Hyponatremia in Cirrhosis—Pathogenesis, Treatment, and Prognostic Significance

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Cirrhosis is characterized by systemic and splanchnic vasodilation that leads to excessive nonosmotic secretion of vasopressin (antidiuretic hormone). Hyponatremia is a common electrolyte abnormality in advanced liver disease that results from the impaired ability of the kidney to excrete solute-free water that leads to "dilutional" hyponatremia—water retention disproportionate to the retention of sodium. Hyponatremia in liver diseases carries the prognostic burden, correlates with the severity of cirrhosis, and, in recent studies, has also been implicated in the pathogenesis of hepatic encephalopathy. The current treatment options are limited to conventional therapies like fluid restriction, and the outcomes are unsatisfactory. Although currently available vasopressin (V2 receptors) antagonists have been shown to increase serum sodium concentrations and improve ascites control, their role in the treatment of hyponatremia in liver disease patients remains questionable because of adverse effect profiles, high cost, and poor data on long-term mortality benefits. More information is needed to argue the benefits vs risks of short-term use of vaptans for correction of hyponatremia especially just hours-to-days before liver transplant.

Key Words: Hyponatremia, Cirrhosis, Vasopressin, Vaptans, Treatment

INTRODUCTION

Hyponatremia (serum Na <130 mmol/L) is a well-identified complication of advanced liver disease with prevalence rate up to 22% in patients with decompensated cirrhosis.[1,2] Studies over the last 60 years have refined our understanding of the complex hemodynamic changes that occur in patients with cirrhosis leading to hyperdynamic circulation and hyponatremia. The development of hyponatremia correlates with the severity of liver disease and predicts poor outcomes not only in patients with cirrhosis but also in post-liver transplant (LT) patients. This review will summarize the current understanding of the pathogenesis, treatment, and prognostic significance of hyponatremia in liver disease.

PATHOGENESIS

Hyponatremia in cirrhosis results from the impaired ability of the kidney to excrete solute-free water despite a state in which total body sodium is markedly increased.[3,4] Although hyponatremia in cirrhosis can occasionally result from hypovolemic states, our discussion will focus on hypervolemic hyponatremia. The hemodynamic disturbances in cirrhosis cause systemic vasodilation, activating 3 compensatory neurohormonal mechanisms to restore effective circulatory volume—activation of sympathetic nervous system and renin-angiotensin system and nonosmotic release of antidiuretic hormone (ADH) (Fig 1).

Kowalski and Abelmann[5] noted that cirrhotics have high cardiac output resulting from peripheral vascular bed dilatation, suggesting a hyperdynamic circulatory state. Many peptides have been studied to identify the agent responsible for this phenomenon, with nitric oxide being the most promising.[6,7] Both in vitro[8,9] and in vivo[10,11] studies have demonstrated vasodilatory effects of NO on the systemic and splanchnic circulation, and competitive inhibition of NO biosynthesis in cirrhotic rats increased arterial pressure and glomerular filtration rate.[12]

Synthesis of NO by activation of inducible nitric oxide synthase (INOS) present in endothelial and smooth muscle cells in response to bacterial endotoxins and various cytokines is a well-known phenomenon.[13,14] The intestinal micro-organisms and endotoxins bypass portal circulation in cirrhosis and enter systemic circulation—leading to endotoxemia.[15,16] Studies have shown high levels of circulating endotoxins in both portal and peripheral circulation of cirrhosis patients[17] and a significant association between high levels of plasma endotoxins and NO production.[18] Thus, endotoxemia and NO synthesis are believed to be the 2 major factors responsible for widespread systemic vasodilatory state in cirrhotics.

The overall effect of this widespread arterial vasodilation is activation of renin-angiotensin system, sympathetic nervous system, and ADH.[19-21] Contrary to the previous "underfilling" hypothesis (in which ascites formation causes hypovolemia leading to sodium and water retention)[22] and "overflow" hypothesis (primary sodium and water retention lead to ascites),[23] the above concept of "peripheral arterial vasodilation" as the initial event leading to sodium and water retention was first proposed by Schrier and colleagues[24] in 1988. In early compensated cirrhosis (without ascites), these mechanisms cause transient sodium and water retention restoring the intravascular compartment. Thus, elevation of plasma renin, norepinephrine, and vasopressin may not always be seen.[25-27] As cirrhosis decompensates, this sodium and water retention is no longer able to restore the effective arterial blood volume leading to a state of persistent elevation of plasma renin, aldosterone, norepinephrine, and ADH; severe peripheral vasodilation; high cardiac output; and ascites formation.[24] The decline in kidney

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perfusion and GFR in this stage of cirrhosis correlates with the degree of rise in plasma norepinephrine and renin.[28] Imaging of kidney vasculature has demonstrated greater compromise in kidney blood flow in cirrhotics with ascites compared with those without ascites.[29] About 25% of decompensated cirrhotics have normal kidney perfusion likely from nonpersistently elevated levels of vasoconstrictors and compensatory stimulation of vasodilator prostaglandins in the kidney.[28,30]

Hyponatremia in cirrhosis develops from an impaired ability to excrete solute-free water (C_{H_2O}).[31] Kidneys normally respond to a water load by excreting large volumes of dilute urine.[32] This ability to regulate C_{H_2O} is impaired in cirrhosis and correlates with the severity of disease.[33] The 3 main factors that regulate C_{H_2O} are the rate of fluid delivery to the thick ascending limb (TAL) of loop of Henle (which is determined by GFR and proximal tubular sodium and water absorption), sodium chloride absorption in TAL, and vasopressin-dependent water reabsorption in the collecting tubule. The impairment in C_{H_2O} can theoretically result from a disturbance in any of these 3 factors. The relation between elevated plasma ADH and impaired C_{H_2O} in cirrhotic patients was first demonstrated by Bichet and colleagues.[34] In this study, plasma ADH concentrations were not only elevated at baseline in cirrhotics but were not suppressed after free water load unlike controls where water load suppressed ADH concentrations to undetectable levels.

The stimulus for increased secretion of ADH in cirrhosis is decreased effective arterial volume,[27,35] which has been shown experimentally.[36-38] Claria and colleagues[39] demonstrated a significant decrease in mean arterial pressures in cirrhotic rats treated with either an ADH-V1-receptor antagonist or an angiotensin-II inhibitor (saralasin). The decrease in mean arterial pressures was significantly greater (twice) in cirrhotic rats treated with both ADH-V1 receptor and saralasin. These results clearly solidified the concept of ADH hypersecretion in response to low arterial pressures in cirrhosis.

C_{H_2O} is also dependent on the rate of sodium and water delivery to the TAL. Evidence of increased fluid resorption in proximal tubule in cirrhotic rats[40] and reduced clearance of lithium in the kidney (which estimates distal delivery)[41] suggests the role of reduced delivery of filtrate to TAL in impairment of C_{H_2O} in cirrhosis. Conversely, maneuvers that improve effective central volume (like head-out total body water immersion and insertion of LeVeen peritoneovenous shunt), thus leading to increased delivery of glomerular filterate to TAL, have also been shown to improve C_{H_2O} in cirrhotics despite elevated levels of plasma ADH.[35,42] Overall, a decline in GFR (which also increases proximal sodium resorption) further decreases distal delivery of fluid, thus hampering C_{H_2O}.[43]

Decreased kidney prostaglandin synthesis may also contribute to the decreased C_{H_2O} in cirrhotics. PGE2 is known to decrease the action of ADH by inhibiting cyclic adenosine monophosphate generation (necessary for aquaporin channel insertion in the luminal membrane of collecting ducts cells) and by inhibiting sodium and urea absorption in the TAL and distal collecting duct, respectively (reducing renal interstitial tonicity). Cirrhotic patients able to maintain their C_{H_2O} have high urinary excretion of PGE2,[30] and inhibition of prostaglandin synthesis in the kidney (by non-steroidal anti-inflammatory drugs) decreases C_{H_2O} despite similar levels of plasma ADH.[28,44]

CLINICAL SUMMARY

- The decision to treat hyponatremia in cirrhosis should be based on the patient's clinical and neurologic status rather than absolute serum sodium levels, especially in mild hyponatremia.
- Although studies emphasize hyponatremia as an important risk factor for impaired early post-liver transplant outcome, the potential benefits of treating pre-liver transplant hyponatremia still need to be evaluated in prospective studies.
- V2-receptor antagonists appear promising in treatment of hypervolemic hyponatremia in cirrhosis and, in recent studies, have not reported a significant difference in adverse events including kidney failure, liver injury, or gastrointestinal bleeding using vaptans compared with placebo.
- In those with cirrhosis the established benefits of V2-receptor antagonists in raising serum sodium concentrations should be tested in further studies for long-term mortality and morbidity benefits.

PROGNOSTIC IMPLICATIONS OF HYPONATREMIA IN CIRRHOSIS

Hyponatremia is not only a predictor of complications of cirrhosis like hepatic encephalopathy (HE) and infection rates but also a predictor of mortality in liver disease.

Hyponatremia and Encephalopthy

The effects of cellular swelling caused by movement of water into cells as a result of hyponatremia are most evident in the brain because of the fixed skull size. Besides serum sodium concentration, the most important factor determining the severity of neurologic symptoms is the rate of fall in serum sodium concentration.[45] Neurons limit the water entry into the cells by extruding intracellular solutes to decrease intracellular osmolality. Initially, cations like potassium are lost from neurons, followed by extrusion of small organic osmolytes like myoinositol (MI) and glutamine.[46] Low levels of cerebral myoinositol in cirrhotics support its role in adaptive mechanisms against hyponatremia.[47]

Hyponatremia has been implicated in the pathogenesis of HE. The combination of astrocyte swelling along with adaptive loss of intracellular cations and amino acids results in inhibition of metabolic functions of astrocytes and neurotransmitter release.[48-50] Hyperammonemia also causes astrocyte swelling by increasing intracellular glutamine synthesis.[51] Magnetic resonance imaging has shown cerebral edema with HE.[52,53] Thus, it not surprising that hyponatremia strongly correlates