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EDITORIAL

Microalbuminuria, systemic inflammation, and multiorgan dysfunction in decompensated cirrhosis: evidence for a nonfunctional mechanism of hepatorenal syndrome

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Multiorgan/system dysfunction or failure (MOD/F) is a frequent complication of severe acute diseases (i.e., sepsis, acute liver failure due to toxic or viral hepatitis or acute alcoholic hepatitis, acute pancreatitis, or severe trauma) that share a common pathophysiological mechanism consisting of massive release of inflammatory inducers [pathogen-associated molecular patterns (PAMPs) by bacteria and/or damage-associated molecular patterns (DAMPs) by injured tissue] [1]. These molecules cause intense and generalized activation of the innate immune system and systemic inflammation. In systemic circulation, there is leukocytosis and very high plasma levels of inflammatory cytokines, acute-phase proteins (C-reactive protein, fibrinogen, and ferritin), and markers of oxidative stress. In tissue and cells, there is increased infiltration by granulocytes and macrophages, increased production of reactive oxygen species (ROS) and nitrogen species, and overexpression of myriad inflammatory genes. Hyperacuteness, extreme severity, high associated mortality, and potential reversibility are the main characteristics of these diseases. Cardiocirculatory failure due to arterial vasodilation and left ventricular dysfunction and the associated organ hypoperfusion was the initial mechanism proposed to link systemic inflammation and multiorgan failure. However, there is now much evidence that inflammatory mediators and ROS have direct deleterious effects upon essential mechanisms of tissue homeostasis, including microcirculatory and mitochondrial function and cell death, which may produce organ failure in absence of impaired organ perfusion [2].

Systemic and organ inflammation is also a characteristic feature of many chronic diseases, including type 2 diabetes (T2D), chronic obstructive pulmonary disease, obesity, and nonalcoholic fatty liver disease and steatohepatitis. However, in contrast to what occurs in severe acute diseases, systemic inflammation in chronic disease is a low-grade sustained process that develops insidiously and does not cause acute impairment in organ function but rather slow chronic inflammation and fibrosis of primary and peripheral organs that contribute to progression towards disease or development of specific complications.

T2D is a representative disease associated with chronic systemic inflammation [3]. In addition to moderate increase of circulating levels of inflammatory mediators, there is local inflammation of metabolically sensitive organs. Such inflammation, which is prominent in abdominal adipose tissue, is also present in skeletal muscle and liver. Insulin resistance and hyperglycemia are related to the inhibitory effect of inflammatory mediators in the insulin signaling cascade in these organs. There is also inflammation at pancreatic islets, which negatively impacts β-cell function, increases apoptosis and local fibrosis, leads to insufficient compensatory increase in insulin secretion, and contributes to progression of metabolic syndrome. A recent study has also shown that the increased hepatic glucose production in T2D is related to a direct effect of inflammatory stress on the hepatic mevalonate pathway [4]. The pathophysiology of inflammation in diabetes is multifactorial and involves metabolic stimuli (direct proinflammatory effects of hyperglycemia, increased plasma fatty acids, adipose tissue hypoxia, and endothelial reticulum stress) and increased translocation of bacterial products from intestinal lumen to systemic circulation related to dysbiotic gut microbiota,

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impaired intestinal epithelial function, and increased gut permeability [5].

Inflammation is the key pathophysiological mechanism of diabetic nephropathy and other specific complications of diabetes (arteriosclerosis, retinopathy, and neuropathy). Changes in intraglomerular hemodynamics due to afferent arteriolar vasodilation induce damage of the glycocalyx and endothelial stress, which together with metabolic stimuli lead to increased glomerular release of nitric oxide, inflammatory mediators, and ROS, inflammation, and fibrosis [6]. The initial clinical manifestation of diabetic nephropathy is microalbuminuria, which develops when histological renal lesions are already significant. However, microalbuminuria not only reflects underlying glomerular injury but is also a significant mechanism contributing to progression of diabetic nephropathy to end-stage chronic renal failure through activation of renal tubular cells to release adhesion molecules and proinflammatory cytokines, interstitial infiltration by inflammatory cells, and progressive fibrosis [7].

The clinical course of cirrhosis is traditionally divided into two stages: compensated and decompensated. The boundary between these stages is the development of one of the major complications of the disease (ascites, variceal bleeding, and/or hepatic encephalopathy). Progression of compensated to decompensated cirrhosis is associated with an abrupt decrease in survival probability to less than 3–5 years.

The traditional view is that decompensation of cirrhosis is a direct consequence of progression of portal hypertension and liver failure to a critical threshold, and that the development of the major complications of the disease is the result of independent and specific mechanisms; For example, whereas ascites and renal dysfunction are consequences of splanchnic arterial vasodilation, which leads to homeostatic stimulation of endogenous vasoactive systems (renin–aldosterone system, sympathetic nervous system, and antidiuretic hormone) and renal retention of fluid, encephalopathy is a consequence of ammonia toxicity and impairment in neurotransmission.

During the last few years, however, various pieces of evidence have suggested that decompensation of cirrhosis is a much more complex process. First, the list of organ dysfunctions associated with decompensated cirrhosis has expanded to include also the immune system, intestines, heart, lungs, adrenal glands, muscles, and thyroid gland. This strongly suggests a common rather than specific mechanism for each organ dysfunction. Second, recent studies indicated that systemic inflammation is an important mechanism in the pathogenesis of decompensated cirrhosis [8, 9].

Systemic inflammation in compensated and decompensated cirrhosis differs in two major aspects. First, whereas systemic inflammation in compensated cirrhosis is a low-grade, sustained process, it is intense in decompensated cirrhosis [10]. Second, patients with decompensated cirrhosis are predisposed to develop acute episodes of severe systemic inflammation superimposed on the underlying chronic systemic inflammation, and this feature is frequently associated with acute MOD/F and high short-term mortality, a syndrome known as acute-on-chronic liver failure (ACLF) [11].

Chronic systemic inflammation in compensated and decompensated cirrhosis is probably due to sustained bacterial and PAMP translocation from intestinal lumen to systemic circulation and organs. The development of complications associated with decompensated cirrhosis is attributed, among other factors, to the deleterious effects of inflammatory mediators on cardiovascular and renal function (ascites) and brain function (hepatic encephalopathy) [8–10]. Acute systemic inflammation in decompensated cirrhosis frequently occurs in the setting of precipitating events, such as sepsis or acute liver injury superimposed on cirrhosis (i.e., acute alcoholic hepatitis), which promote intense activation of immune cells [9–11]. Acute bursts of PAMP translocation from intestinal lumen have been proposed as the most likely mechanism of ACLF not associated with identifiable precipitating events [11].

The results presented in the article by Cholongitas and colleagues [12] in the current issue of *Hepatology International* support these new concepts, showing that, as occurs in patients with T2D, chronic systemic inflammation (as manifested by increased serum ferritin) in decompensated cirrhosis is associated with chronic renal injury [reduction in glomerular filtration rate and microalbuminuria] and significant impairment in the function of other organs/systems, including the cardiovascular system [high plasma renin activity and low mean arterial pressure] and brain (high frequency of hepatic encephalopathy).

The Cholongitas study, as well as other recent investigations [10], do not support the traditional concept that renal failure in cirrhosis is a functional disorder unrelated to structural lesions in the kidneys. First, Cholongitas et al. show that renal dysfunction occurs in close association with microalbuminuria, which is a sensitive marker of glomerular and tubular lesions. Second, the Canonic study recently showed that, whereas renal failure is closely associated with systemic inflammation, the strength of association between cardiocirculatory dysfunction and renal failure is weaker [10]. This observation, therefore, does not support cardiocirculatory dysfunction and renal hypoperfusion as the main mechanism of hepatorenal syndrome. Finally, in a recent study on transjugular kidney biopsies in 65 patients with decompensated cirrhosis awaiting liver transplantation, only 1 patient did not present significant histological renal lesions [13]; In the rest of the patients, there were numerous and often simultaneous glomerular, vascular, and tubulointerstitial lesions.

Interestingly, only cortical and medullary infiltration by mononuclear and polymorphonuclear leukocytes associated with tubular cell injury was independently associated with renal failure. Therefore, although impaired circulatory function and renal perfusion is important in the development of renal failure in cirrhosis, chronic or acute-on-chronic systemic inflammation is the most likely predominant mechanism.

In summary, over the last few years, our concepts on the pathophysiology of acute decompensation and organ dysfunction/failure in cirrhosis have undergone major changes. First, we are realizing that the axis formed by the bowel, liver, and immune system is of major importance. Sustained translocation of viable bacteria and bacterial products from intestinal lumen and secondary activation of the innate immune system give rise to a chronic systemic inflammatory syndrome, which may be a mechanism for acute decompensation and multiorgan dysfunction. Second, these features make patients with decompensated cirrhosis very sensitive to any further proinflammatory stimuli, and this may be the reason for their predisposition to develop ACLF and to die. Finally, the traditional concept that extrahepatic organ dysfunction/failure in decompensated cirrhosis is a functional disorder related to organ hypoperfusion or the toxic effects of endogenous substances retained as a consequence of liver failure is not sustainable.

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