Infection and Alcoholic Liver Disease

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KEYWORDS

• Cellular immunity • Infectious disease • Alcoholic hepatitis • Cirrhosis

KEY POINTS

- Acute and chronic alcohol use affects multiple arms of the immune system by a variety of direct and indirect mechanisms.
- Dysregulation of the immune system due to alcohol use can lead to both an immunocompromised state with an increased risk of infection and a proinflammatory state contributing to acute and chronic liver disease.
- Alcohol use can alter the clinical course and treatment of patients infected with various chronic viral and bacterial illnesses such as hepatitis B, hepatitis C, human immunodeficiency virus, and tuberculosis.
- Alcoholic hepatitis is marked by a state of immune derangement, leading to an increased risk of morbidity and mortality from infection and liver failure.

THE EFFECT OF ALCOHOL ON IMMUNE RESPONSES

The body has two broad categories of defense when challenged by pathogens: innate and adaptive immunity. The initial line of defense is carried out by the innate immune response, which consists primarily of epithelial cells and immune cells (ie, cell-mediated response) such as neutrophils, monocytes, macrophages, other antigen presenting cells, and natural-killer cells.[1] The innate immune system plays a role in activating the second line of defense, the adaptive response (T and B cells), which creates immune memory to a specific pathogen for more effective responses when encountering the same pathogen in the future.[2] The innate and adaptive immune systems are closely intertwined and interact with each other via cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin (IL), and chemokines that attract additional inflammatory cells to sites of infection.

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The Effect of Alcohol on the Innate Immune System

Both animal and human research studies have shown that acute and chronic alcohol use have negative effects on structural host defense mechanisms as well as on the cell-mediated response of the innate immune system (Fig. 1). Complex interactions between hepatocytes and the immune system are key in the development of alcohol-induced liver damage because the liver acts a primary responder to bacteria and cell wall components released in the gut in response to alcohol ingestion.[3]

Effect on gut permeability

Epithelial cells lining the skin and mucosa of the gut and airways function as the initial physical barrier of entry for pathogens, producing the first line of defense of the innate immune system. Several studies have shown that alcohol can alter this structural barrier, leading to increased gut permeability and leakage of bacteria-derived products such as lipopolysaccharide (LPS) or endotoxins into the portal circulation. Metabolism of alcohol releases metabolites such as acetaldehyde, which impair trafficking of tight junction proteins.[4] Alcohol also alters the expression of microRNAs that lead to decreased zona occludens production, further contributing to impaired integrity of tight junctions.[5] Oxidative injury from chronic alcohol use is also noted in the gut from the overproduction of nitric oxide and formation of peroxynitrite, which can damage microtubules and lead to increased gut permeability. In mice chronically fed alcohol, reactive oxygen species (ROS) release may lead to zinc deficiency, which further exacerbates gut barrier dysfunction.[3]

These gut permeability changes allow translocation of bacteria-derived products such as LPS or endotoxin to enter the blood stream and the liver via the portal system.[6–8] These endotoxins are components of gram-negative bacteria, which have been implicated in mechanisms leading to sepsis, shock, and organ failure, particularly in alcoholic patients. Once exposed, these endotoxins activate multiple cells such as Kupffer cells, endothelial cells, and hepatocytes, creating a cascade of events and leading to proinflammatory responses.[9] Thus, it is not surprising that the severity of alcohol-induced liver injury and infection risk correlates with endotoxin levels.[10] Reduction in bacterial colonization with antibiotics or lactobacillus has been shown to prevent hepatic injury in alcohol-fed rats.[11,12]

Effect on phagocytic responses

Once activated, Kupffer cells clear bacterial antigens from the circulation via phagocytosis, and produce oxidants and cytokines. This response is exaggerated in response to larger influxes of endotoxins due to alcohol, leading to accelerated production of superoxide and TNF-α via the LPS–toll-like receptor (TLR) 4 signaling pathway. LPS binds to the coreceptor LPS-binding protein (LBP) and interacts with CD14 receptor on Kupffer cells. This binding triggers intracellular signaling, which activates transcription factors such as nuclear factor $\kappa\beta$ (NF-$\kappa\beta$), which induce proinflammatory cytokine gene expression of TNF-α and IL-1β.[3] Kupffer cells in female rats demonstrate a significantly greater response to LPS than male rats and produce higher levels of TNF-α in the setting of chronic alcohol use, suggesting a possible female predisposition to alcohol-induced liver injury that is clinically well described.[13]

Paradoxically, alcohol also leads to an immunosuppressed state by altering the production and function of monocytes, macrophages and neutrophils. This effect is reflected in a reduction of bactericidal serum activity in subjects with acute alcohol intoxication and relative granulocytopenia and is seen in 10% of chronic alcoholics. In several studies, alcohol abuse induces a state of hypoplasia in the bone marrow, leading to decreased production of new granulocytes.[14] This is further exacerbated