Kidney Biomarkers in Hepatorenal Syndrome

Abstract

Cirrhosis is the result of advanced liver disease characterized by fibrosis due to increased portal hypertension. Patients with cirrhosis are prone to develop acute kidney injury (AKI) triggered by bacterial infections, hypovolemia, nephrotoxic drugs and intrinsic kidney disease. The diagnostic criteria for the diagnosis of HRS continue to rely on serum creatinine levels which should be interpreted with caution in patients with cirrhosis. To date, accurate biomarkers indicative of renal function are lacking. Further validation with prospective studies is warranted to evaluate the value of novel biomarkers.

Keywords: Hepatorenal syndrome; Acute kidney injury; Cirrhosis; Biomarkers

Abbreviations: HRS: Hepatorenal syndrome; IAC: International Ascites Club; GFR: Glomerular Filtration Rate; AKI: Acute Kidney Injury; SCr: Serum Creatinine; NGAL: Neutrophil Gelatinase Associated Lipocalin; KIM-1: Kidney Injury Molecule 1; L-FABP: Liver-Type Fatty Acid Binding Protein; TTF3: Trefoil Factor 3

Introduction

Hepatorenal syndrome (HRS) is a rapidly progressive functional form of acute renal failure. It occurs as a complication of advanced liver disease and is associated with significant mortality [1]. Recurrent episodes of acute kidney injury are common in end-stage cirrhosis. Evaluation of kidney function and identification of kidney changes in patients with cirrhosis is crucial in predicting reversibility, treatment, and prognosis. In patients with cirrhosis, currently available noninvasive tools to assess renal function are inaccurate. Several novel biomarkers have recently emerged to help identify HRS from acute tubular necrosis (ATN) and enhance management and outcome.

Discussion

HRS was initially defined in 1996 by the International Ascites Club (IAC) Table 1 [2]. However, the IAC criteria had several limitations including a serum creatinine (SCr) of ≥1.5 mg/dL. This creatinine cut off excludes physiological fluctuations and a true estimate of glomerular filtration rate (GFR) [3]. In 2015, the IAC proposed a new definition of acute kidney injury (AKI) in cirrhosis. AKI is defined as the abrupt loss of kidney function with a subsequent increase of 0.3 mg/dl in SCr in 48 hours or a 50% increase from baseline within 7 days [4]. Data suggest that early detection of kidney failure may increase the probability of kidney regression and reduce mortality rates [5].

In patients with cirrhosis, SCr levels should be interpreted with caution. Creatinine is a marker of filtration and can be used to detect a decline in kidney function, but lacks specificity. Serum creatinine in patients with cirrhosis may be influenced by increased volume of distribution, reduced production of endogenous creatinine, muscle wasting, medications and elevated bilirubin [3,6]. To date, the diagnosis of HRS is based solely upon clinical criteria and more discriminating tests are required to guide the allocation of treatment and to help predict progression of AKI. In this review, we discuss novel biomarkers of renal function that can improve diagnostic accuracy.

Nearly 30 biomarkers of kidney tubular injury have been investigated for early detection, differential diagnosis and prognosis of AKI in cirrhosis [7]. Ischemia-related events are a common mechanism in AKI that can lead to tubule injury. Cystatin C is a low molecular weight protein that is independent of sex, gender, inflammatory condition, and malignancy [8]. Studies have suggested that serum cystatin C is a more sensitive marker of GFR than SCr since it freely crosses the glomerular membrane to be reabsorbed and metabolized in the proximal tubular cells, without being eliminated [7]. Cystatin C has been also shown to be a predictor of HRS and mortality in patients with liver cirrhosis and ascites [9].

Other tubular proteins unregulated by injury include Neutrophil Gelatinase-Associated Lipocalin (NGAL), Kidney injury molecule 1 (KIM-1), and Liver-type fatty acid binding protein (L-FABP) [7-10]. In animal models, NGAL is released in the urine following an ischemic or nephrotoxic insult. Human studies suggest that NGAL measurements either in urine and serum may differentiate acute tubular necrosis from type 1 HRS, pre-renal azotemia or chronic kidney disease [11]. Two recent studies suggest that elevated urinary NGAL is predictive of early mortality in cirrhotic patients with AKI [12,13]. However, NGAL lacks specificity as it is also elevated in other acute and chronic inflammatory conditions.

Kidney injury molecule 1 (KIM-1) is a transmembrane protein and a marker of proximal tubular injury [14]. Few studies have monitored KIM-1 in patients with cirrhosis and AKI. However, KIM-1 levels have been shown to predict the development of HRS in patients with advanced cirrhosis. Interestingly, KIM-1 levels are not as accurate as NGAL, osteopontin, albumin and trefoil factor 3 (TTF3) for the diagnosis of ATN in patients with cirrhosis [15].
Liver-type fatty acid binding protein (L-FABP) is a small protein that is also expressed in the proximal tubular epithelium in humans [16]. In animal models, urinary L-FABPs elevated in kidney disease with tubule-interstitial damage [15]. L-FABP has been evaluated in the diagnosis of AKI and sepsis complicated by AKI [5]. The prognostic utility of L-FABP as a biomarker in HRS needs to be further elucidated.

Interleukin-18 (IL-18) is a marker released by recruited inflammatory cells [16]. IL-18, in addition to other biomarkers (KIM-1 and L-FABP), has been associated with progression of AKI and mortality in patients with cirrhosis. A recent meta-analysis showed that urine levels of IL-18 and NGAL are elevated in ATN compared to non-ATN AKI [17]. IL-18 has also been described as a prognostic tool in patients with cirrhosis.

Activation and up regulation of toll like receptors (TLRs) may play a role in HRS. In AKI, necrotic tubular cells release TLR legends which could activate other tubular cells and other immune molecules in the kidney. High levels of TLR-4 have been found in patients with cirrhosis and AKI suggesting a potential role of TLR-4 as a mediator of renal injury [18]. Further studies are needed to determine if urinary TLR-4 could help to diagnose AKI.

Other kidney biomarkers including osteopontin have been shown to be predictive of early mortality in intensive care unit patients with AKI. Osteopontin is a cytokine that is mainly expressed in the proximal and distal tubular cells [19]. Serum osteopontin, NGAL and TFF-3 have been found to be associated with acute on chronic liver failure. Moreover, it has been linked to a 3-month survival in patients with acute decomposition of cirrhosis [15].

### Table 1: Initial diagnostic criteria for hepatorenal syndrome-1996.

| Diagnostic Criteria for Hepatorenal Syndrome |
|---------------------------------------------|
| Chronic or acute liver disease with advanced hepatic failure and portal hypertension |
| Low GFR as indicated by serum creatinine > 1.5mg/dL or 24-hour creatinine clearance < 40 mL/min |
| Absence of shock, on-going bacterial infection, and current or recent treatment with nephrotoxic drugs and absence of gastrointestinal fluid losses or renal fluid losses. |
| No sustained improvement in renal function (decrease in serum creatinine ≤ 1.5mg/dL or increase in creatinine clearance to ≥40 mL/min) following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline. |
| Proteinuria < 500 mg/dL and no sonographic evidence of obstructive uropathy or parenchymal renal disease. |

*RBCs-Red Blood Cells, HPF-High Power Field.

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**Conclusion**

Kidney impairment in cirrhosis occurs due to both systemic vasodilatation and inflammation leading to chronic kidney vasoconstriction. Currently available noninvasive tools to assess renal function are inaccurate in patients with cirrhosis. Novel kidney biomarkers (cystatin C, NGAL, IL-8, L-FABP and KIM-1) may be able to predict progression and mortality in patients with AKI and may be able to diagnose AKI earlier than a change in a creatinine or estimated GFR. As additional markers become clinically available, clinicians should combine functional and structural biomarkers to more precisely elucidate the etiology and course to initiate prompt therapy in AKI in cirrhosis.
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