

Bile acids are important contributors to AKI associated with liver disease: PRO

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The development of acute kidney injury (AKI) in patients with liver disease and jaundice, presents a particularly difficult challenge, even for the most experienced clinician. Occasionally, a single factor may damage both organs simultaneously (*e.g.* mushroom poisoning or *Leptospirosis icterohaemorrhagiae* infection). However, most cases are due to the combined effects of several factors, including endotoxins, chemokines, cytokines, hemodynamic disturbances and drug toxicity [1, 2]. Similarly, patients with cirrhosis may develop AKI due to one overriding factor, such as in “pure” hepatorenal syndrome (HRS-AKI) where the prevailing mechanism is the altered hemodynamics, suggesting that it is functional form of renal failure [1, 2]. However, from a clinician’s perspective, only a minority of HRS- AKI patients suffer from “pure HRS,” since other factors, including inflammation and nephrotoxins are superimposed on the hemodynamic abnormalities, and thus likely contributing to the AKI [1, 2]. Support for this view comes from post-mortem studies that show that patients who were clinically labeled as HRS-AKI, had severe parenchymal kidney injury and even full-blown cholemic nephropathy at autopsy [3, 4, 5]. These histologic findings by themselves preclude the diagnosis HRS-AKI and reflect the fact that it remains difficult to precisely diagnose HRS-AKI, which in turn affects the appropriateness of our therapeutic choices. Indeed, there is growing evidence suggesting that while AKI in patients with liver diseases may be due to sharply demarcated entities (Table 1), the majority reflect a disease spectrum that may incorporate several of these elements.[2]. In this paper, we summarize evidence that supports the hypothesis that bile acids cause AKI in cholestasis and/or liver cirrhosis.

The role of bile acids in physiology and pathophysiology, has long been underappreciated. Bile acids are sterol-derived compounds that are essential in the absorption, digestion and regulation of lipids, the metabolism of protein and glucose, and innate immunity. Their synthesis and transport involve tightly regulated mechanisms that predominantly transpire in the liver, small intestine, and kidney. Bile acids exert numerous functions via specific receptors [including ones expressed in the kidney such as farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor (Gpbar1 or TGR5)], and thus are now considered as hormones [6]. Bile acids are produced and conjugated in the hepatocytes, secreted (via bile) into the intestine, and where 95% is reabsorbed, taken up by hepatocytes, and re-secreted into the bile. This enterohepatic recirculation allows the production of bile acids to be only 400-600 mg, despite the daily secretion of 12-18 grams. The small amount of reabsorbed bile acids that escape hepatic uptake are spilled into the systemic circulation. Circulating bile acids are filtered by the kidney, but almost completely reabsorbed by the proximal renal tubules (via apical ASBT and basolateral OST α/β transporters) so that only 5% of the approximately 100 μmol of filtered bile acids appear daily in urine [7]. However, this urinary excretion rate of bile acids is increased in experimental and clinical cholestasis. This increased excretion is thought to be a renal compensatory mechanism to offset the defective biliary bile acid secretion. A role for the kidney in the regulation of bile acid homeostasis is also supported by the observations that the reduction in urinary excretion of bile acids associated with chronic kidney disease is accompanied by elevated serum bile acid levels [8]. It should be noted that the bile acids that escape proximal reabsorption have direct tubular effects; they regulate renal water handling via their tubular FXR and TGR5 receptors, particularly in the collecting duct where they modulate aquaporin 2 expression [9]. Interestingly, collecting tubules of cholestatic mice and humans with cholemic nephropathy have decreased aquaporin 2 expression, suggesting that the increased amount of bile acids reaching the collecting tubules is downregulating the number of aquaporin 2 channels. However, this decrease may also be secondary to their toxicity with resultant tubular cell injury and death [10, 11].

In cholestasis, bile acids and bilirubin are both elevated and excreted by the kidney. While both may theoretically cause AKI, two main experimental findings suggest that bile acid toxicity is the key

culprit. First, increasing the hydrophilicity of the bile acid pool in chronic bile duct ligated (CBDL), significantly ameliorated AKI. That is, supplanting the more toxic hydrophobic bile acids with the less toxic hydrophilic ones, caused less AKI. This strategy would not have been effective if the bile acids were not contributing significantly to the injury. Second, CBDL FXR (-/-) mice, that also have a much more hydrophilic bile acid pool, are protected from AKI [12]. Finally, serum bile acid levels peak at day 3 after CBDL, coinciding with epithelial injury in collecting ducts, which is followed by interstitial nephritis and subsequently tubulointerstitial fibrosis [10]. Additionally, there is no substantial evidence that bilirubin directly incites renal injury. Kidneys from CBDL mice do not show tubular bilirubin accumulation and renal tubular casts in CBDL mice do not contain abundant amounts of bilirubin, even in the presence of AKI, suggesting that bilirubin is not a major culprit.

Whether the bile acids are acting via hemodynamic changes, directly upon the renal cells, or indirectly via other mechanisms is unknown. There is good evidence that bile acids can compromise renal perfusion via their effects on cardiac function and systemic hemodynamics [13,14]. In the heart, they cause reduced contractility, cardiomyocyte apoptosis, electrical conductance defects, and cardiac hypertrophy, which result in a decreased cardiac output. Their effects on the systemic vasculature include splanchnic vasodilatation and reduced systemic vascular resistance. Indeed, infusing taurochenodeoxycholic acid and taurodeoxycholic acid has been shown to increase mesenteric arterial blood flow and decrease blood pressure. This effect has been shown to be secondary to activation of muscarine-like receptors, FXR-dependent stimulation of eNOS synthesis and inhibition of endothelin-1 production [13,14,15]. These vascular effects, particularly when in the presence of the cardiac defects, compromise renal perfusion, which in turn increases the susceptibility to AKI. Further evidence for a hemodynamic-driven mechanism, albeit indirect, is suggested via their association with portal hypertension. Indeed, patients with advanced liver disease (from several etiologies) frequently have elevated serum bilirubin and bile acid levels, which strongly correlate with the hepatic venous pressure gradient, serving as the most reliable marker to assess the degree of portal hypertension, predict new-onset acute decompensation and acute on chronic liver failure in patients with liver cirrhosis [16].

The cardiovascular effects of cholestasis and its association with clinical decompensation is clear. However, at some point tubular injury develops. Indeed, as mentioned in the first section, a considerable number of deeply jaundiced patients with clinical HRS-AKI had histopathological evidence of parenchymal injury and cholemic nephropathy [3, 4, 5]. This tubular injury may explain why a high percentage of patients are refractory to hemodynamic therapy. For instance, 70% of patients with infection-related HRS-AKI did not recover from HRS despite receiving adequate treatment that normalized the hemodynamic disturbances. Likewise, 61% of patients with HRS-AKI did not respond to terlipressin in the recently published CONFIRM trial [17]. This tubular damage may result from different modes of action: (1) prolonged ischemia, leading to acute tubular necrosis (ATN); (2) indirect damage via circulatory changes due to systemic inflammation, and (3) direct toxic changes due to elevated levels of bile acids in urine and serum. The salient point is that bile acids can be responsible for all 3 mechanisms and thus may be a key causative factor to the development of tubular injury [18,19]. The importance of bile acids in the progression of AKI from a functional state to parenchymal injury, is supported by several clinical studies. Barreto et al. [20] showed that the degree of cholestasis served as an independent predictor of irreversibility of HRS-AKI. Nazar et al. [21] also showed that the proportion of HRS-AKI terlipressin responders was significantly greater in patients with serum bilirubin levels < 10 mg/dl, again indicating that the degree of cholestasis is an important prognostic factor in HRS-AKI patients. It is

important to point out that we are assuming that these patients had elevated serum bile acid levels because of their elevated bilirubin measures. While this is a relatively safe assumption (bile acids account for ~80% of bile), there is no data available in these studies to confirm this assumption. Additionally, we do not know serum bile acid levels in patients who are clinically classified as having HRS-AKI and whether these levels correlate with renal function. Therefore, further clinical studies are needed to confirm this assumption, and to measure serum and urinary bile acid levels at different stages of AKI during diverse liver diseases, so that we may precisely characterize the contribution of bile acids as a possible player in the pathophysiology of the “mixed-bag” of AKI.

We recognize several limitations to our arguments. First, experimental studies need to be interpreted with caution; even perfectly done studies in experimental animals do not necessarily translate directly to human disease. Second, many of the experimental studies mentioned were performed using the CBDL model, which may not be directly comparable to most forms of human cirrhosis, since this model represents a model of severe cholestatic liver disease with a biliary type of liver fibrosis [22]. And third, the clinical studies are thus far associative in nature; hence, causality cannot be established. However, despite these limitations, we believe that the preponderance of evidence strongly favors the argument that bile acids are involved in the pathogenesis of AKI in patients with advanced liver diseases. We share the view of many authors that AKI in these patients will frequently be due to a progressive spectrum that will vary according to the AKI subtype and contributing etiologies. We submit that bile acids are key players in this spectrum, likely via direct effects on the kidney and/or indirect effects on systemic hemodynamics, oxidative stress and inflammation. The specific impact of bile acids may depend on the clinical context (e.g. with and without infection, SIRS), past medical history (e.g. new-onset liver disease versus liver decompensation such as ACLF), and the type of liver disease (i.e. primarily cholestatic versus non-cholestatic liver disease).

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