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Renal dysfunction in cirrhosis is not just a vasomotor nephropathy

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The short-term mortality of cirrhotic patients who develop renal dysfunction remains unacceptably high, and as such the treatment of this condition is an unmet need. Although features of kidney injury are well recognized in these patients, the pathophysiology is complex and not completely understood. Improved understanding of the pathophysiological mechanisms involved in renal dysfunction occurring on a background of cirrhosis is key to developing effective treatment strategies to improve survival. Renal dysfunction due to hepatorenal syndrome (HRS) is characteristic of cirrhosis. Our current understanding is that HRS is functional in nature and occurs as a consequence of hemodynamic changes associated with portal hypertension. However, there is evidence in the literature suggesting that, histologically, the kidneys are not always normal in the vast majority of patients who present with renal dysfunction on the background of cirrhosis. Furthermore, there is emerging data implicating nonvasomotor mechanisms in the pathophysiology of renal dysfunction in cirrhosis. This mini-review aims to present the evidence suggesting that factors other than hemodynamic dysregulation have an important role in the development of this major complication for patients with progressive cirrhosis.

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Renal dysfunction is a common manifestation of advanced cirrhosis that is associated with significant mortality and morbidity. Although acute renal dysfunction in cirrhosis can be due to a number of causes such as hypovolemia and nephrotoxins, hepatorenal syndrome (HRS) is the most characteristic. However, it is becoming increasingly evident that renal dysfunction in cirrhosis is a heterogeneous condition, and some patients who were previously diagnosed with HRS actually have renal dysfunction associated with infection/inflammation, which is likely to have a different pathophysiological basis.

An estimated 11% of patients with advanced cirrhosis and refractory ascites develop HRS.[1] This condition is traditionally ascribed to functional renal failure in patients with chronic liver disease associated with no significant morphologic changes in renal histology and with largely preserved tubular function.[2,3] This is because kidneys from patients with HRS have been reported to recover function post liver transplantation,[4] and they have also been successfully used as renal allografts for kidney transplantation.[5] However, only a small proportion of patients who develop renal dysfunction in association with cirrhosis suffer from HRS.

Two types of HRS are recognized. Type 1 HRS occurs in an acute setting, with a rapidly progressive decline in renal function, which is characterized by a doubling of the initial creatinine to a level $>226\,\mu mol/l$ (2.5 mg/dl) in <2 weeks.[6] Untreated, type 1 HRS is associated with a mortality rate of 80% at 2 weeks.[7] Type 2 HRS follows a more progressive course with a moderate rise in serum creatinine levels to a level $>133\,\mu mol/l$ (1.5 mg/dl).[6] Type 2 HRS has a median survival of 4–6 months.[7] In addition to the above definitions for HRS 1 and 2, in 2007, the International Ascites Club proposed a revised version of the original criteria, and this is shown in the table below (Table 1).

As is evident from the above criteria, the diagnosis of HRS requires a set of stringent criteria that rely on serum creatinine levels. Evidence suggests that a smaller increase in serum creatinine, insufficient to make a diagnosis of HRS, is also associated with a poor prognosis in patients with cirrhosis.[8] It is possible that the severity of renal dysfunction is underestimated by the measurement of serum creatinine levels, as it is most commonly measured using a modified colorimetric Jaffe assay, which is prone to interference from

Table 1 | Diagnostic criteria for hepatorenal syndrome in cirrhosis (Adapted from Salerno *et al.*[6])

Cirrhosis with ascites
Serum creatinine >133 μmol/l (1.5 mg/dl)
No improvement of serum creatinine (decrease to a level of ⩽133 μmol/l) after at least 2 days with diuretic withdrawal and volume expansion with albumin
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease, as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field), and/or abnormal renal ultrasonography

bilirubin and other compounds.[9,10] In addition, patients with cirrhosis often have muscle wasting, reduced hepatic creatine synthesis, and increased renal tubular creatinine secretion.[11] As such, smaller increases in serum creatinine reflect much larger changes in renal function than would be anticipated from the rises in serum creatinine. For this reason, there has been a move to redefine HRS to fall in line with the Acute Kidney Injury Network (AKIN) criteria for acute renal failure,[12] which is more sensitive for the early detection of smaller increases in serum creatinine.[13] Several studies have been carried out using the AKIN criteria in a cirrhotic population, but there is a lack of consensus as to whether the AKIN or classical HRS criteria best predict prognosis in cirrhotic patients with acute renal dysfunction.[14–16]

Although the classical diagnostic criteria for HRS now includes patients with HRS secondary to infection (but not septic shock), it is likely that patients with renal dysfunction or HRS associated with infection are distinct from patients with 'classical HRS' (HRS not associated with infection).[17] A recent study by Barreto *et al.*[17] describing outcomes in patients diagnosed with HRS associated with infection showed that in approximately two-thirds of patients this condition is not reversible with standard of care for HRS using terlipressin and albumin, indicating a different pathophysiological underlying mechanism of disease.[12] In addition, patients with renal dysfunction associated with infection have been shown to have higher levels of urinary biomarkers of tubular damage compared with patients with classical HRS.[13] It therefore stands to reason that different pathophysiological mechanisms may be responsible for the development of renal dysfunction in the patients with classical HRS compared with patients with renal dysfunction associated with infection.[18]

'TRADITIONAL' VIEW OF HRS

In 1970, Epstein *et al.*[19] demonstrated using renal angiography that in cirrhotic patients with renal failure, the main pathophysiological feature is marked vasoconstriction of the renal vasculature associated with a redistribution of blood flow away from the renal cortex. The hypothesis is that vasoconstriction of the renal circulation, which occurs in HRS, develops as a result of the hemodynamic dysregulation associated with portal hypertension. In this setting, the

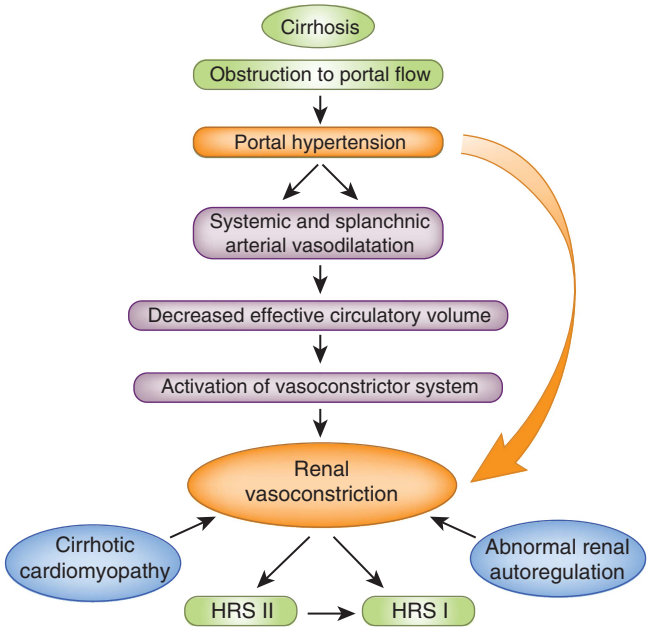

Figure 1 | The vasodilatation hypothesis of hepatorenal syndrome. (Adapted from Wong *et al.*[13]). In cirrhosis, portal hypertension leads to splanchnic and systemic vasodilatation, which results in a decrease in effective arterial volume. This in turn leads to the activation of vasoconstrictor systems leading to a reduction in renal blood flow. An impairment of cardiac function (cirrhotic cardiomyopathy) and abnormal renal blood flow autoregulation further contributes to renal hypoperfusion, resulting in HRS.

increase in shear stress in the splanchnic vascular bed leads to overproduction of nitric oxide and other potent vasodilators, thus resulting in splanchnic vasodilatation.[20] The consequence of this is a decrease in effective arterial volume, which leads to severe renal vasoconstriction via activation of the renin–angiotension–aldosterone system, causing renal hypoperfusion.[13,21] Impaired cardiac function in patients with decompensated cirrhosis leads to further arterial underfilling, decreased mean arterial pressure, and further impairment of renal blood flow and function.[22] In addition, activation of the sympathetic nervous system through a hepatorenal reflex arc also contributes to the pathophysiology of HRS.[23] There is an altered autoregulation of renal blood flow in patients with HRS (Figure 1).[24]

The evidence in the literature implicating the above factors in the pathophysiology of HRS is strong, as increasing the mean arterial pressure in patients with HRS by using splanchnic vasoconstrictors and albumin improves renal function.[25,26] Furthermore, a recent pilot study showed that patients with diuretic-refractory ascites, who have the highest risk of developing HRS, have lower renal plasma flow and higher right main kidney and arcuate artery resistive indices compared with patients without ascites.[27] However, this study only involved 10 patients and was therefore underpowered for any statistical inferences to be made. Clearly, there is a need to investigate whether these findings are reproducible in a larger cohort.