Bile Acids Are Important Contributors to AKI Associated with Liver Disease: PRO

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The development of 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 *Leptospira icterohaemorrhagiae* infection). However, in most patients it is 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 it is functional form of renal failure (1,2). However, from a clinician’s perspective, only a minority of patients with HRS-AKI suffer from "pure HRS," because 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 postmortem studies that show patients who were clinically labeled as having HRS-AKI, had severe parenchymal kidney injury and even full-blown cholemic nephropathy at autopsy (3–5). These histologic findings by themselves preclude the diagnosis of 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 although 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 supporting 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), 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 resecreted 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 g. 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 OSTα/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 CKD is accompanied by elevated serum bile acid levels (8). It should be noted the bile acids that escape proximal reabsorption have direct tubular effects; they regulate renal water handling via their tubular FXR and G-protein-coupled bile acid 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 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. Although both may theoretically cause AKI, two main experimental findings suggest bile acid toxicity is the key culprit. First, increasing the hydrophilicity of the bile acid pool in chronic bile duct ligation (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

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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 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 vasodilation 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 muscarinic-like receptors, FXR-dependent stimulation of endothelial nitric oxide synthase synthesis, and inhibition of endothelin-1 production (13–15). These vascular effects, particularly 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

| Differential Diagnosis | Causing Factors | Characteristics/Clinical Clues | Unmet Clinical Needs and Problems |
|------------------------|----------------|--------------------------------|----------------------------------|
| Prerenal azotemia      | Bleeding, vomiting, diarrhea, large volume paracentesis, diuretics, NSAR | Past medical history, clinical signs of bleeding, vomiting, diarrhea, dehydration, and specific medication (e.g. diuretics, RAAS blockers) | Current incidence and prognosis due to changes in treatment unclear, lack of a single diagnostic test, lack of reliable biomarker |
| HRS-AKI                | Portal hypertension, cardiovascular dysfunction, relative adrenal insufficiency, in essence reduction in effective intraarterial blood volume | Diagnosis of exclusion, ICA guidelines for the diagnosis of HRS-AKI | Diagnostic tests: urinalysis |
| Drug-induced           | NSAR, ACE inhibitors, β-blockers, aminoglycosides, amphotericin B, tenofovir, adenovir, antibiotics | Past medical history, temporal coherence | Diagnostic tests: urinalysis |
| Cholemic nephropathy   | Deep jaundice, obstructive cholestasis/jaundice, decompensated liver disease, ASH, ACLF | Temporal coherence between jaundice and AKI, kidney histology | Incidence and prognosis unclear, lack of a specific (non-invasive) diagnostic test and reliable biomarker, most studies retrospective analysis, case reports, and postmortem analysis, overlap with HRS-AKI unclear; high risk of complications in renal biopsy in this setting |
| Infectious             | With preexisting liver disease: SBP, spontaneous bacteremia, urinary tract and respiratory tract infections, cryoglobulinemia in Hep B and C patients Miscellaneous: Leptospirosis, malaria, CMV | Past medical history, clinical picture/context | Diagnostic tests: urinalysis |
| Intrinsic renal disease| IgA nephropathy, glomerulonephritis, glomerulosclerosis, myoglobin, diabetes and arterial hypertension | Past medical history, clinical picture, kidney histology | Incidence and prognosis in liver patients in many cases unclear, lack of a specific (non-invasive) diagnostic test and reliable biomarker |

Table 1. Differential diagnosis, causing factors, and characteristics of kidney involvement/renal failure in patients with liver diseases

Unmet Clinical Needs and Problems
etiol ogies) 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 above, a considerable number of patients who were deeply jaundiced and with clinical HRS-AKI had histopathologic evidence of parenchymal injury and cholemic nephropathy (3–5). 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; (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 three 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 the degree of cholestasis served as an independent predictor of irreversibility of HRS-AKI. Nazar et al. (21) also showed the proportion of HRS-AKI terlipressin responders was significantly greater in patients with serum bilirubin levels <10 mg/dL, again indicating the degree of cholestasis is an important prognostic factor in patients with HRS-AKI. It is important to point out we are assuming these patients had elevated serum bile acid levels because of their elevated bilirubin measures. Although this is a relatively safe assumption (bile acids account for approximately 80% of bile), there are 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 und urinary bile acid levels at different stages of AKI during diverse liver diseases, so we may precisely characterize the contribution of bile acids 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 conducted 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, because 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 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 effect of bile acids may depend on the clinical context (e.g., with and without infection, systemic inflammatory response syndrome), past medical history (e.g., new-onset liver disease versus liver decompensation such as acute-on-chronic liver failure), and the type of liver disease (i.e., primarily cholestatic versus noncholestatic liver disease).

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See related debate “Bile Acids are Important Contributors to AKI Associated with Liver Disease: CON,” and commentary, “Bile Acids are Important Contributors to AKI Associated with Liver Disease: COMMENTARY,” on pages 21–24 and 25–27, respectively.