DOI: 10.53469/jcmp.2025.07(02).19

Potential Role of Bile Acids in the Pathogenesis and Treatment of PBC

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Abstract: ***Primary biliary cholangitis (PBC) is a chronic cholestatic disease whose pathogenesis involves a complex interplay of genetic predisposition, environmental triggers, and aberrant activation of the immune system. It is characterized by immune-mediated bile duct injury and chronic intrahepatic cholestasis, which ultimately leads to biliary cirrhosis and even liver failure. Cholestasis is an important pathogenetic feature and pathophysiological alteration of PBC, in which toxicity accumulation, inflammatory activation, fibrosis drive, and immunomodulatory abnormalities combine to drive disease progression. In addition, targeted bile acid (bile acid) therapy has shown therapeutic efficacy in improving liver biochemistry and survival in the majority of patients, and the current first-line therapy for PBC is bile acid therapy, with bile acids thought to play an important role in disease progression and treatment. This review focuses on the potential impact of bile acids in the disease process of PBC and its treatment, and discusses the current state of research with a view to informing further studies in PBC.***

Keywords: Primary Biliary Cholangitis, Bile Acid, Therapy.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease characterized by T-lymphocyte-mediated destruction of the interlobular bile ducts and the presence of autoantibodies against mitochondria (AMA), which, if left untreated, can ultimately progress to hepatic fibrosis and cirrhosis [1]. PBC is prevalent in females over the age of 40 years [2], and recent epidemiologic data suggest that the male The prevalence has increased from previous studies [3], and the clinical manifestations are mainly fatigue and depression.

labor, malaise, and pruritus, and liver function tests are dominated by elevated cholestatic enzyme profiles. The pathogenesis of PBC is complex and involves a complex interplay of genetic susceptibility, environmental triggers, and aberrant activation of the immune system, leading to biliary epithelial cell (BEC) injury and finally to the development of a chronic cycle of cholestasis and hepatic fibrosis [4,5]. Thus, in addition to the autoimmune response, metabolic imbalance of bile acids has been shown to be a key driver of PBC progression. Currently, the first-line treatment for PBC is bile acid therapy, with ursodeoxycholic acid (UDCA) and obeticholic acid (OCA) being the cornerstones of PBC therapy [6,7], which improves clinical symptoms and biochemical abnormalities and delays disease progression in the majority of patients. UDCA is the standard therapeutic agent in PBC, and is thought to act through a number of mechanisms, including protection of bile duct cells from toxic bile acids, stimulation of secretion of bile acids by hepatocytes and bile ducts, etc. [8]. OCA, an agonist of farnesol X receptor (FXR), is a new drug for patients who are unresponsive to or intolerant of UDCA [9]. This shows that bile acids not only play an important role in the progression of PBC, but also play a key role in the therapeutic process, and an in-depth analysis of the role of bile acids in PBC can provide a theoretical basis for novel therapeutic strategies.

Bile acids are the major lipid component of bile and are synthesized from cholesterol in the liver, which converts cholesterol to bile acids and subsequently excretes them in the feces Bile acids represent the major pathway of cholesterol excretion [10]. Bile acids can be categorized into two groups according to their origin: primary and secondary bile acids. Bile acids synthesized directly in hepatocytes from cholesterol are called primary bile acids and include bile acids, goose deoxycholic acid, and their combination products with glycine or taurine. The bile acids generated by deoxygenation of the 7th alpha hydroxyl group of primary bile acids by the action of enterobacteria are called secondary bile acids, which mainly include deoxycholic acid and lithocholic acid and their conjugation products generated in the liver by binding to glycine or taurine, respectively [11]. Bile acids are important physiological agents for intestinal nutrient absorption and bile secretion of lipids, toxic metabolites, and exogenous substances. In addition, bile acids function as signaling molecules and metabolic regulators, maintaining metabolic and immune homeostasis, primarily through the activation of farnesol X receptor (FXR) and G protein-coupled bile acid receptor Gpbar1 (TGR5) signaling [12,13]. Disruption of bile acid transport, metabolism, and physiological signaling functions leads to the development of a variety of liver diseases, including cholestatic diseases and metabolic dysfunction-associated steatohepatopathy (MASLD) [14,15]. In this review, we discuss the biological role of bile acids in PBC disease, and understanding the characterization and function of bile acids may further clarify the pathogenesis of the disease as well as provide new options for disease therapeutic approaches.

2. Altered Bile Acid Metabolic Profile in Patients with PBC

Bile duct injury in PBC patients leads to downregulation of FXR expression and negative feedback failure of bile acid synthesis, which ultimately leads to bile acid metabolism disorder [16]. The proinflammatory and anti-inflammatory effects of bile acids vary with different components and concentrations. Chen et al. found that the serum levels of total bile acids in PBC patients were significantly higher than those in healthy subjects, and the total bile acid levels showed a positive correlation with the clinical indexes and the severity

of the disease in patients with PBC. The serum levels of total primary bile acids (bile acids, taurocholic acid, glycine-ammonia bile acids, goose deoxycholic acid, taurogoose deoxycholic acid, and glycoammonium goose deoxycholic acid) were significantly elevated, with a lower percentage of total serum secondary bile acids (deoxycholic acid, taurodeoxycholic acid, glycoammonium deoxycholic acid, lithocholic acid, and taurolithocholic acid). In feces, total bile acid levels in patients with PBC differed from the changes in serum total bile acids, not showing a significant increase, but also showing a change in compositional proportions, with an increased proportion of primary bile acids and a decreased proportion of secondary bile acids [17] . These results suggest that changes in bile acid fractions play an important role both as an etiology and outcome of PBC disease. Therefore, exploring PBC from the perspective of bile acids has important theoretical and practical implications for a deeper understanding of disease progression and targeted interventions.

3. Toxic Effects of Bile Acids and Their Mediated Inflammatory Response

In patients with PBC, bile excretion is impeded due to bile duct destruction, and toxic bile acids (e.g., hydrophobic bile acids) accumulate in the liver, leading to hepatocellular injury [18]. Continued bile acid toxicity triggers recurrent liver injury and eventual progression to cirrhosis [19]. Hydrophobic bile acids induce mitochondrial dysfunction and abnormalities in the electron transport chain (ETC), inducing the production of MPT and reactive oxygen species (ROS), which oxidize mitochondrial membrane lipids and proteins, disrupting the integrity of mitochondria and further exacerbating oxidative stress and mitochondrial damage [20,21]. Hydrophobic bile acids partially activate the death receptor-dependent survival pathway, whereas hydrophilic bile acids do not induce apoptosis because they simultaneously activate the survival signaling pathway, preventing mitochondrial dysfunction and apoptosis [22]. Chlorine/hydrochloric acid-3-anion exchanger 2 (AE2) is a widely expressed membrane solute carrier that is expressed in BEC and regulates intracellular pH and biliary HCO3 secretion [23]. AE2 protects BEC from toxic hydrophobicity by forming a bicarbonate-rich "umbrella" structure on the apical surface of bile duct cells. hydrophobic bile acids. However, when AE2 is deficient, the bile salts become acidified and transformed into hydrophobic bile acids, which eventually penetrate the cell membrane and lead to apoptosis [24,25]. Cell death and inflammation play a key role in chronic tissue damage in cholestatic liver injury leading to fibrosis and cirrhosis, and bile acids are the major triggers of cell death and inflammation in cholestatic liver disease. Allen et al. suggest that bile acids can stimulate the production of inflammatory mediators to induce liver injury, including cytokines, chemokines, and adhesion molecules [26]. Interferon regulatory factor 3 (IRF3) regulates apoptosis and inflammation, and it has been found that IRF3 phosphorylation is increased in the livers of patients with PBC, and bile acids induce IRF3 phosphorylation and mediate cell death, inflammatory response, and fibrosis in cholestasis-induced hepatic and renal injuries by regulating its target gene, Z-DNA binding protein-1 (ZBP1) [27]. Bile acids induce the release of inflammatory factors by activating receptors (e.g. TGR5, FXR) on the surface of hepatocytes and cholangiocytes. Under conditions of high concentrations of hydrophobic bile acids, TGR5 signaling may be inhibited, leading to overactivation of NLRP3 inflammatory vesicles and inflammatory factor release [28]. The release of inflammatory factors leads to inhibition of hepatic bile salt efflux pump (BSEP) expression, which exacerbates cholestasis [29,30]. In addition, downregulation of FXR expression or impaired function results in bile acids promoting inflammatory responses via TGR5 or other receptors [31]. In immunomodulation, bile acids affect T cell differentiation by modulating Treg/Th17 cell balance, which in turn promotes activation of immune responses [32]. In liver-gut interactions, abnormal bile acid metabolism alters gut flora composition, leading to gut barrier disruption and bacterial product translocation, among other things, activating hepatic immune responses [33,34]. Therefore, modulation of bile acid-immune interactions provides PBC therapy. New targets, combined with immunomodulation and bile acid metabolism modulation may better improve the therapeutic efficacy.

4. Bile Acids and PBC Treatment

The current first-line therapy for PBC is bile acid therapy, and UDCA is the cornerstone of PBC treatment [6,35]. UDCA is a hydrophilic bile acid that promotes the excretion of toxic bile acids, decreases the proportion of hydrophobic bile acids, and reduces the damage they cause to hepatocytes and bile duct cells [17]. Just as toxication of the bile acid pool leads to cell death, detoxification of the bile acid pool reduces cell death. UDCA treatment significantly reduces serum alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), and bilirubin levels, delaying the progression of hepatic fibrosis, and decreasing the need for liver transplantation and the risk of death [36]. UDCA can reduce the risk of liver transplantation and death by inhibiting the NF-κB signaling pathway and the NLRP3 inflammasome and down-regulate the release of pro-inflammatory cytokines, thereby reducing intrahepatic lymphocyte infiltration and attenuating hepatic inflammatory responses [37,38], and inhibiting the development of hepatic fibrosis by affecting the TGFβ1/Smad signaling pathway [39]. However, there are still about 40% of PBC patients with poor biochemical response to UDCA in the clinic, and the risk of disease progression and poor prognosis are significantly increased in these patients. Based on the available evidence-based medical evidence, international guidelines recommend obeticholic acid (OCA) as a second-line therapeutic agent for patients with poor response to UDCA therapy [40,41]. OCA is a potent agonist of the FXR receptor, which reduces bile acid synthesis by inhibiting the key enzyme of bile acid synthesis, cholesterol 7α-hydroxylase (CYP7A1) [42]. In addition, OCA reduced inflammatory factor release and HSC activation by inhibiting the NF-κB and TGF-β signaling pathways, improved clinical biochemical indices in PBC patients, delayed the progression of hepatic fibrosis, and reduced the need for liver transplantation [43]. OCA exerts better hepatoprotective effects than UDCA due to induction of signaling pathways that regulate fibroblast growth factor-19 (FGF-19) activity [44,45]. OCA in combination with UDCA significantly reduces hepatic biochemical markers but does not differ significantly from monotherapy in terms of improvement in bound bilirubin,

IgM, or adverse events [46]. With the exception of UDCA and OCA, drugs for the treatment of PBC are still in the experimental or clinical phase [47,48]. Currently, drugs targeting bile acid metabolism, including FXR agonists [16], apical sodium-dependent bile acid transporter protein (ASBT) inhibitors [49], and peroxisome proliferator-activated receptor (PPAR) agonists [48], slow down the disease progression of PBC by reducing cytotoxicity and inflammation. In addition to conventional drug therapy, novel therapies based on modulating the enterohepatic circulation are being explored. For example, regulating the balance of intestinal flora by means of specific probiotic preparations or fecal bacteria transplantation improves bile acid metabolism and plays an adjunctive therapeutic role [50]. In addition, Kennedy et al. demonstrated that glucagon treatment promotes bicarbonate and mucin secretion as well as hepatic bile acid excretion and attenuates cholestasis-induced injury in a mouse model of advanced PBC [18,51]. With in-depth studies on the bile acid signaling pathway and gut flora interaction mechanisms, individualized treatment and novel drug development will bring more hope to PBC patients.

5. Conclusion

Bile acids contribute to disease progression in PBC through a variety of mechanisms, acting not only as a pathogenetic factor in PBC, but also as a concomitant of disease progression and a significant contributor to poor outcomes. Treatment targeting bile acids remains a central strategy in the current management of PBC. Therapeutic strategies targeting bile acid metabolism show good potential for treating PBC, especially in modulating the inflammatory response and preventing disease progression. However, some patients still respond poorly to bile acid therapy and have a poor clinical prognosis. In the future, it is necessary to further analyze the bile acid-immune-gut flora interactions network and develop more efficient and low-toxicity combination therapeutic regimens in order to ultimately achieve the goal of curing PBC.

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