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# Alcohol–Organ Interactions: Injury and Repair

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## Why Study Alcohol-Related Organ Damage?

The association between alcohol misuse and organ damage, specifically liver disease, has been recognized for more than 200 years (Maher 1997). Yet it was not until the early 1970s that researchers demonstrated a direct causal relationship between drinking and this serious—and sometimes fatal—condition. In their seminal paper, Rubin and Lieber (1973) established that baboons consuming up to 50 percent of their daily caloric intake in the form of ethanol developed the "entire constellation of histologic features characteristic of human alcoholic hepatitis," p. 712. Because the animals' diet otherwise provided adequate nutrition, the researchers concluded that ethanol was responsible for the development of liver disease. Subsequent studies determined that the risk of alcoholic liver disease (ALD), and particularly cirrhosis, increased with alcohol consumption levels.

Since those early studies, research has shown that excessive drinking can affect nearly all major organ systems, contributing significantly to alcohol-related morbidity and mortality. Indeed, the International Classification of Diseases, Tenth Edition (ICD–10) lists more than 20 disorders that are entirely attributable to alcohol, as well as a similar number of conditions for which alcohol consumption is a component cause (Shield et al. 2013).

According to the Centers for Disease Control and Prevention (CDC), a large proportion of alcohol-related deaths are the consequence of organ damage and disease. To quantify the impact of harmful drinking on morbidity and mortality, the CDC developed the Alcohol-Related Disease Impact (ARDI) application, which assesses the deaths and years of potential life lost (YPLL) attributable to alcohol misuse (CDC 2013). The most recent analyses of these data found that in the United States from 2006 through 2010, about 38,250 deaths annually could be attributed to chronic conditions related to alcohol misuse. Of these, more than 32,000 were related to alcohol-associated organ damage, including liver disease, various types of cancer, or cardiovascular disease. These deaths corresponded to 705,000 YPLL (Stahre et al. 2014).

Given these serious adverse effects of alcohol on organ function, it is crucial that we gain a deeper understanding of the relationship between alcohol consumption, organ function, and disease, as well as the physiological mechanisms underlying these effects. This issue of *Alcohol Research: Current Reviews* presents an overview of key findings in the field, with each article focusing on alcohol's effects on either an organ or organ system.

## Alcohol's Impact on Organs and Organ Systems

Alcohol is a toxin that can damage tissues and organs both directly and indirectly through its metabolic byproducts. As the primary site of alcohol metabolism, the liver is particularly vulnerable to alcohol-induced damage. More than 90 percent of long-term heavy drinkers develop fatty liver, and about 35 percent develop advanced liver disease, underscoring the need for effective treatments for ALD (see article by Osna and colleagues in this issue).

The gastrointestinal tract is the primary site at which alcohol is absorbed into the blood, and it is also susceptible to alcohol-induced damage. Bishehsari and colleagues describe how alcohol and its metabolites contribute to intestinal inflammation, which may promote gastrointestinal cancers and inflammatory bowel disease. Damage to the pancreas—part of the digestive system, along with the liver and gastrointestinal tract—is also linked to alcohol consumption. Pandol reviews research showing that the relationship between heavy drinking and acute and chronic pancreatitis is well established. However, experimental data suggest that alcohol consumption alone does not initiate pancreatitis, but instead sensitizes the pancreas to disease from other insults.

The effects of alcohol on the brain also have been documented extensively. Zahr and Pfefferbaum review the structural brain changes found in people with alcohol-related neurological conditions, such as Wernicke's encephalopathy and Korsakoff syndrome, as a framework for understanding brain changes that occur in individuals with alcohol use disorder (AUD) in the absence of those conditions. They also discuss research demonstrating that although some alcohol-induced brain changes appear to be permanent, other patients recover over time with abstinence.

Skeletal muscle dysfunction (i.e., myopathy) is common in patients with AUD, and its incidence exceeds that of alcoholic liver cirrhosis. Simon and colleagues review the epidemiology of alcoholic myopathy, the pathophysiologic mechanisms underlying alcohol's effects on mechanisms involved in maintaining muscle mass, the clinical implications of these effects, and emerging literature on treatment options.

The association between alcohol and cardiovascular diseases (CVD), including hypertension, coronary heart disease, and stroke, has been studied extensively. Piano reports that the dose and pattern of alcohol consumption seem to be important moderators of the link between alcohol and CVD, with larger amounts of alcohol consumption being associated with increased CVD risk and low-to-moderate amounts with reduced CVD risk. The relationship between alcohol and CVD is complex, and ongoing research will help clarify the dose and health conditions for which alcohol may have potential benefits, as well as those for which alcohol may have adverse effects.

As described by Mehta and Guidot, people with AUD are particularly susceptible to lung diseases, such as pneumonia, tuberculosis, and acute respiratory distress syndrome. Researchers have identified several pathways through which alcohol misuse may interfere with lung function. This work has led to the identification of potential therapeutic targets for treating alcohol-related lung conditions.

Because hormones control virtually all important bodily functions and are essential for maintaining a constant internal environment, alcohol's effects on the endocrine system have potentially far-reaching impact. Rachdaoui and Sarkar review how the effects of alcohol on hormonal systems contribute to a broad range of debilitating disorders, including stress intolerance, reproductive dysfunction, thyroid problems, immune abnormalities, diabetes, cardiovascular disease, cancer, and psychological disorders. Alcohol's effects on hormone

function can be particularly harmful during puberty, resulting in delayed pubertal development (see article by Dees and colleagues in this issue).

## Next Steps

The articles in this issue review the significant advances that have been made toward elucidating how alcohol affects organ systems and contributes to organ-related pathology. They also highlight the many gaps in our knowledge. For example, there is a relative dearth of research on the relationship between alcohol and kidney function. As Varga and colleagues note, although studies suggest several potential mechanisms by which alcohol may affect the kidneys, there is little experimental evidence demonstrating that alcohol consumption leads to kidney injury, and epidemiological data linking the two are inconclusive. This area is ripe for further investigation. Likewise, Piano notes that most data on the link between alcohol and CVD in humans are derived from epidemiological studies, pointing to the need for a prospective randomized controlled trial in this area.

Even with diseases such as ALD, in which the role of alcohol has been well established, the complex underlying pathophysiological mechanisms are not fully understood. Moreover, the body's organs do not operate in isolation—they interact with each other such that alcohol-induced damage in one organ can perturb others. For example, studies have shown that a single episode of binge drinking can cause bacterial toxins to leak from the gut into the bloodstream, inducing inflammation in other organ systems. Inflammation is implicated in much of the organ damage associated with alcohol misuse, and it is emerging as an important contributor to the development of AUD.

Developing a better understanding of the mechanisms by which alcohol affects organ function will lead to improved interventions for preventing and treating alcohol-induced organ damage. One promising area of study described by Barve and colleagues is the use of nutritional interventions. Although alcohol–nutrition interactions may contribute to various types of organ damage (e.g., liver, intestinal, and lung dysfunction), nutritional supplementation with micronutrients such as zinc may help prevent or ameliorate some of this damage. We hope that this issue will spark additional interest in this topic and lead to a greater menu of effective therapies for alcohol-related conditions.

## Resources


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