Role of endotoxemia in causing renal dysfunction in cirrhosis

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ABSTRACT

Renal failure is a challenging problem in patients with cirrhosis since mortality increases with worsening renal function, hence the inclusion of serum creatinine in calculating the Model for End-Stage Liver Disease score for liver transplant evaluation. Among the various causes, infection is the leading etiology of mortality associated with cirrhosis. Bacterial infection frequently precipitates renal failure in patients with cirrhosis with the reported prevalence around 34%. Patients with cirrhosis are at increased risk of infections due to impaired immunity and increased gut permeability leading to bacterial translocation in the setting of portal hypertension. One of the most feared complications of severely decompensated liver and renal failure is hepatorenal syndrome, of which liver transplant may be the only available treatment. Furthermore, in those with spontaneous bacterial peritonitis and urinary tract infection, progressive renal failure occurs despite resolution of infection. Thus, the effects of endotoxemia on renal function in cirrhosis have become a major focus of research. The mechanisms of the damaging effects of endotoxin on renal function are complex but, in essence, involve dysregulated inflammation, circulatory dysfunction, poor clearance of endotoxin burden, as well as vasomotor nephropathy. In this article, we will review the mechanisms of endotoxemia-induced renal dysfunction in the setting of cirrhosis through the effects on renal blood flow, renal vascular endothelium, glomerular filtration rate, and tubular function.

INTRODUCTION

Cirrhosis, the most advanced consequence of chronic liver disease, has become a significant health concern given the increased morbidity and mortality from decompensated hepatic function.[1] Between 1999 and 2016, annual deaths secondary to cirrhosis in the USA increased by 65%.[1] Furthermore, models have projected the incidence of deaths from non-alcoholic-related cirrhosis to increase by 178% by 2030.[1] The mechanism by which decompensated cirrhosis creates such complications stems from disruption in systemic homeostasis that leads to widespread effects on hepatic function and other organs. Specifically, hepatic and renal functions are closely related, and, in the setting of cirrhosis significant renal impairment can occur. Insults to both systems lead to detrimental outcomes, as seen in hepatorenal syndrome which occurs in patients with cirrhosis, refractory ascites, and compromised renal function that, at its worst, can only be resolved with liver transplant.[2]

Among the various causes, bacterial infection is the leading etiology of complications associated with cirrhosis and frequently precipitates renal failure with the reported prevalence around 34%.[3 4] The majority of infections are due to intestinal translocation of Gram-negative bacteria in the setting of spontaneous bacterial peritonitis.[5] Renal failure is evaluated to be caused by bacterial infection when either acute or pre-existing renal injury appears or worsens in the setting of infection.[3] Acute kidney injury is defined as increased serum creatinine of at least 0.3 mg/dL if it occurred within 48 hours or 1.5 times from baseline within 7 days.[6] Of note, serum creatinine may not accurately reflect glomerular filtration rate (GFR) in patients with cirrhosis due to muscle wasting leading to falsely low levels, increased tubular secretion of creatinine, dilution due to increased distribution volume, and elevated bilirubin which can affect accurate measurement of creatinine.[7]

Understanding the effects of endotoxemia at the level of renal blood flow, GFR, renal vasculature, and tubular function will be crucial to identify potential targets of intervention to mitigate the complications of acute renal failure secondary to bacteremia in patients with cirrhosis.

CIRRHOSIS AND ETIOLOGY OF ENDOTOXEMIA

Portal and peripheral blood endotoxin levels have been found to be higher in patients with cirrhosis when compared with healthy controls.[8 9] The etiology of endotoxemia in decompensated cirrhosis is multifactorial and related to impaired defense barriers within the intestinal lumen leading to systemic-wide complications. In the normal condition, the integrity of the intestinal lumen depends on a mechanical barrier consisting of tight gap junctions, an immune barrier (comprising secretory IgA, intramucosal lymphocytes, mesenteric lymph nodes) as well as systemic

host immunity.[9–12] Patients with cirrhosis have structural changes of the intestinal mucosa, such as widening of intercellular spaces, loss of tight junctions, and defects in the mucosal immune system with reduction in secretory IgA leading to the translocation of gut bacteria into the circulation.[13–16] In addition, endotoxemia leads to alterations in intestinal motility and a decrease in luminal bile acid, which is a suppressor of bacterial overgrowth; hence, the colonization of bacteria with high translocation capability was observed in locations with low bacterial counts such as the proximal small intestine.[16 17] Finally, decompensated cirrhosis can promote a predominantly immunodeficient state which, in the setting of systemic inflammation, can progress to multiorgan failure, septic shock, and death.[18]

Kupffer cells within the liver sinusoids express toll-like receptors, which play an important role in the phagocytosis and clearance of gut-derived bacterial endotoxins such as lipopolysaccharide (LPS).[16 19] Hepatocytes similarly express toll-like receptor-4 (TLR-4) receptors responsive to LPS, and, thus, are also responsible in the uptake and removal of LPS.[16 20] However, with large amounts of intestinal bacterial translocation, the functional capacity of the liver can become overwhelmed and endotoxin cannot be effectively removed.[10] Additionally, increased systemic activation of neutrophils by mediators like LPS results in inappropriate sequestration of leukocytes in hepatic microvasculature. As a result, this can lead to impaired sinusoidal perfusion and subsequent impaired Kupffer cell function.[21] Endotoxemia also leads to increased levels of tumor necrosis factor α (TNFα), which binds to TNF receptor on Kupffer cells and inhibits phagocytosis.[22] Ultimately, in the setting of cirrhosis, dysfunctional Kupffer cells and hepatocytes lead to defective hepatic clearance of LPS, which allows LPS to enter systemic circulation.[16 20 23]

MECHANISMS OF ENDOTOXEMIA-INDUCED RENAL DYSFUNCTION IN CIRRHOSIS

Endotoxemia and renal blood flow

While nitric oxide (NO) is thought to have a vasodilatory effect to help increase renal blood flow and prevent kidney injury, an excessive production of NO can adversely affect kidney function.[24] In the presence of endotoxemia, increased levels of NO secondary to activated inducible nitric oxide synthase (iNOS) lead to systemic vasodilation and organ hypoperfusion.[25] LPS-injected rats had a fall in cortical and medullary perfusion.[26] Interestingly, when they were treated with NG-methyl-L-arginine, an NO synthase inhibitor, renal function improved with greater insulin clearance.[26] NO has been evaluated for its potential toxic effects on renal function. High levels of NO cause DNA strand damage, which triggers an energy-consuming process involving nuclear enzyme poly-ADP-ribosyltransferase that depletes cellular storage of nicotinamide adenine dinucleotide (NAD+) and ATP, leading to cell death.[27] Additionally, excess levels of NO can also block key enzymes in mitochondrial respiration and in the Krebs cycle, resulting in the disruption of cellular function.[28] Thus, these data suggest inhibition of the reactive species produced from iNOS in endotoxemia may prevent the capillary perfusion defects creating compromised renal blood flow.

Endotoxemia and GFR

GFR is both a function of filtration fraction as well as renal plasma flow (RPF). In mild to moderate reductions in RPF, increased renal vasoconstriction from angiotensin II on efferent arterioles and vasodilation from prostaglandins on afferent arterioles can lead to increased filtration fraction. Thus, GFR will be normal in patients with cirrhosis. However, during the course of sepsis and the aforementioned reductions in RPF, increased filtration fraction fails to compensate, leading to decreased GFR.[29]

Additionally, LPS causes damage to the glomerular barrier due to reduction in size selectivity and increase in glomerular pore size.[30] The mechanism by which this is thought to occur is secondary to inflammation given podocytes have LPS receptors, such as TLR-4 and CD14.[31] Thus, endotoxemia creates an inflammatory state leading to release of cytokines such as TNFα and oxidative stress which can impair podocytes, the specialized cells within Bowman's capsule that function in glomerular filtration.[32] Mice injected with LPS exhibited 70% reduction in GFR.[33] However, when these mice were pretreated with TNF-soluble receptor p55, GFR was reduced by only 30% and RPF was preserved, demonstrating the negative impact of LPS-induced release of TNFα on glomerular integrity and function.[33] In addition, during endotoxemia, the expression of renal extracellular superoxide dismutase, an important antioxidant, was decreased, leading to the reduction in the protective mechanism against LPS-induced reactive oxygen species. Treatment with antioxidants prevented the reduction in GFR.[34]

Bile cast nephropathy is an additional pathology to consider in renal dysfunction in cirrhosis. Patients with cirrhosis who develop renal dysfunction often have increased serum concentrations of bilirubin, leading to cholestasis of sepsis, which may have a direct toxic effect on renal tubules.[35] The exact pathogenesis remains to be elucidated, but current theory suggests that the low water solubility of bile acids leads to cast formation and a proximal bile cast tubulopathy leading to reduced GFR.[36]

Endotoxemia and effects on vasculature/endothelium

The vascular endothelium is a dynamic structure that maintains a semipermeable membrane to water and other biomolecules, mediates leukocyte diapedesis through adhesion molecules, and regulates vascular tone as well as hemostasis.[37] Numerous molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and TNFα, among many others, are indicated in the pathophysiology of endotoxin-induced endothelial damage.[37] What exacerbates this microvascular dysfunction is the stagnation of microvascular flow.[38] Additionally, leukocytes have decreased velocities and increased transit time during endotoxemic states.[39] Rats with induced acute renal failure via LPS injection had increased levels of ICAM-1 and VCAM-1, which both promote inflammation by facilitating leukocyte adhesion to microvascular endothelium.[40] Given delayed microvascular flow with the aforementioned increased levels of inflammatory markers, this prolonged transit time may lead to increased exposure of renal tubular endothelial cells to an amplified inflammatory response and cause greater damage.[38 41]

Endotoxemia also leads to increased vascular tone due to the activation of renal endothelin receptor type A (ETA), which is involved with vasoconstriction on vascular smooth muscle.[41–44] LPS injection in rats led to the increase of endothelin-1 and upregulation of ETA.[45] The inability to block the dominating vasoconstrictive effects of endothelin during endotoxemia may cause intrarenal vasoconstriction, leading to compromised renal function in cirrhosis. Interestingly, pretreatment using an ETA antagonist blocked renal vascular hyperreactivity.[45]

Newer research by Parikh[46] has focused on the angiopoietin-Tie-2 axis in sepsis. The main biomolecules implicated are angiopoietin-1 (Angpt-1) which is produced in periendothelial cells, angiopoietin-2 which is a competitive antagonist of Angpt-1, and Tie-2 which is a transmembrane tyrosine kinase from endothelial DNA.[47] The significance of Angpt-1 lies in that its activation leads to multimerization and cross-phosphorylation into large aggregates to maintain vascular integrity.[48] As a result, Angpt-1 serves a defense function that can create a barrier to the effects of Gram-negative endotoxin. Studies have shown Angpt-1 in murine endotoxemia reduced vascular leakage as well as cellular inflammation via transcription inhibition for inflammatory molecule nuclear factor kappa-light-chain-enhancer of activated B cells.[49 50]

Endotoxemia and effects on tubular function

Endotoxemia has been shown to upregulate TLR-4 expression in the proximal tubules.[51] Filtered endotoxin can interact with TLR-4 on the S1 segment of the proximal tubules and directly cause damage in the downstream S2 and S3 tubules through the secretion of proinflammatory cytokines such as TNFα.[52] Filtered endotoxin also reduces tubular flow rate and can cause oliguria. Thus, mice injected with LPS had significantly reduced tubular urine flow due to the accumulation of LPS in the proximal tubules.[53] In addition, endotoxemia causes a decrease in peritubular capillary flow due to the increased production of reactive nitrogen species (RNS) by the renal tubules.[54] Antioxidant resveratrol, which is capable of scavenging reactive nitrogen species, reversed the decline in cortical capillary perfusion and lead to restoration of renal microcirculation.[45] The schematic diagram illustrating the role of endotoxemia in causing renal dysfunction in cirrhosis is shown in figure 1.

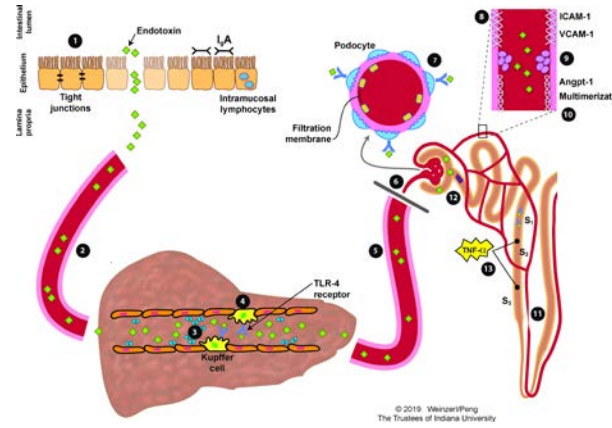

Figure 1 The cascade of endotoxemia leading to renal dysfunction in patients with cirrhosis starts at the intestinal lumen. (1) Translocation of gut bacterial endotoxin LPS from the intestinal lumen occurs due to impaired intestinal epithelial defense barrier, which includes tight junctions, intramucosal lymphocytes, and IgA. Subsequently, (2) endotoxin enters systemic circulation and the cirrhotic liver sinusoid. As part of the inflammatory reaction, (3) sequestration of neutrophils leads to decreased sinusoidal perfusion and endotoxin clearance. Additionally, (4) large burden of LPS overwhelms the functional capacity of TLR-4 receptors on Kupffer cells and cannot be effectively cleared. Thus, (5) endotoxin continues circulation to kidneys. At the level of the glomerulus, (6) endotoxemia activates nitric oxide and leads to vasodilation and decrease in medullary perfusion. Within the podocytes, (7) LPS binding on TLR-4 receptors damages podocyte membrane integrity and increases glomerular pore size. Within the renal vasculature, (8) inflammatory response to endotoxin activates ICAM-1 and VCAM-1 and leads to endothelial damage. (9) Leukocyte adhesion causes prolonged transit and exposure to inflammation. However, (10) Angpt-1 multimerization does create a protective effect to maintain vascular integrity. (11) ETA activation also leads to abnormal vasoconstriction. Within the tubules, (12) bile cast nephropathy also occurs and can lead to reduced GFR. (13) Endotoxin binding to TLR-4 receptors in the proximal tubules in S1 causes downstream damage on S2 and S3 with proinflammatory TNFα. Angpt-1, angiopoietin-1; ETA, endothelin receptor type A; GFR, glomerular filtration rate; ICAM-1, intercellular adhesion molecule-1; LPS, lipopolysaccharide ; TLR-4, toll-like receptor-4; TNFα, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1.

CONCLUSION

The full extent of the effects and complications of endotoxemia on renal function in cirrhosis remains to be elucidated. At the backbone of the derangements occurring in endotoxemia is dysregulated homeostatic regulation within the body. The evidence in understanding the full pathophysiology of this issue is complex, and the treatment modality to address the full spectrum of effects will need to be equally, if not more, multifaceted.

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