Review

JOURNAL OF HEPATOLOGY

Kidney biomarkers in cirrhosis

Claire Francoz[1,2,3,4,*], Mitra K. Nadim[5], François Durand[1,2,3,4]

Summary

Impaired renal function due to acute kidney injury (AKI) and/or chronic kidney diseases (CKD) is frequent in cirrhosis. Recurrent episodes of AKI may occur in end-stage cirrhosis. Differential diagnosis between functional (prerenal and hepatorenal syndrome) and acute tubular necrosis (ATN) is crucial. The concept that AKI and CKD represent a continuum rather than distinct entities, is now emerging. Not all patients with AKI have a potential for full recovery. Precise evaluation of kidney function and identification of kidney changes in patients with cirrhosis is central in predicting reversibility. This review examines current biomarkers for assessing renal function and identifying the cause and mechanisms of impaired renal function. When CKD is suspected, clearance of exogenous markers is the reference to assess glomerular filtration rate, as creatinine is inaccurate and cystatin C needs further evaluation. Recent biomarkers may help differentiate ATN from hepatorenal syndrome. Neutrophil gelatinase-associated lipocalin has been the most extensively studied biomarker yet, however, there are no clear-cut values that differentiate each of these conditions. Studies comparing ATN and hepatorenal syndrome in cirrhosis, do not include a gold standard. Combinations of innovative biomarkers are attractive to identify patients justifying simultaneous liver and kidney transplantation. Accurate biomarkers of underlying CKD are lacking and kidney biopsy is often contraindicated in this population. Urinary microRNAs are attractive although not definitely validated. Efforts should be made to develop biomarkers of kidney fibrosis, a common and irreversible feature of CKD, whatever the cause. Biomarkers of maladaptative repair leading to irreversible changes and CKD after AKI are also promising.

Keywords: Cirrhosis; Renal dysfunction; Acute kidney injury (AKI); Chronic kidney disease (CKD); Biomarkers.

Received 22 November 2015; received in revised form 10 May 2016; accepted 18 May 2016

[1]*Hepatology and Liver Intensive Care, Hospital Beaujon, Clichy, France*;
[2]*University Paris VII Diderot, Paris, France;*
[3]*INSERM U1149, Paris, France*;
[4]*Département Hospitalo-Universitaire UNITY, Clichy, France*;
[5]*Division of Nephrology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*

Introduction

For many years, it has been clearly established that kidney function plays a major role in the prognosis of cirrhosis [1,2]. Hepatorenal syndrome (HRS), which is functional in nature, is a characteristic feature of advanced cirrhosis [3] although it does not represent the only cause of acute kidney injury (AKI) in this context [4]. Several mechanisms are involved in the development of HRS, including circulatory changes [5], kidney factors and systemic inflammation [6].

Hypoperfusion is a central mechanism in most patients with advanced cirrhosis and HRS [7]. In the early stages of compensated cirrhosis splanchnic vasodilation due, at least in part, to the release of nitric oxide (NO) is moderate. Decreased systemic vascular resistance resulting in a reduction in arterial pressure is balanced by increased cardiac output to maintain adequate perfusion of the kidney (Fig. 1). Glomerular filtration rate (GFR) is preserved. In advanced stages of cirrhosis, as splanchnic vasodilation intensifies, systemic vasoconstriction systems, namely renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS) and arginine vasopressin (AVP), are activated, resulting in renal sodium and water retention [4,7]. Indeed, major splanchnic vasodilatation is associated with a state of decreased effective blood volume. At the most advanced stages of cirrhosis, renal vasoconstriction can no longer be balanced by increased cardiac output and renal blood flow markedly decreases [8]. The so called cirrhotic cardiomyopathy may contribute to decreased renal perfusion [8].

Abbreviations: HRS, hepatorenal syndrome; AKI, acute kidney injury; NO, nitric oxide; RAAS, renin-angiotensin-aldosterone system; SNS, sympathic nervous system; AVP, arginin vasopressin; PAMPs, pathogen-associated molecular patterns; PRRs, patterns recognition receptors; TNF-α, tumor necrosis alpha; IL-6, interleukine 6; SIRS, systemic inflammatory response syndrome; TLR, toll-like receptor; ATN, acute tubular necrosis; NASH, non-alcoholic steatosis hepatitis; CKD, chronic kidney disease; GFR, glomerular filtration rate; KDIGO, kidney disease improving global outcome; SCr, serum creatinine; MDRD, modified diet in renal disease; SLK transplantation, simultaneous liver and kidney transplantation; BUN, blood urea nitrogen; β2M, beta-2 microglobulin; RIFLE, risk, injury, failure, loss, end-stage kidney disease; AKIN, acute kidney injury network; UO, urinary output; ADQI, acute dialysis quality initiative; ICA, International Club of Ascites; FE_{Na}, fractional excretion of filtered sodium; FE_u, fractional excretion of urea; NGAL, neutrophil gelatinase-associated lipocalin; IL-18, interleukin 18; KIM-1, kim injury molecule 1; L-FABP, liver-type fatty acid-binding protein; TFF3, trefoil factor 3; MCP-1, monocyte chemoattractant protein-1; TIMP1, tissue inhibitor of metalloproteinase-1; miRNA and MiR, microRNA;

EMT; epithelial-mesenchymal transition; TGF β1, transforming growth factor beta 1; suPAR, soluble urokinase-type plasminogen activator receptor; MRI, magnetic resonance imaging.

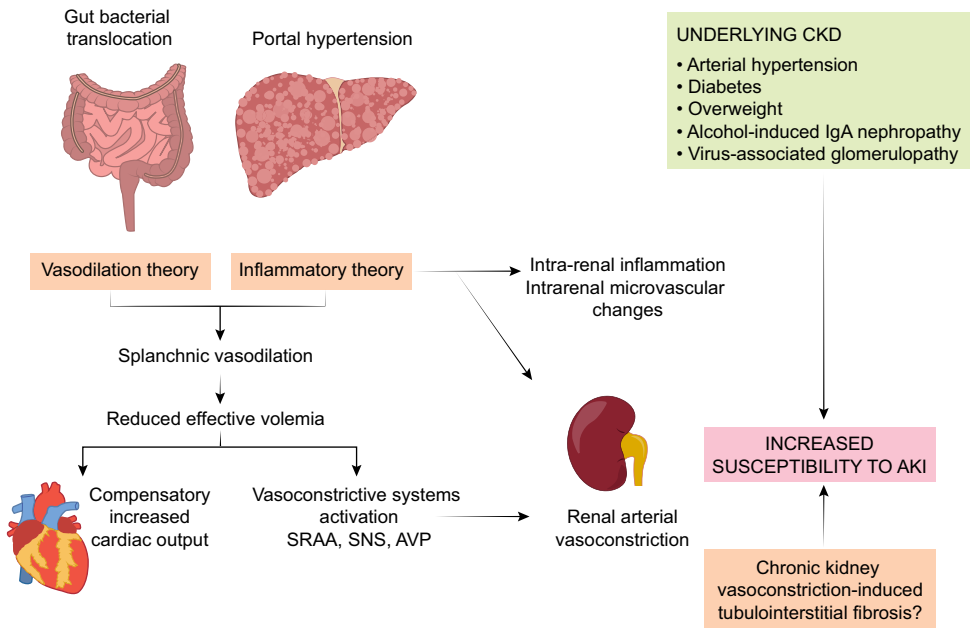

Fig. 1. Mechanisms contributing to impaired renal function in cirrhosis. In end-stage liver diseases, several factors contribute to increase susceptibility of the kidney to AKI. Both vasodilation secondary to portal hypertension and systemic inflammation induced by gut bacterial translocation tend to induce renal arterial vasoconstriction, due to the activation of vasoconstrictive systems (SRAA, SNS and AVP) in response to decreased effective blood volume. Intrarenal inflammation induces intrarenal microvascular changes resulting in decreased GFR with an imbalance between preglomerular and postglomerular resistance (which corresponds to both preglomerular and post glomerular vascular tone) as well as impaired renal microcirculation affecting tubular and glomerular function. Underlying CKD due to associated comorbidities eventually increases the risk for AKI. Consequences of prolonged kidney vasoconstriction are not clearly elucidated but may induce tubular interstitial fibrosis and further increase the risk of AKI.

Kidney factors involve mediators that are protective of kidney function under normal conditions. In advanced cirrhosis, the levels of the vasodilatator prostaglandins E2 and I2 are increased to compensate the activation of vasoconstrictor systems [9]. This is possibly the reason why administration of non-steroidal anti-inflammatory drugs in patients with advanced cirrhosis frequently precipitates AKI [10]. In addition to changes in systemic hemodynamics, alterations of intrarenal hemodynamics along with abnormal autoregulation of renal blood flow contribute to decreased GFR [11].

Circulatory changes resulting from portal hypertension and kidney factors do not explain *per se* all the changes observed during HRS and other phenotypes of AKI. Recently, a theory of systemic inflammatory multiorgan disease has emerged that challenges the vasodilation theory [12]. Sepsis is a common trigger of AKI in patients with cirrhosis. In patients without cirrhosis, there is increasing evidence that sepsis-associated AKI with systemic inflammation results from the combination of hemodynamic, inflammatory and immune mechanisms [13]. During severe sepsis, AKI may be unrelated to decreased renal blood flow [14]. Indeed, sepsis-associated AKI can occur in the context of hyperdynamic circulation with normal or even increased renal blood flow [14–16]. In patients with preserved renal blood flow, intrarenal microvascular changes resulting in decreased GFR may include an imbalance between preglomerular and postglomerular resistance (which corresponds to both preglomerular and post glomerular vascular tone) as well as impaired renal microcirculation affecting tubular and glomerular function [14]. Finally, it has been hypothesized that sepsis could lead to internal redistribution of blood flow out of the cortex and inducing corticomedullary junction ischemia with subsequent tubular injury [14].

In most clinical situations, hemodynamic abnormalities are accompanied by or preceed systemic and/or renal inflammatory responses leading to abnormal changes in microcirculation and significant reduction of perfused capillaries [14].

Even in the absence of bacterial infection, cirrhosis is associated with systemic inflammation, which is correlated to the severity of liver disease and portal hypertension [12]. The main mechanism is the translocation of bacteria and/or pathogen-associated molecular patterns (PAMPs) from the gut. Translocation induces a wide spectrum of genes that encode molecules responsible for inflammation via specific receptors (pattern recognition receptors or PRRs) [12]. Inflamma-

Key point

Kidney impairment in cirrhosis is due to both systemic vasodilation and inflammation, leading to chronic kidney vasoconstriction.

* Corresponding author. Address: Service d'Hépatologie, Hôpital Beaujon, 100 Boulevard du Général Leclerc, 92110 Clichy, France. Tel.: +33 1 40 87 50 91; fax: +33 1 40 87 44 55.
E-mail address: claire.francoz@bjn.aphp.fr (C. Francoz).