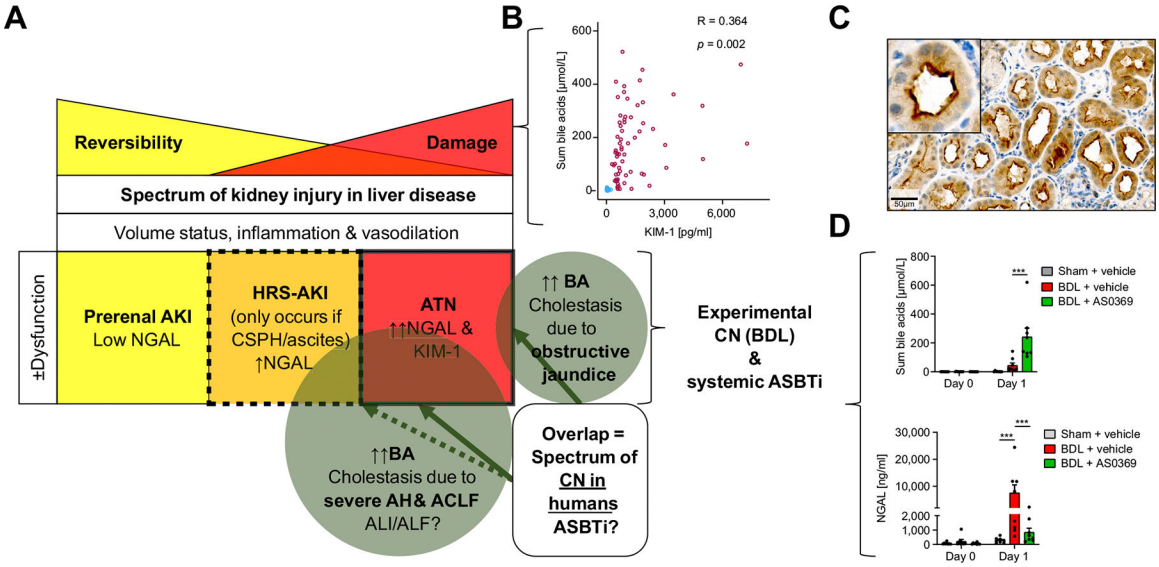


Fig. 4. Spectrum of kidney injury in liver disease.

(A) Clinically, AKI in patients with liver disease is currently defined and detected by indicators of kidney dysfunction (*i.e.* primarily increased serum creatinine), although kidney damage detected by biomarkers may precede the development of dysfunction. Prerenal AKI is exclusively functional and not accompanied by relevant damage (*i.e.* tubular injury). Thus, damage markers such as urinary NGAL are usually low and this condition, which does not overlap with CN, is highly reversible upon volume resuscitation. Hepatorenal syndrome-AKI (HRS-AKI) is primarily a consequence of vasodilatation and may respond to treatment with vasoconstrictors plus albumin. However, BA toxicity could play a role in a subset of HRS-AKI. Finally, ATN is the most severe form of kidney damage and may represent the main population in which CN is encountered in the clinic. (B) Spearmańs correlation of sum bile acid and KIM-1 levels in serum from patients with liver disease and bilirubin levels ≥6 mg/dl (red circles) and heathy volunteers (blue circles); R: Spearman's correlation coefficient; *p*: Spearman's *p* value. (C) ASBT staining (brown) in kidney tissue of a patient with advanced CN showing preserved ASBT expression at the luminal side of the proximal tubular epithelial cells. (D) Urinary bile acid and NGAL concentrations in mice with a humanised BA spectrum (*Cyp2c70*$^{-/-}$) on day 1 after BDL with and without treatment with the systemic ASBT inhibitor AS0369; the data are presented as mean values ± standard error; the dots inside the bars represent individual mice. Level of significance: ***p <0.001 (Tukey's multiple comparisons test). (B-D) are reproduced from Ghallab *et al.*[66] ACLF, acute-on-chronic liver failure; AH, alcohol-related hepatitis; ALF, acute liver failure; ALI, acute liver injury; ATN, acute tubular necrosis; BA, bile acid; BDL, bile duct ligation; CSPH, clinically significant portal hypertension; ASBTi, ASBT inhibitors; KIM-1, kidney injury molecule-1; NGAL, neutrophil gelatinase-associated lipocalin.

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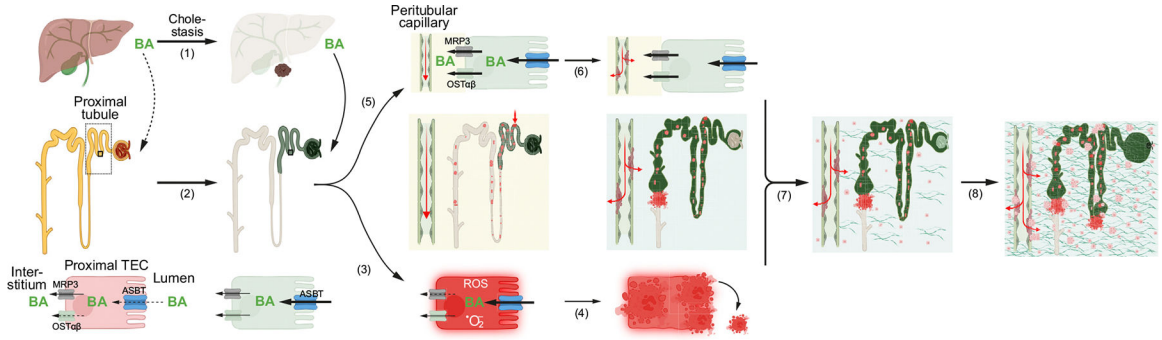


Fig. 5. New model for the pathophysiological steps in the development of CN.

(1) Blood BAs increase due to cholestatic liver disease, leading to enhanced glomerular filtration and increased BA concentrations in the lumen of renal tubules; (2) BAs accumulate in proximal TECs due to persistent ASBT activity, leading to (3) oxidative stress, cell death, and release of cell debris from a subset of proximal TECs. (4) The released cell debris floats downstream in the tubular lumen, becomes concentrated as water is absorbed in the distal collecting tubules, and forms casts (obstructions) leading to tubule dilatation upstream of the obstruction. (5) Concurrently, proximal TECs continue to transport BAs from the tubule lumen into the interstitium. (6) This leads to elevated BA concentrations in the interstitial space, which may act to compromise peritubular capillary endothelial cell barrier function and increase the leakiness of those vessels. (7) Progressive fibrosis is triggered by the cell death events of proximal TECs, increased tubule pressure, and the leakage of blood and primary urine into the interstitium. (8) A late event in the progression of CN is the formation of glomerular cysts. These glomeruli maintain their filtration capacity but often they are connected to damaged tubules, thereby releasing primary urine into the interstitium. BAs, bile acids; ROS, reactive oxygen species; TECs, tubular epithelial cells. Created in https://BioRender.com.

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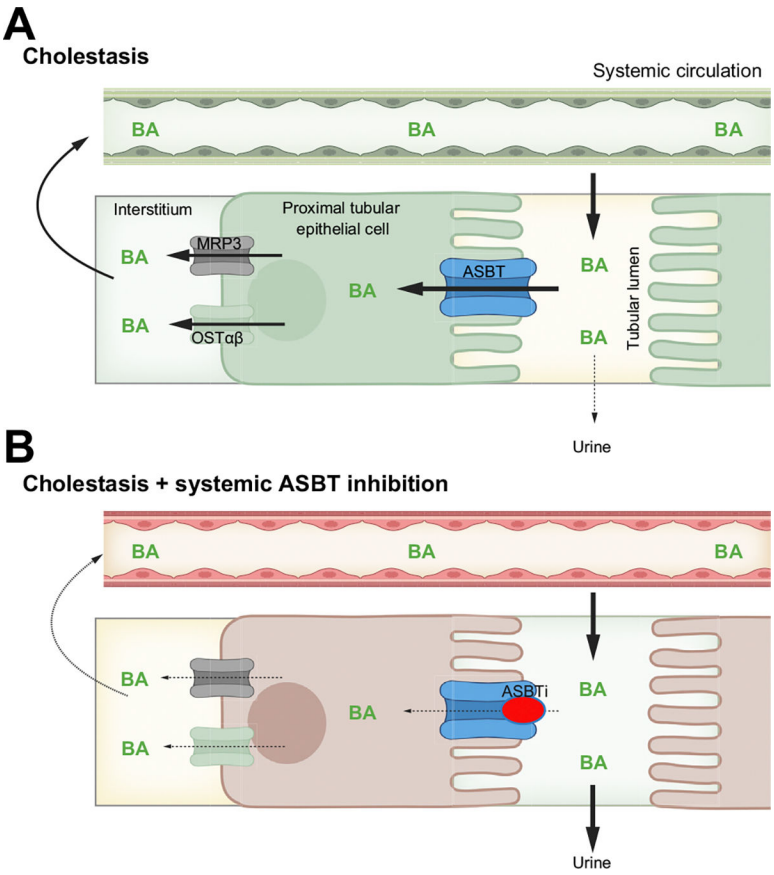


Fig. 6. Treatment of CN with systemic ASBT inhibition.

Systemic ASBT inhibitors prevent excess BA enrichment in proximal tubular epithelial cells in cholestasis (target protection) and reduce the systemic BA load by increasing urinary bile acid excretion. BA, bile acid; CN, cholemic nephropathy. Created in https://BioRender.com.

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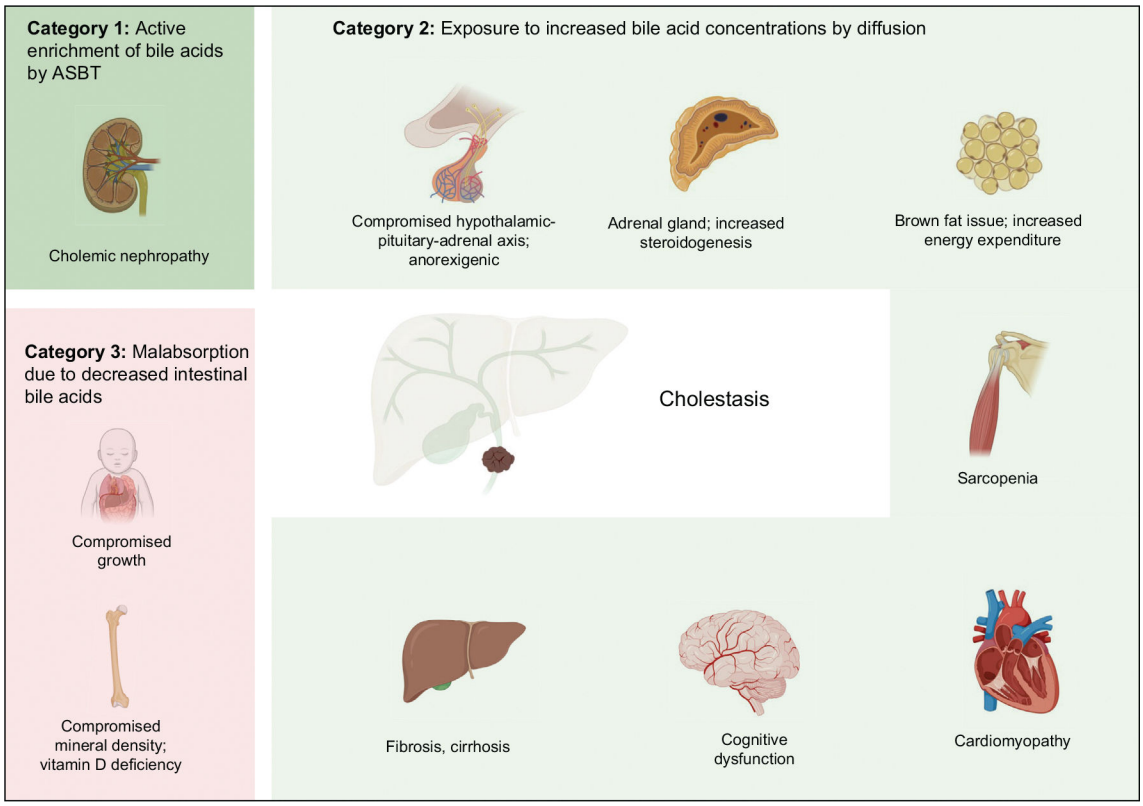


Fig. 7. Systemic complications of increased blood bile acid concentrations.

Category 1 represents active enrichment of bile acids in the target cells of the disease. The only known example thus far is CN. Systemic ASBT inhibitors hold significant potential for such occurrences. ***Category 2*** comprises different types of complications where the target cells are passively exposed to bile acids. Also, these complications may be ameliorated by systemic ASBT inhibition, it remains to be determined if the systemic bile acid reduction that can be achieved using transporter inhibitors is sufficient for benefit. ***Category 3*** represents complications linked to cholestasis with intrahepatic bile acid retention (liver/biliary cirrhosis) and/or malabsorption (vitamin D and other fat-soluble vitamin deficiency, growth failure). These complications are not an indication for ASBT inhibitors. Created in https://BioRender.com.