Dual Organ Duel: The Hepatorenal Axis

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Recent developments in our understanding of the pathogenesis of kidney disease in the setting of liver failure have highlighted that kidney injury, rather than occurring in isolation, is a marker of systemic disease and poor prognosis. The differential diagnosis of kidney disease associated with liver failure is broader than formerly described and new biopsy data, along with better acute kidney injury classification tools, have increased appreciation for distinct pathophysiological mechanisms. Evidence suggests that acute kidney injury contributes to worsening hepatic failure by directly injuring hepatic cells and by imposing restrictions on therapeutic strategies for portal hypertension. Furthermore, kidney injury limits the use of various therapeutic agents and increases their toxicity due to altered pharmacodynamics. A greater appreciation of CKD in this population is also overdue because management decisions are affected and increased vigilance may avoid further kidney injury. A multidisciplinary approach to kidney injury in the setting of liver failure will enable targeted therapeutic strategies that are safe and effective and serve to guide further research, while limiting clinical potential for harm. Finally, new hepatitis C antiviral therapies promise to change the landscape of liver failure, and a discussion of kidney risk factors and antiviral therapy of patients with kidney disease and hepatitis C is worthwhile.

Key Words: Type of renal disease, Liver failure

INTRODUCTION

Liver disease is the fourth leading cause of death in those 45 to 54 years old in the United States. Nearly 5.4 million Americans have chronic hepatitis B or C infection, and an increasing number of the population are getting diagnosed with nonalcoholic steato-hepatitis.[1] Acute kidney injury (AKI) in the setting of liver disease is associated with increased mortality and is a major consideration for liver transplant candidacy.[2] Hepatorenal syndrome (HRS), a purely hemodynamic phenomenon, is commonly identified as the major cause of AKI; however, other types of kidney injury are increasingly recognized.[3] A discussion of the various forms of kidney disease in the setting of liver disease will help to increase awareness and improve diagnostic acumen. Moreover, a comprehensive approach to HRS as a systemic disorder, much like systemic inflammatory response syndrome, accompanied by parenchymal end organ damage, will help inform efforts to improve safety and quality outcomes in liver disease patients.[4] In this article, we review (a) new developments in our understanding of the types of kidney disease in the setting of liver disease, (b) the systemic nature of HRS and its underlying pathophysiology, (c) the efficacy and safety of AKI therapeutics in the setting of liver disease, and (d) kidney risk factors of the new generation of antiviral agents for the treatment of hepatitis C.

TYPES OF KIDNEY DISEASE ASSOCIATED WITH LIVER FAILURE

The following categories of kidney disease occur in the setting of liver failure: pre-renal, intrinsic (including glomerular disease and acute tubular necrosis [ATN]), HRS, and postobstructive.[4,5] The incidence of each category varies according to the severity of liver disease, with HRS predominating in those with decompensated cirrhosis where 20% develop HRS within 1 year and 40% within 5 years.[2-5] Prevalence estimates of HRS type 2, a more indolent form of kidney failure, are closer to 11% of those with advanced liver disease.[2-5] Type 2 HRS is marked by refractory ascites and diuretic resistance and has an average survival of 6 months, whereas type 1 HRS presents with severe AKI and a mortality rate that exceeds 80% within weeks.[2-4] HRS types 1 and 2 are distinguished by the rapidity of onset of kidney failure, but most knowledge regarding HRS pathophysiology comes from type 1.[2-5] Septic ATN and bile cast nephropathy are increasingly considered in the differential diagnosis of type 1 HRS.[6] Bile acids increase reactive oxygen species, solubilize mitochondrial membranes, and have a direct toxic effect on kidney tubules.[7] Also, systemic inflammatory response syndrome is a well-recognized etiology for "septic" ATN and is associated with both kidney ischemia, from shunting, and kidney inflammation.[2-6] In the setting of decompensated cirrhosis, especially with concomitant infection, septic ATN is both common and underdiagnosed.[2] It is difficult to distinguish these various forms of AKI in the setting of severe liver disease, but accurate diagnosis has major implications for management decisions.[6]

Underlying kidney parenchymal disease plays an underrecognized role in the pathophysiology of AKI associated with liver disease. Kidney parenchymal changes have been demonstrated in biopsy series in those liver disease patients with presumed hemodynamic kidney disease.[8-10] These biopsies have shown vascular disease, interstitial fibrosis, and tubular atrophy. Pre-transplant kidney biopsies also demonstrate various types and stages of glomerular injury.[8-10] Glomerular diseases that have been associated with hepatitis C and B infection and cirrhosis include cryoglobulin-mediated microangiopathy, membranoproliferative glomerulonephritis, membranous

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disease, and IgA nephropathy (Table 1). The extent of glomerulosclerosis was found to predict post-transplant GFR in 1 study (Table 1).[8] Parenchymal kidney involvement, including glomerular disease, is highly prevalent in liver disease patients, likely underdiagnosed, and as a cause of CKD, an important consideration for transplant selection, medication dosing, and portal hypertension management. CKD also increases the risk of AKI and mortality in this population.[11,12] The coexistence of Diabetes and CKD, in 1 study, increased short-term mortality in cirrhotic patients admitted with esophageal variceal bleeding.[12] CKD, irrespective of cause, complicates diuretic dosing and management of cardiac dysfunction and portal hypertension. Agents such as spironolactone, β blockers, diuretics, and renin-angiotensin and aldosterone (RAAS) inhibitors must be used with caution in patients with CKD and liver disease because of the risk of worsening AKI and hyperkalemia.[11,12]

Hemodynamic kidney disease is reversible and associated with better kidney outcomes than parenchymal kidney disease; therefore, correct categorization of AKI is crucial in prognostication and transplant planning. Distinguishing between hemodynamic and parenchymal AKI has proved difficult, however, because multiple pathophysiological mechanisms are at play and may contribute to kidney dysfunction. Increasingly, biomarkers have been used to distinguish between parenchymal kidney disease and hemodynamic AKI. Urinary NGAL, thought to be a marker of intrinsic kidney disease, is disproportionately elevated in patients with AKI and peritonitis, indicating that presumed septic ATN is playing an important role.[13] A panel of 4 biomarkers discriminated between adjudicated ATN and HRS better than did urine sodium and helped to prognosticate outcomes in 1 study.[13] Consideration of kidney disease etiology and parenchymal involvement, in the setting of liver failure, necessitates a deeper appreciation of acute pathophysiological changes and chronic parenchymal processes.

CLINICAL SUMMARY

- Kidney disease is highly prevalent in patients with liver disease and represents both hemodynamic changes and progressive parenchymal damage.
- Updated classification schemes for kidney disease include more sensitive markers of kidney injury that offer earlier detection and consideration of a broader differential diagnosis.
- Kidney disease contributes to the systemic manifestations of hepatic disease.
- Pharmacokinetic changes accompany kidney disease and should be considered in medication dosing.
- New hepatitis C antiviral therapies have set the stage to cure hepatitis C and its associated renal co-morbidities. The pharmacokinetic and renotoxic effects of these agents must be considered in therapeutic decisions.

DIAGNOSTIC CRITERIA FOR HRS

Criteria for the diagnosis of HRS type 1 include presence of ascites, serum creatinine >1.5 mg/dL, no improvement of serum creatinine after at least 48 hours of diuretic withdrawal and volume expansion, and absence of shock or parenchymal kidney disease.[14] The AKI network criteria classify HRS within a spectrum of disorders coined: "hepatorenal dysfunction," a term that implies more than 1 pathophysiological process.[5] Because creatinine is a poor marker of kidney disease in liver failure, frequently overestimating kidney function and underestimating kidney injury, and because the MELD score uses creatinine as a marker of kidney disease, the lack of sensitivity of creatinine for AKI diagnosis is problematic.[15] In patients with cirrhosis, where significant muscle atrophy and reduced hepatic conversion of creatine to creatinine is commonplace, significant kidney dysfunction may be masked by an ostensibly normal creatinine value. This danger is compounded by cirrhotic patients' unique hemodynamic and pharmacokinetic vulnerability to AKI.[15] Patients with liver disease are at risk for receiving diuretics, contrast procedures, and nephrotoxins under the incorrect assessment that kidney function is normal, whereas at the same time not receiving timely liver transplants because their creatinine-based MELD scores are not high enough. Clearly, refining the diagnostic sensitivity and early management of AKI in this setting is a top priority.

NEW DEVELOPMENTS IN OUR UNDERSTANDING OF HRS PATHOPHYSIOLOGY

Type 1 HRS is defined as a kidney event, but our improved understanding of liver disease suggests that it is also a marker of severe systemic inflammation, indolent multiorgan dysfunction, and failure of hemodynamic compensatory mechanisms (Fig 1). Release of systemic vasodilators and upregulation of RAAS and the sympathetic nervous system in response to decreased organ perfusion, constitute the hallmarks of this disorder.[2-5] Proposed vasodilatory agents are numerous and include nitric oxide, calcitonin gene-related peptide, adrenomedullin, andro-cannabinoids, and plasma substance P.[16-18] Compensatory kidney vasodilators, such as prostaglandins, are reduced.[5,16-18] The "hepatorenal reflex" describes the relationship between ascites, renal artery resistive index, and altered autoregulatory compensation.[16] Osmo- and baro-receptors in the liver have direct neural connections to the kidneys. Hepatic baroreceptor activation increases kidney sympathetic activity and kidney denervation increases kidney vascular resistance in animal models of portal vein obstruction, supporting this direct connection.[17] Acute induction of portal hypertension also reduces renal blood flow and increases levels of endothelin 1, a vasoconstrictive agent.[18] Renal resistive index assessed by Doppler sonography showed that an index greater than 7 was associated with development of HRS and worse renal outcomes in 1 cohort.[19] Controversy still exists as to whether the alterations