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Medium-chain phosphatidylcholine (MCPC) as a putative option for suppressing hepatocellular inflammation in cholestatic conditions and steatotic liver diseases

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Abstract

The mechanisms of hepatocellular injury in steatotic liver disease (SLD) and cholestasis remain unclear. One hypothesis is that hepatocytes are exposed to unconjugated toxic bile acids due to damage to the biliary mucus layer. Loss of mucus phosphatidylcholine (PC) impairs sealing, allowing unconjugated bile acids secreted in bile to be reabsorbed through leaky biliary epithelium and recirculated via portal blood to hepatocytes (cholehepatic shunting). Augmenting mucus PC could block cholangiocellular uptake of these bile acids and consequent hepatocyte exposure, which is postulated to be achieved through PC supplementation. Medium-chain PC (MCPC), secreted by multidrug resistance protein 3 (MDR3) across the canalicular membrane into bile, does not form micelles with bile acids, thus remaining available to enrich the mucus PC layer. Hepatocellular MCPC for biliary secretion can be increased by direct MCPC delivery or hepatic remodeling of oral long-chain PC provided together with medium-chain triglycerides. The reassembled breakdown products yield MCPC, helping mitigate hepatocellular injury in cholestatic states, including SLD.

Keywords: Cholestasis, phosphatidylcholine, mucus barrier, cholehepatic shunting, unconjugated bile acids, medium-chain phosphatidylcholine



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INTRODUCTION

Steatotic liver diseases (SLD) such as metabolic dysfunction-associated fatty liver disease (MAFLD) and alcohol-related liver disease (ALD) are considered major health challenges because of their widespread prevalence in Western populations and the lack of effective therapy for MAFLD. Phosphatidylcholine (PC) has been applied for therapy of these conditions^[1]. The rationale was that it is a key component of cellular membranes which might be stabilized by excess oral application of PC. It was reported to improve metabolic health and, thus, liver function and inflammation^[1,2]. PC containing medium-chain fatty acids (MCFA) modulate lipid and glucose metabolism, with positive effects on insulin sensitivity, which represent a key metabolic goal of therapy for SLD^[3].

What is the link between SLD and cholestasis? SLD is not generally considered to be a cholestatic condition although data in the literature report an interplay between both entities^[4-6]. The proposed pathogenetic mechanisms vary. One group suggests a common interaction involving the modulation of intracellular pathways, specifically on a nuclear receptor level^[6]. Here we claim that another process is of consideration, namely the exposure to toxic bile acids. Indeed, both entities, SLD and cholestasis, are consistently associated with elevated levels of cholestatic enzymes, particularly gamma-glutamyl transferase (GGT) and sometimes alkaline phosphatase (AP). SLD begins with hepatocellular fat accumulation. In the case of MAFLD, this is due to various factors, such as hypercholesterolemia, hypertriglyceridemia, obesity, or diabetes. The accumulation of fat could lead to impaired bile flow due to mechanical compression of bile ducts or tissue stiffness, resulting in elevated cholestatic parameters such as GGT and AP. In severe cases, conjugated bilirubin is also elevated, though transaminases are initially not necessarily affected. Indeed, among MAFLD phenotypes, those with a cholestatic profile show worse outcomes^[7]. Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels indicate hepatocellular inflammation, as observed in metabolic dysfunction-associated steatohepatitis (MASH) and alcohol-related steatohepatitis (ASH).

A complementary mechanism is observed in cholestatic syndromes. As a typical example, primary sclerosing cholangitis (PSC) is a metabolic condition of unknown origin, often occurring together with ulcerative colitis. Primary biliary cholangitis (PBC), on the other hand, is recognized as an immunologically triggered cholestatic liver disease. As with SLD, in these conditions, elevation of transaminases defines the switch over to cholangitis from pure cholestasis. Liver inflammation (transaminase elevation) can trigger the progression of liver disease to fibrosis and, eventually, cirrhosis. The reason for this escalation to hepatic injury is speculative.

One possibility could be the exposure of hepatocytes to certain unconjugated and toxic bile acids, including primary bile acids such as cholic acid and chenodeoxycholic acid, and secondary bile acids such as lithocholic acid and deoxycholic acid which are intestinally produced by colonic bacteria before undergoing enterohepatic recirculation. Their toxicity arises from the ability to accumulate in cells, especially at acidic pH, where they act as detergents causing membrane destruction^[8].

Hepatocellular unconjugated toxic bile acids accumulate in cholestasis, because after canalicular excretion via multidrug resistance protein 3 (MDR3), they recirculate from the biliary lumen through cholangiocytes back to the liver via the portal blood (a second hit by cholehepatic shunting). Other unconjugated bile acids, particularly ursodeoxycholic or nor-ursodeoxycholic acids (UDCAs), as well as conjugated bile acids, are water-soluble and less likely to accumulate in cells, thus exhibiting no toxicity but rather providing protection by increasing bile flow^[9].

The reason for the accelerated biliary absorption of unconjugated bile acids could be a PC-deficient biliary mucus layer, leading to a leaky mucus barrier. PC in mucus is arranged as a bilayer with attachment of its positively charged head group to the negatively charged mucins. Lack of PC impairs this bilayer construct and, thus, its repelling wall effect against penetrating unconjugated bile acids and other pathogens, including bacteria [Figure 1]. This disruption of a protective PC bilayer shield could be due to a tight junction (TJ) defect, whether genetically induced, as in PSC, or autoimmune cholangiopathy, as in PBC, or acquired, as in mechanical cholestasis from cholelithiasis or hypoxia. The latter could be suggested in MASH or ASH, where fat-loaded hepatocytes compress the branches of the hepatic artery adjacent to the biliary tree. The same is true for surgically or immunologically induced stenosis of the hepatic artery following liver transplantation and for the therapeutic use of non-steroidal anti-inflammatory drugs (NSAIDs), which cause hypoxia through vasoconstriction. The defective mucus barrier hypothesis is the basis for the proposed pathogenesis of cholangitis and steatohepatitis and respective treatment options.

THE HYPOTHESIS

PC plays a key role in establishing a mucus barrier

Previous studies have conclusively shown that colonic mucus contains PC bound to mucin 2, creating a stable repelling mucus barrier^[10,11]. The main purpose of this barrier is to prevent the invasion of the microbiota consisting of one trillion bacteria per gram of stool. If the mucus barrier is defective, however, colonic bacteria can attack the mucosal epithelium from the intestinal lumen side, leading to inflammation^[11]. This protective PC-containing mucus barrier mechanism is not exclusive to the intestine, but also exists at other mucosal surfaces, such as the biliary epithelium^[11].

The secretion of PC into mucus is complex and involves various steps [Figure 1]. PC is a component of lipoproteins in the blood that are in equilibrium with a lipoprotein-free fraction (LPFF) containing predominantly PC and some lyso-phosphatidylcholine (L-PC)^[11]. The LPFF can pass through interendothelial gaps and distribute into the interstitial space between mucosal cells, because PC, due to its complex molecular structure, cannot enter mucosal cells. Vectorial transport of PC to the apical side of the mucosal cell layer utilizes the lateral TJ barrier. The positively charged choline headgroup of PC associates with the negatively charged TJ and, over time, is translocated to the apical surface across the TJ protein bundles via a flip-flop exchange or a channel. Luminal PC secretion is driven by an additional negative charge generated at the apical surface through HCO_3^- and Cl^- secreted there by the cystic fibrosis transmembrane conductance regulator (CFTR) and/or anion exchange protein 2 (AE2)^[11]. On the outer surface of the epithelium, PC is taken up by strongly negatively charged mucins. First, it binds to the membrane-anchored mucins (e.g., mucin 1 and 3) and then is transferred to mobile mucins, such as goblet cell-released mucin 2 in the intestine and cholangiocyte-derived mucin 5B in the biliary mucosa^[11,12] [Figure 1].

In the gut, PC bound to mucin 2 moves from the ileum distally along the colonic wall to the rectum within the mucus layer to establish a bilayer barrier against the microbiota, before finally being excreted in stool. PC is most effectively secreted in the ileum compared to the upper parts of the intestine and the colon. The marginal colonic secretion capacity of PC is due to its reduced mucosal surface area compared to the ileum^[11]. Therefore, the protective properties of PC in colonic mucus depend on its delivery from the ileum. If this path is interrupted by a surgically installed diverting loop ileostomy or colostomy, mucosal inflammation distal to the stoma occurs, known as diversion colitis. Bile acids stimulate the ileal supply by acting as a luminal sink for PC secretion. Thus, in the ileum, a PC–bile acid “foam” is generated, which, after bile acid absorption in the terminal ileum, is attracted to the mucus surface in the colon, forming a tightly packed bilayer shield.

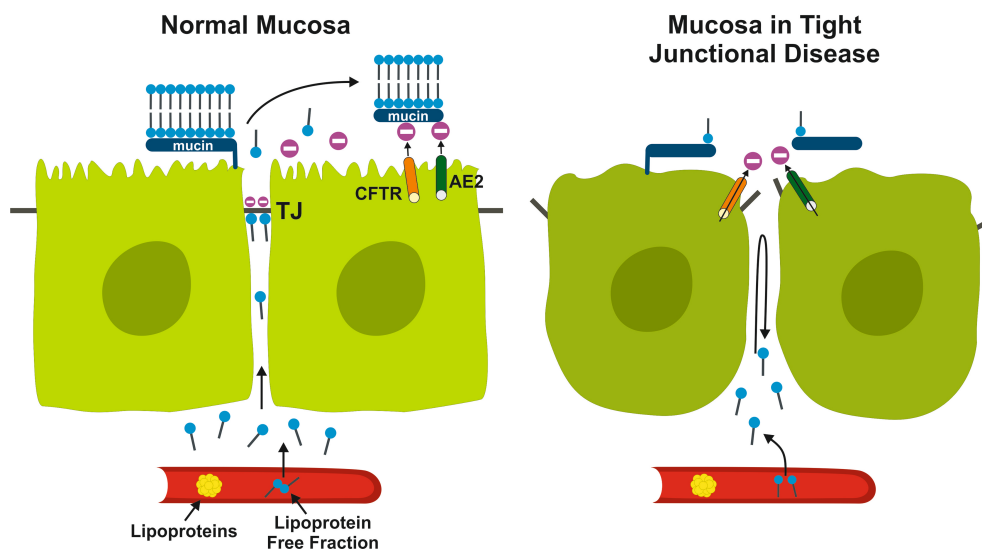


Figure 1. A hypothesis on the pathophysiology of mucosal diseases due to disturbed TJs. PC in mucus originates from systemic sources. In a LPFF, PC leaves capillaries through endothelial gaps and moves into the interstitial spaces between mucosal cells. Due to its complex structure, PC cannot enter the mucosal cells themselves. With its positively charged head group, PC is attracted to the negatively charged TJs. Over time, PC accumulates and passes through the protein strands of the TJ to the outer surface of the mucosal cells, driven by the negative charge generated by the CFTR and the AE2. Extracellular PC arranges itself in the mucus as a bilayer, with the positively charged choline head group attached to negatively charged mucin. First PC binds to membrane-anchored mucins before transferring to secretory mucins to continue its movement distally within the mucosa system. In cases of TJ disease, PC translocation to the mucus layer fails. The resulting lack of mucus PC leads to a defective mucus barrier, allowing luminal pathogens to enter. This image was made with CorelDRAW. TJs: Tight junctions; PC: phosphatidylcholine; LPFF: lipoprotein-free fraction; CFTR: cystic fibrosis transmembrane conductance regulator; AE2: anion exchange protein 2.

The secretion of PC into the intestine is as effective as the secretion of PC into bile via the MDR3 (ABCB4) transporter in the hepatocyte canalicular plasma membrane^[11]. These are two distinct transport mechanisms. The hepatocellular excretion of PC into bile is necessary to coat bile acids within micelles. In the upper intestine, bile acids are crucial for fat digestion. However, their solubilization property could potentially harm the biliary epithelium. Therefore, PC in micelles may play a role in preventing bile acid-induced damage to the biliary epithelium. In addition to the hepatocellular secretion of bile acids, the biliary epithelium can also secrete PC to the apical surface (the biliary lumen side) using the same molecular mechanism as intestinal PC secretion to the mucus layer [Figure 1]. This process has been demonstrated in experiments using the polarized biliary epithelial cell line Mz-ChA-1^[11,13]. The PC secreted in this manner integrates into the biliary mucus to form a bilayer barrier against bile acids [Figure 1].

A deficiency of mucus PC causes inflammation of the mucosal tissue

Disturbed TJ-mediated PC secretion into mucus can lead to cell injury and subsequent inflammation by allowing pathogens to penetrate. This can result in bacteria-induced colitis in the intestine or unconjugated toxic bile acids in bile causing cholangitis. In the intestine, disrupted TJ-mediated transport of PC is the cause of ulcerative colitis, with a 70% reduction in mucus PC content^[11]. Although the remaining 30% of PC content is usually enough to protect against bacterial invasion, a further decrease in PC levels can compromise the protective barrier, allowing microbiota to invade and leading to colitis. The severity of colitis is linked to the reduction in mucus PC levels, ranging from proctitis to pancolitis. The low PC content in ulcerative colitis can be attributed to any point in the PC translocation process, with the TJ barrier being particularly sensitive. Studies in mice have demonstrated that the genetic deletion of intestinal kindlin 1 or 2, crucial adapter proteins for TJ establishment, results in an ulcerative colitis phenotype^[11]. In humans with ulcerative colitis, even those in remission, electron microscopy and histology have shown

disrupted TJs and altered villous crypt architecture. Biopsy samples have also revealed impaired translocation of fluorescent PC to the mucosal surface^[11]. Genetic mouse models exhibit rapid mucosal inflammation due to the complete absence of TJ and loss of PC secretion. Due to genetically induced incomplete disruption of TJ in humans, ulcerative colitis only develops when mucus PC levels drop below the critical threshold of 30%. This can be triggered by hormonal changes in puberty, exposure to NSAIDs (e.g., aspirin or ibuprofen), infections causing gastrointestinal injury, or changes in the microbiota pattern following antibiotic exposure. An imbalance towards bacteria that consume mucosal PC using their ectophospholipase makes the mucosa more vulnerable to injury^[11].

In order to address the lack of mucus PC, which causes mucosal inflammation in the colon, it was believed that applying PC to the intestinal lumen would fill empty PC-binding sites on mucin 2, thus restoring an intact mucosal barrier. Orally administered PC is usually absorbed from the intestinal lumen into the bloodstream and then passes into intestinal mucus by the mechanism described. However, in ulcerative colitis, the delivery of PC to mucus is blocked in the intestine by the disturbed TJ architecture, rendering oral PC application ineffective. Therefore, it was suggested that a delayed-release PC preparation could fill empty PC-binding sites on mucins from the intestinal lumen side. For this approach, a lecithin preparation containing 30% PC was encapsulated using an anionic methacrylate copolymer to create a non-absorbable, microencapsulated PC with gradual release in the distal ileum and colon. Three randomized controlled trials (RCTs) and one maintenance of remission trial demonstrated the efficacy of this approach^[14]. A daily dose of 1 g PC already resulted in clinical remission within five weeks, which could be maintained with continued PC administration. However, a phase 3 follow-up trial using only gastric acid-resistant PC (rather than PC designed for intestinal release) was unsuccessful, most likely because the protocol required the concurrent administration of mesalazine, which impairs the incorporation of PC into mucus. Mesalazine acts as a detergent for PC, creating foam that cannot integrate into the mucus and thus does not compensate for the lack of PC^[11].

A NEW HYPOTHESIS SUGGESTS THAT PSC IS A TJ DISEASE INVOLVING IMPAIRED TRANSLOCATION OF PC TO THE BILIARY MUCUS

Ulcerative colitis and PSC often occur together, with 10% of ulcerative colitis patients also having PSC, and 80% of PSC patients also having ulcerative colitis. This indicates a potential common pathogenesis in a subgroup of ulcerative colitis patients. A disturbance of the TJ barrier as a cause of impaired PC secretion to the apical mucosal surface has been demonstrated in tissue culture experiments using polarized Caco-2 (human colorectal adenocarcinoma) cells of intestinal origin and the biliary epithelial cell line Mz-ChA-1^[13]. Thus, disruption of TJs results in a leaky mucus layer [Figure 1]. Moreover, *in vivo* data obtained in mice and humans with an ulcerative colitis phenotype^[11], along with mice with a PSC phenotype^[15], confirmed these findings. This supports the notion of various other investigators that TJ disruption of the biliary epithelium is a cause of the development of certain hepatobiliary diseases, including PSC^[16,17]. However, for classical cholestatic diseases such as PSC, a reduction of PC in the biliary mucus could, for technical reasons, not be experimentally shown *in vivo*.

Under physiological conditions, the biliary mucus shield is tight, allowing only a small fraction of unconjugated free bile acids to pass from the biliary lumen across cholangiocytes via cholehepatic shunt back to hepatocytes. However, in the presence of a lack of mucus PC, as proposed under cholestatic conditions, the recirculation of unconjugated toxic bile acids is facilitated, enabling easier access to bile acid carriers on the surface of cholangiocytes and allowing passage through the biliary mucosa into the portal bloodstream for recirculation to hepatocytes (cholehepatic shunt) [Figure 2A and B]. This process triggers hepatocellular injury, inflammation (cholangitis) and periductular fibrosis, characteristic features of PSC.

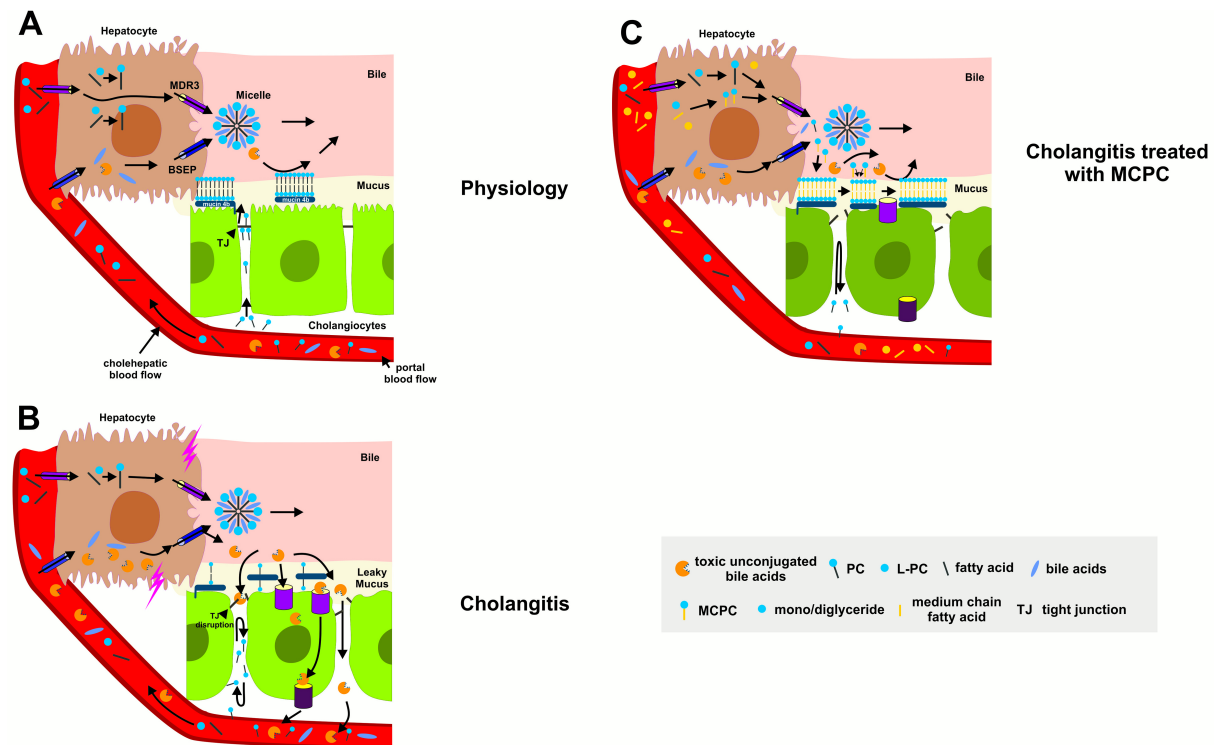


Figure 2. Hypothesis for the protective action of generated MCPC to combat hepatocellular injury induced by toxic unconjugated bile acids hitting hepatocytes via cholehepatic shunting. (A) Physiology of PC and bile acid pathways in biliary epithelium and hepatocytes connected via the portal blood flow. 1. PC in portal blood moves into the interstitial space between cholangiocytes for translocation to biliary mucus, binding to mucin 3 followed by transfer to mucin 5B to establish a bilayer shield preventing the luminal invasion of unconjugated toxic bile acids. 2. Absorbed bile acids and the hydrolyzed PC products, L-PC and fatty acids, are presented in portal blood to hepatocytes for carrier-mediated uptake. In hepatocytes, bile acids are exported into bile at the canalicular membrane, as is reconstituted PC, using different ABC transporters - BSEP and MDR3, respectively - to form micelles. In bile, only unconjugated bile acids remain in their monomeric form and are repelled by the PC bilayer shield; (B) Cholestasis due to a TJ defect impairing paracellular PC movement to the biliary mucus, resulting in mucins devoid of PC without bilayer formation. This leaky mucus layer allows unconjugated toxic bile acids to invade, pass through cholangiocytes, and recirculate to hepatocytes, followed by hepatocellular destruction (inflammation with transaminase elevation); (C) A hypothetical treatment option utilizing intrinsic MCPC, generated in hepatocytes after oral application of LCPC and MCT. The hydrolytic breakdown products of both supplements (L-PC, mono/di-glycerides and fatty acids) enter hepatocytes and reconstitute to LCPC and MCPC for excretion in bile. MCPC incorporates from the biliary lumen into empty PC binding sites to reestablish a protective phospholipid bilayer shield, protecting against the invasion of unconjugated toxic bile acids. This image was made with CorelDRAW. MCPC: Medium-chain phosphatidylcholine; PC: phosphatidylcholine; L-PC: lyso-phosphatidylcholine; ABC: ATP binding cassette; BSEP: bile salt export pump; MDR3: multidrug resistance protein 3; TJ: tight junction; LCPC: long-chain phosphatidylcholine; MCT: medium-chain triglyceride.

The leaky mucus also creates an opportunity for bacterial invasion and further disease progression. A similar mechanism of enhanced recycling of unconjugated toxic bile acids via cholehepatic shunting to hepatocytes may contribute to the progression of steatosis to steatohepatitis.

To prove the concept that TJ disruption causes PSC, a pilot study was conducted using a genetic mouse model with biliary deletion of kindlin 2 to disrupt the TJ barrier and hinder the paracellular translocation of PC to the biliary mucus layer. This resulted in the characteristic peribiliary fibrosis (onion-skin type of fibrosis) observed in PSC^[15]. A deficiency of mucus PC on top of the biliary epithelial cell layer may play a role in the pathogenesis of PSC, analogous to what is seen in ulcerative colitis [Figure 1]. To address this deficiency for therapeutic purposes, it would be beneficial to find a way to compensate for the lack of PC in order to restore a PC bilayer barrier against the harmful effects of luminal unconjugated toxic bile acids. Improving the sealing of the mucus layer by PC reduces their cholehepatic shunting. This raised the

question of how to compensate for the assumed reduction of mucus PC in PSC. Systemic administration of PC is not effective because the paracellular transepithelial pathway from systemic PC in lipoproteins to the mucus layer is blocked due to the disturbed TJ architecture. However, the hepatic secretion of PC by canalicular MDR3 is not disrupted in PSC, as well as in other types of cholestasis and steatosis^[11]. The challenge lies in the fact that PC in bile is tightly bound to bile acids within micelles, making it inaccessible for incorporation into biliary mucus and filling the empty PC binding sites on mucins.

It has been proposed to use unconjugated non-toxic bile acids as a therapeutic option for treating PSC^[11,15]. These bile acids are only loosely associated with PC in bile and, therefore, particularly under cholestatic conditions, undergo a cholehepatic shunt after being absorbed by the biliary epithelium. This leaves the accompanying PC in the bile alone, to be incorporated into the mucus, which fills the empty PC binding sites on the mucins and restores a protective bilayer barrier against the luminal bile acids. Although the underlying concept proposed here was not taken into consideration, the unconjugated bile acid Nor-ursodeoxycholic acid (NorUDCA) has been suggested as a treatment for PSC^[18]. Initial clinical trials with NorUDCA showed promising results^[19]. However, due to the expected low therapeutic efficacy, alternative, more direct treatment approaches with supplementation of PC in mucus are desirable.

A NEW TREATMENT OPTION FOR HEPATOCELLULAR INFLAMMATION IN CHOLESTATIC CONDITIONS AND SLD

The aim is to strengthen the biliary mucus barrier to prevent cholehepatic shunting and exposure of hepatocytes to unconjugated toxic bile acids, which can lead to liver damage^[20]. This can present as cholangitis with increased transaminases (PSC, PBC), or as the MASH/ASH phenotype involving intrahepatic fat accumulation-induced cholestasis (elevated GGT) and hepatocellular injury with transaminase elevation.

The new therapeutic option involves the use of medium-chain phosphatidylcholine

The therapeutic goal at the mechanistic level is the restoration of an intact biliary mucus barrier shield through topical supplementation with PC. Since the paracellular route from blood across the biliary TJ to the apical surface of the biliary epithelium is blocked, only the path from hepatocytes via MDR3 to bile is accessible to compensate for the missing PC from the luminal side. The therapeutic use of long-chain PC (LCPC) is not considered successful, because it is lipophilic and, in bile, is tightly associated with bile acids within micelles, leaving no free PC moiety to fill empty mucin binding sites. Therefore, by LCPC alone, no improvement of the leaky biliary mucus is expected and it would not lead to meaningful data.

The usefulness of medium-chain phosphatidylcholine (MCPC) with fatty acid substitutes containing 6-12 carbon atoms seems to be more appropriate. This concept is derived from the distinctive properties of medium-chain triglycerides (MCTs) [Figure 2C]. MCTs are used in cases of malabsorption with steatorrhea to compensate for the inability to absorb fat. The advantage of these is that, due to the water-soluble MCFA substitutes, they do not require bile acids for solubilization. The pancreatic lipase breaks MCT down to mono/di-glycerides. These pass through the mucosal cell layer without being incorporated into lipoproteins. They are then transported via the portal vein system from the intestine to the liver, where they are taken up by hepatocytes and either reassembled into triglycerides or used as components in the synthesis of other compounds, such as phospholipids. Thus, the MCFA moiety facilitates membrane permeation and does not require micelle formation with bile acids for its aqueous solubility.

Comparable to the absorption of MCT, it is proposed that orally administered MCPC is hydrolyzed by pancreatic phospholipases, leading to the formation of lyso-MCPC (L-MCPC) and MCFAs. These

hydrolytic breakdown products are then absorbed by mucosal cells. It is uncertain whether they are resynthesized into MCPC within mucosal cells or, more likely, remain in their hydrolyzed form and are transported in the blood bound to albumin. They reach the liver through the portal blood, where hepatocytes re-esterify them into PC with a significant portion of MCPC. The resulting MCPC is excreted via MDR3 into the biliary lumen. The underlying concept is that MCPC does not form micelles in bile and is therefore available in its monomeric form to enhance the mucus barrier function by incorporating into empty PC mucin binding sites. This, in turn, protects against the cholehepatic shunting of unconjugated toxic bile acids from bile to the hepatocytes.

Theoretically, MCPC could also be synthesized in the liver through the cytidin-5'-diphosphocholine (CDP choline) pathway or through mitochondrial synthesis from MCFAs provided externally as MCT supplementation. However, the metabolic capacity of the liver to produce sufficient MCPC for release in bile is expected to be too low when MCT is provided alone without the addition of external LCPC. The option of MCT and LCPC supplementation as a two-sided approach is discussed below. In addition to the proposed utilization of MCPC as a structural component in biliary mucus, it is also used by the liver for the activation of metabolic pathways^[21]. The physiological advantage of MCPC is based on the fact described above that, due to MCFA substitution at least at one position of the glycerophosphocholine backbone, MCPC is more soluble in aqueous media compared to LCPC. This allows for altered membrane fluidity, a smaller bilayer thickness and better bioavailability^[22]. Therefore, MCPC serves as an easily available and powerful tool for the structural and functional demands of the organism, not only for the liver but also for the brain^[3,23-25]. In contrast, short-chain PC with fatty acid chain lengths of 6-8 carbons does not exist in nature. It only acts as a detergent to solubilize membranes and is used for technical applications.

According to the proposed mechanism of action, MCPC is believed to be an effective new treatment for PSC and other destructive conditions affecting the biliary epithelium such as SLD. This therapy is believed to be effective when administered orally. In cases of an inherited lack of mucus PC, as observed in PSC, MCPC substitution therapy is required permanently. The same applies to an acquired lack of mucus PC, as observed in cases of ischemia of the biliary epithelium, for example, after liver transplantation. In cases of reversible injury to the biliary epithelium, application of MCPC is only necessary until the induced disorder is causatively corrected. Steatohepatitis due to metabolic dysfunction (MASH) or alcohol (ASH), which is associated with cholestasis (GGT elevation), may also benefit from the proposed therapeutic concept. Initially, a daily dose of 1.564 g of MCPC with chain lengths of C18/C10 (molecular weight 731) is assumed to be sufficiently effective. The final dose depends on the results of toxicology and dose-finding (phase 1 and 2) trials and may be higher. The rationale for the proposed initial dose is based on the assumption that for LCPC (C18/C18, molecular weight 838), a daily dose of 1.8 g (2.14 mmol) is recommended^[26]. When effective, the advantages of the proposed therapy are its physiological mode of action and the absence of adverse events.

A DISEASE- AND DOSE- ADAPTED TWO-SIDED APPROACH TO ENRICH PC IN THE MUCUS IN ORDER TO COMBAT INFLAMMATION AND REVERSE STEATOSIS

The MCPC is again the key actor in this process. LCPC is provided and absorbed as L-PC and fatty acid. After reconstitution to LCPC in mucosal cells, it is transported in lipoproteins via lymph in the thoracic duct and released in the blood at the venous angle to reach the liver. It is given orally along with MCT, using the same uptake route as LCPC, but does not require bile acids for digestion. Within hepatocytes, LCPC is hydrolyzed to L-PC and long-chain fatty acids, which combine with the MCT-derived metabolites as medium-chain mono/di-glycerides and MCFAs. The intracellular pool of long- and medium-chain fatty acids determines the fraction of newly synthesized MCPC. Therefore, the required amount for the

treatment of hepatic inflammation depends on the dose of orally administered LCPC and MCT. As an initial trial dose, it is suggested to apply 1.8 g LCPC (C18/C:18) daily (2.14 mmol) with its two fatty acid substitutes, which is significantly below the Generally Recognized as Safe (GRAS) recommended maximal dose of 30 g daily^[27]. The LCPC is provided together with 0.792 g MCT with its three fatty acid substitutes (C10/C10/C10, molecular weight 554), corresponding to 1.43 mmol. Thus, C10 and C18 fatty acids are provided in comparable concentrations of 4.28 and 4.29 mmol each, respectively. The calculation is theoretical because the amount of the physiological presence of LCPC in the liver is disregarded, while the MCT concentration is believed to be marginal. Thus, the orally applied amount of MCT is the rate-limiting step of MCPC synthesis. The re-esterified MCPC (C10/C18) is secreted via MDR3 of the canalicular plasma membrane into bile serving to reconstitute the PC deficient mucus layer [Figure 2C]. The newly formed mucus barrier is expected to have better sealing properties due to the densely packed PC within bilayers anchored on mucins, even when the PC backbone consists of MCFA residues with a smaller diameter, allowing the polar choline head groups to exhibit stronger repelling characteristics. This compact structure serves to re-establish a mucus barrier against the aggressiveness of luminal bile acids and prohibits the recirculation of unconjugated toxic bile acids via cholehepatic shunting to hepatocytes, combating hepatocellular injury and consequent inflammation [Figure 2C]. The actual amount of LCPC with MCT provided orally will be evaluated in trials and depends on the severity of the inflammation (cholangitis or MASH/ASH), as determined by the response to this therapy over time and measured by a drop in transaminase levels. The recommended daily intake is initially 1.8 g of PC and can gradually be increased to 10 g or even higher dosages daily when requested and tolerated by the patient. It is suggested that in steatohepatitis, intracellular fat accumulation causes cholestasis as the primary pathological factor. The observation that MCT reduces hepatocellular steatosis, enhances insulin sensitivity and fights obesity indicates that the application of higher MCT doses may provide additional benefits^[28,29]. Regarding the dosage of MCT, the German Association for Dietary Medicine suggests an initial dose of 5-10 g of MCT which can be increased in weekly increments of 5-10 g daily up to 100-150 g^[30,31]. A dose of 20 g daily is the most commonly applied. The higher the dose, the greater the risk of abdominal discomfort and diarrhea^[31]. Therefore, an individual increase in the dosage of MCT oil should be tested to find an effective and tolerable dose. Since MCT is in liquid form, we recommend increasing the dose by 5 mL at a time.

The outcome of this new putative option for the therapy of hepatic inflammation can be explored by conducting an initial clinical trial to examine the effects of orally administering 1.8 g of PC and 0.8 g of MCT yielding 1.564 g MCPC. Control groups could include: no therapy (placebo), UDCA (1,000 mg daily), LCPC alone (1.8 g), MCT alone (0.8 g daily), MCT (0.8 g daily) and CDP choline (a PC precursor) at a dose of 2.14 mmol, or MCT (0.8 g daily) and choline (a PC precursor) at a dose of 2.14 mmol. A dose-finding trial with the combination of LCPC and MCT in the same ratio will follow. Finally, a trial with increasing doses of MCT and a fixed high dose of LCPC will be initiated. As the duration of the trial, a period of 4 weeks is initially proposed, with the possibility of 4-week interval extensions. The parameters tested are improvement in GGT, AP, ALT, and AST levels. These are just the initial parameters of interest to demonstrate efficacy. Visualization of liver architecture by ultrasound, measurement of density and elasticity of liver tissue, magnetic resonance imaging (MRI) or even liver biopsy are further parameters, as indicated in guidelines for respective trial assessments. Unfortunately, bile acid profiles or determination of biliary or fecal PC content will not be helpful, as the key determinant is only the inaccessible biliary mucus. Patients will be included when diagnosed with PSC, PBC, cholestasis of any other origin or MASH/ASH with elevated GGT levels. If the concept proves beneficial for patients, RCTs will be conducted.

ROADMAP AND CHALLENGES, LIMITATIONS AND SAFETY CONCERNS

After demonstrating the efficacy of MCPC and the fixed combination of LCPC and MCT in clinical trials, the mechanism of action needs to be verified. Key questions to consider include:

- What is the effect of these compounds on a molecular, cellular, or organ level?
- Is it MCPC that reduces inflammation?
- Does MCPC impact steatosis?
- Can MCT alone reduce steatosis and consequently inflammation?

As outlined, the proposed mechanism aims to stabilize biliary mucus to prevent the cholehepatic shunting of unconjugated toxic bile acids. Appropriate animal models of SLD and cholestatic diseases are required. The isolated perfused rat liver with simultaneous bile collection can provide insights through the analysis of bile and portal blood. This analysis focuses on transaminases and cholestatic enzymes, in conjunction with quantification of bile acids and their profile, as well as their modulation by MCPC administration. In animal models that have not yet been tested, as well as in non-pretreated isolated perfused rat livers, application of unconjugated toxic bile acids to the portal vein could help to confirm the hypothesis that they trigger hepatic inflammation. If MCPC can prevent hepatocellular damage in this scenario, it could potentially be a beneficial treatment option also for non-cholestatic liver diseases, including viral and autoimmune hepatitis, as well as inborn metabolic liver diseases when toxic bile acids are of pathogenetic significance.

Due to the lack of preclinical/clinical studies, the hypothesis presented here may have potential limitations, such as unexpected efficacy failure and a prolonged time to see positive treatment results. A safety concern could be abdominal cramps or diarrhea if the oral dose of MCT is too high. Therefore, the application of oral MCT must be slowly adjusted step by step based on tolerability to avoid these potential adverse events.

DECLARATIONS

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None.

Conflicts of interest

Stremmel W is an Editorial Board Member of *Metabolism and Target Organ Damage*. Weiskirchen R is an Associate Editor of the journal. Neither of them was involved in any steps of the editorial process, including reviewers' selection, manuscript handling, or decision-making.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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REFERENCES

1. Minárik P, Koscova E. Essential phospholipids in fatty liver diseases. *Evid Self Med*. 2021;1:210346. DOI
2. Sánchez V, Baumann A, Brandt A, Wodak MF, Staltner R, Bergheim I. Oral supplementation of phosphatidylcholine attenuates the onset of a diet-induced metabolic dysfunction-associated steatohepatitis in female C57BL/6J mice. *Cell Mol Gastroenterol Hepatol*. 2024;17:785-800. DOI PubMed PMC
3. Huang L, Gao L, Chen C. Role of medium-chain fatty acids in healthy metabolism: a clinical perspective. *Trends Endocrinol Metab*. 2021;32:351-66. DOI PubMed
4. Fuchs CD, Trauner M. Role of bile acids and their receptors in gastrointestinal and hepatic pathophysiology. *Nat Rev Gastroenterol Hepatol*. 2022;19:432-50. DOI PubMed
5. Trauner M, Fuchs CD. Novel therapeutic targets for cholestatic and fatty liver disease. *Gut*. 2022;71:194-209. DOI PubMed PMC
6. Lionarons DA, Heger M, van Golen RF, et al. Simple steatosis sensitizes cholestatic rats to liver injury and dysregulates bile salt synthesis and transport. *Sci Rep*. 2016;6:31829. DOI PubMed PMC
7. Apodaka-Biguri M, Simão AL, González-Romero F, et al. E2F2 transcription factor promotes a cholestatic MASH phenotype by regulating hepatobiliary metabolism through miR-34a-5p. *Hepatology*. 2025. DOI PubMed
8. Zhou W, Anakk S. Melancholé: the dark side of bile acids and its cellular consequences. *Cell Mol Gastroenterol Hepatol*. 2022;13:1474-6. DOI PubMed PMC
9. Xie AJ, Mai CT, Zhu YZ, Liu XC, Xie Y. Bile acids as regulatory molecules and potential targets in metabolic diseases. *Life Sci*. 2021;287:120152. DOI PubMed
10. Lichtenberger LM. The hydrophobic barrier properties of gastrointestinal mucus. *Annu Rev Physiol*. 1995;57:565-83. DOI PubMed
11. Stremmel W, Lukasova M, Weiskirchen R. The neglected biliary mucus and its phosphatidylcholine content: a putative player in pathogenesis of primary cholangitis-a narrative review article. *Ann Transl Med*. 2021;9:738. DOI PubMed PMC
12. Vandenhaute B, Buisine MP, Debailleul V, et al. Mucin gene expression in biliary epithelial cells. *J Hepatol*. 1997;27:1057-66. DOI PubMed
13. Stremmel W, Staffer S, Weiskirchen R. Phosphatidylcholine passes by paracellular transport to the apical side of the polarized biliary tumor cell line Mz-ChA-1. *Int J Mol Sci*. 2019;20:4034. DOI PubMed PMC
14. Stremmel W, Braun A, Hanemann A, Ehehalt R, Autschbach F, Karner M. Delayed release phosphatidylcholine in chronic-active ulcerative colitis: a randomized, double-blinded, dose finding study. *J Clin Gastroenterol*. 2010;44:e101-7. DOI PubMed
15. Lukasova M, Weinberger K, Weiskirchen R, Stremmel W. Onion-skin type of periductular sclerosis in mice with genetic deletion of biliary kindlin-2 as tight junction stabilizer: a pilot experiment indicating a primary sclerosing cholangitis (PSC) phenotype. *Metab Target Organ Damage*. 2024;4:36. DOI
16. Merlen G, Tordjmann T. Tight junction proteins and biliary diseases. *Curr Opin Gastroenterol*. 2024;40:70-6. DOI PubMed
17. Roehlen N, Roca Suarez AA, El Saghire H, et al. Tight junction proteins and the biology of hepatobiliary disease. *Int J Mol Sci*. 2020;21:825. DOI PubMed PMC
18. Beuers U, Kullak-Ublick GA, Pusch T, Rauws ER, Rust C. Medical treatment of primary sclerosing cholangitis: a role for novel bile acids and other (post-)transcriptional modulators? *Clin Rev Allergy Immunol*. 2009;36:52-61. DOI PubMed
19. Fickert P, Hirschfield GM, Denk G, et al.; European PSC norUDCA Study Group. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol*. 2017;67:549-58. DOI PubMed
20. Benedetti A, Alvaro D, Bassotti C, et al. Cytotoxicity of bile salts against biliary epithelium: a study in isolated bile ductule fragments and isolated perfused rat liver. *Hepatology*. 1997;26:9-21. DOI PubMed
21. Long JZ, Cisar JS, Milliken D, et al. Metabolomics annotates ABHD3 as a physiologic regulator of medium-chain phospholipids. *Nat Chem Biol*. 2011;7:763-5. DOI PubMed PMC
22. Kawaguchi E, Shimokawa K, Ishii F. Physicochemical properties of structured phosphatidylcholine in drug carrier lipid emulsions for drug delivery systems. *Colloids Surf B Biointerfaces*. 2008;62:130-5. DOI PubMed
23. Korbecki J, Bosiacki M, Kupnicka P, et al. Biochemistry and diseases related to the interconversion of phosphatidylcholine, phosphatidylethanolamine, and phosphatidylserine. *Int J Mol Sci*. 2024;25:10745. DOI PubMed PMC
24. Roy P, Tomassoni D, Nittari G, Traini E, Amenta F. Effects of choline containing phospholipids on the neurovascular unit: a review. *Front Cell Neurosci*. 2022;16:988759. DOI PubMed PMC
25. Kenny TC, Scharenberg S, Abu-Remaileh M, Birsoy K. Cellular and organismal function of choline metabolism. *Nat Metab*. 2025;7:35-52. DOI PubMed PMC
26. Maev IV, Samsonov AA, Palgova LK, et al. Effectiveness of phosphatidylcholine in alleviating steatosis in patients with non-alcoholic fatty liver disease and cardiometabolic comorbidities (MANPOWER study). *BMJ Open Gastroenterol*. 2020;7:e000341. DOI

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27. WebMD. Phosphatidylcholine - uses, side effects, and more. Available from: <https://www.webmd.com/vitamins/ai/ingredientmono-501/phosphatidylcholine#overview>. (Last accessed on 15 Dec 2025).
28. Luukkonen PK, Dufour S, Lyu K, et al. Effect of a ketogenic diet on hepatic steatosis and hepatic mitochondrial metabolism in nonalcoholic fatty liver disease. *Proc Natl Acad Sci U S A*. 2020;117:7347-54. [DOI](#) [PubMed](#) [PMC](#)
29. Mumme K, Stonehouse W. Effects of medium-chain triglycerides on weight loss and body composition: a meta-analysis of randomized controlled trials. *J Acad Nutr Diet*. 2015;115:249-63. [DOI](#) [PubMed](#)
30. Bueno NB, de Melo IV, Florêncio TT, Sawaya AL. Dietary medium-chain triacylglycerols versus long-chain triacylglycerols for body composition in adults: systematic review and meta-analysis of randomized controlled trials. *J Am Coll Nutr*. 2015;34:175-83. [DOI](#) [PubMed](#)
31. Shcherbakova K, Schwarz A, Apryatin S, Karpenko M, Trofimov A. Supplementation of regular diet with medium-chain triglycerides for procognitive effects: a narrative review. *Front Nutr*. 2022;9:934497. [DOI](#) [PubMed](#) [PMC](#)