Journal of Clinical Gastroenterology and Hepatology
ISSN: 2575-7733

Open Access Perspective

Vascular Dysfunction of the Liver Sinusoids and Fibrosis Development

Luca Romano*

Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy

DESCRIPTION

Liver sinusoidal endothelial cells play a unique and essential role in maintaining hepatic homeostasis. Unlike vascular endothelial cells in other organs, these cells are highly specialized, characterized by fenestrations and the absence of a basement membrane. This distinctive structure allows efficient exchange of nutrients, oxygen, lipids, and signalling molecules between the blood and hepatocytes. Liver sinusoidal endothelial dysfunction represents an early and critical event in the development and progression of chronic liver diseases and contributes significantly to portal hypertension, inflammation, fibrosis, and cirrhosis.

Under physiological conditions, liver sinusoidal endothelial cells regulate vascular tone, immune tolerance, and metabolic balance within the liver. They produce vasodilators such as nitric oxide, which maintains low intrahepatic vascular resistance and ensures adequate sinusoidal blood flow. They also act as scavenger cells, clearing waste products and macromolecules from the circulation. In addition, these cells participate in immune surveillance by interacting with Kupffer cells, lymphocytes, and hepatocytes, promoting tolerance to gut derived antigens while remaining capable of initiating immune responses when necessary.

Liver sinusoidal endothelial dysfunction begins with the loss of fenestrations, a process known as capillarization. This structural alteration reduces the permeability of the sinusoidal wall and impairs the transfer of substrates between blood and hepatocytes. Capillarization is often accompanied by the deposition of extracellular matrix components in the space of Disse, further disrupting hepatocyte function. These changes are driven by chronic insults such as metabolic stress, alcohol exposure, viral hepatitis, and oxidative injury.

A key functional consequence of sinusoidal endothelial dysfunction is the reduction in nitric oxide bioavailability. Decreased nitric oxide production results from impaired endothelial nitric oxide synthase activity and increased oxidative stress. Reactive oxygen species rapidly inactivate nitric oxide, leading to vasoconstriction and increased intrahepatic vascular resistance. This imbalance between vasodilator and vasoconstrictive forces is a major contributor to the development of portal hypertension, even before significant fibrosis has occurred.

Inflammation further exacerbates liver sinusoidal endothelial dysfunction. Activated endothelial cells express adhesion molecules and chemokines that promote the recruitment of inflammatory cells into the liver. This leukocyte infiltration amplifies local inflammation and perpetuates endothelial injury. Inflammatory mediators such as tumor necrosis factor alpha and interleukins alter endothelial signalling pathways, impair vasoregulation, and promote prothrombotic changes within the sinusoids. These alterations contribute to microcirculatory disturbances and parenchymal hypoxia.

Liver sinusoidal endothelial dysfunction also plays a pivotal role in fibrogenesis. Healthy sinusoidal endothelial cells maintain hepatic stellate cells in a quiescent state through paracrine signalling. When endothelial cells become dysfunctional, this protective influence is lost. Capillarized endothelial cells produce profibrotic mediators that activate stellate cells, leading to increased collagen deposition and extracellular matrix accumulation. This process establishes a vicious cycle in which fibrosis further worsens endothelial dysfunction and vascular resistance.

The metabolic consequences of liver sinusoidal endothelial dysfunction are increasingly recognized. Impaired substrate exchange affects lipid handling, glucose metabolism, and insulin signalling within the liver. In metabolic associated fatty

Received: 29-August-2025; Manuscript No: IPJCGH-25-23456; **Editor assigned:** 01-September-2025; Pre QC No: IPJCGH-25-23456 (PQ); **Reviewed:** 15-September-2025; QC No: IPJCGH-25-23456; **Revised:** 22-September-2025; Manuscript No: IPJCGH-25-23456 (R); **Published:** 29-September-2025; DOI: 10.36648/2575-7733.9.3.25

Corresponding author: Luca Romano, Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy; E-mail: luca.romano@unipd.it

Citation: Romano L (2025). Vascular Dysfunction of the Liver Sinusoids and Fibrosis Development. J Clin Gastroenterol Hepatol. 9:25.

liver disease, endothelial dysfunction contributes to hepatic insulin resistance and steatosis progression. Altered endothelial signalling also affects angiogenesis and vascular remodelling, which are prominent features of advanced liver disease and hepatocellular carcinoma.

Emerging evidence highlights the role of the gut liver axis in sinusoidal endothelial dysfunction. Increased intestinal permeability and bacterial translocation expose the liver to endotoxins and microbial products that activate endothelial toll like receptors. This activation triggers inflammatory and oxidative pathways that damage endothelial cells and reduce nitric oxide availability. The chronic exposure to gut derived signals reinforces endothelial dysfunction and links intestinal dysbiosis to liver disease progression.

Clinically, liver sinusoidal endothelial dysfunction has important diagnostic and therapeutic implications. It occurs early in liver disease and may precede overt fibrosis, making it a potential target for early intervention. Biomarkers reflecting endothelial injury and dysfunction, such as circulating adhesion molecules are being investigated as non-invasive indicators of disease severity and portal hypertension. Imaging techniques that assess hepatic microcirculation also offer promising insights into endothelial health.

Therapeutic strategies aimed at restoring sinusoidal endothelial function are an active area of research. Approaches include enhancing nitric oxide signalling, reducing oxidative stress, and targeting inflammatory pathways. Lifestyle interventions that address metabolic risk factors may indirectly improve endothelial function. Pharmacological agents that modulate endothelial signalling and prevent capillarization hold potential to slow disease progression and reduce portal hypertension.

In conclusion, liver sinusoidal endothelial dysfunction is a central mechanism in the pathogenesis of chronic liver disease. Through structural changes, impaired vasoregulation, inflammation, and promotion of fibrosis, dysfunctional endothelial cells contribute to disease progression and clinical complications. Recognizing the early role of sinusoidal endothelial injury provides valuable opportunities for improved diagnosis and the development of targeted therapies. Continued research into the biology of these specialized cells will be essential for advancing the management of liver diseases and improving patient outcomes.