Alcohol Use in Patients With Inflammatory Bowel Disease

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Abstract: Alcohol consumption is common in patients with inflammatory bowel disease (IBD), but alcohol has been reported to be the most-avoided diet item by this patient population. This article explores the available evidence for the impact that alcohol use has on IBD development, relapse, symptom control, and medication interactions. Although evidence linking the consumption of alcoholic beverages and the development of new-onset IBD is controversial, prospective research has reported that alcohol use is associated with a higher risk of relapse. Moreover, patients with IBD report worse gastrointestinal symptoms following alcohol consumption. On the other hand, alcoholic beverages such as red wine may have anti-inflammatory properties capable of assisting in disease control, although they may also have a negative effect on disease monitoring, namely fecal calprotectin levels. Importantly, the use of alcohol can interfere with the metabolism of several medications, leading to increased adverse events or even loss of efficacy. In the available literature, alcohol use in patients with IBD trends toward harmful effects; however, more research is needed to provide confident recommendations.

Keywords
Alcohol, ethanol, inflammatory bowel disease, ulcerative colitis, Crohn's disease

The rise of ulcerative colitis (UC) and Crohn's disease (CD) in developing countries where these conditions were once uncommon highlights the importance of environmental factors in the development of inflammatory bowel disease (IBD).[1] Although several environmental factors have been proposed as potential triggers for the development of IBD, little is known regarding the impact of alcohol use on the management of IBD.[2] Alcohol consumption in patients with IBD is common.[3] Although the use of alcohol in these patients is similar to that of the general population, alcohol has been reported to be the most-avoided diet item by patients with IBD.[4] Prospective research has reported that alcohol use is associated with a higher risk of relapse in patients with UC.[5] Furthermore, patients with IBD report worse gastrointestinal (GI) symptoms than patients with irritable bowel syndrome (IBS) following alcohol consumption.[3] This article describes

the available evidence for the impact that alcohol use has on IBD development, relapse, symptom control, and medication interactions.

Alcohol and Development of Inflammatory Bowel Disease

Evidence linking alcohol consumption and the development of new-onset IBD is controversial. Many of the claims are based on the hypothesis that alcohol may modulate the microbiome and facilitate intestinal inflammation. This is corroborated by observations demonstrating that patients with alcohol abuse disorder have a similar microbial signature to that of patients with IBD,[6-8] which, therefore, could facilitate IBD pathogenesis. Furthermore, alcohol-induced dysbiosis is known to provide opportunities for pathogenic bacteria, notably *Clostridioides difficile*, to colonize and proliferate.[6,9] Interestingly, research performed in germ-free mice demonstrated that these animals failed to develop systemic inflammatory responses that are often seen after alcohol ingestion, confirming the role of the microbiome on alcohol-mediated inflammatory responses.[10] Whether gut dysbiosis itself is sufficient to initiate intestinal inflammation, or if it is a result of the overall changed inflammatory burden remains unclear, but it highlights a potential role of alcohol promoting IBD pathogenesis.

A large, retrospective, matched-cohort study with over 250,000 individuals from Taiwan showed that individuals hospitalized for alcohol intoxication had an increased risk of IBD over a 10-year period compared with their respective controls (hazard ratio, 3.17; 95% CI, 2.19-4.58).[11] Conversely, a multinational questionnaire-based European study of 262,451 participants found no association between alcohol consumption and the development of IBD after 4 to 10 years of follow-up.[12] Interestingly, a case-control study of 354 participants from China found a protective effect from light alcoholic beverage drinking against the development of UC; however, this protective effect was not confirmed by multivariate analysis of risk factors.[13] Ultimately, a meta-analysis combining epidemiologic studies on this subject found no association between alcohol consumption and the risk of new-onset CD.[14] Although the role of alcohol in facilitating intestinal inflammation has been proposed, there is insufficient evidence at this time to link it to the development of new cases of IBD.

Alcohol and Inflammatory Bowel Disease Relapse

Experimental evidence suggesting mechanisms by which alcohol use can alter the microbiome, disrupt the mucosal barrier, and promote activation of the immune system has raised concerns as to whether alcohol use can trigger an IBD relapse. In particular, disruption of the epithelial barrier by ethanol is a well-characterized mechanism of intestinal inflammation. Alcohol disrupts the normal physical and immunologic barriers of intestinal epithelial cells and gut-associated lymphoid tissue.[3,6,15-18] Mucosal injury promoted by alcohol impairs intestinal absorption and results in increased gut permeability, a known mechanism involved in IBD pathogenesis.[6,15,19,20] This increased permeability, in turn, exposes the submucosal immune system to luminal bacteria, often proinflammatory strains and bacterial products such as endotoxins. The latter has been reported to promote transient endotoxemia, which activates proinflammatory mediators such as tumor necrosis factor–α, interleukin (IL)-1, and IL-6.[6,15,19,20] Increases in these cytokines lead to mucosal ulcerations, damage to the colonic epithelium, and formation of crypt microabscesses, resulting in a flare-up.[6,17,21-26]

A prospective cohort study that evaluated the effects of dietary habits of patients with UC in remission found an increased risk of UC relapse associated with high alcohol intake but no significant risk associated with medium intake.[5] Moreover, alcohol use also has been shown to negatively impact outcomes of hospitalized patients with IBD, including increased intestinal infections, need for antibiotic injections, and the numbers of abdominal computed tomography scans and large intestine biopsies obtained.[6] However, some studies have shown a potential positive effect of alcohol consumption, namely red wine and its association with a reduction in fecal calprotectin. The potential benefit of red wine is speculated to be secondary to other nonalcoholic components such as the antioxidant resveratrol and its anti-inflammatory properties.[27,28] Red wine consumption also is associated with an increase in anti-inflammatory bacterial groups (eg, *Bifidobacterium*) as opposed to other alcoholic beverages (eg, gin) that increase proinflammatory species (*Bacteroides* and *Clostridium*). Although red wine may have a beneficial effect on controlling inflammation, research has confirmed that it is still associated with increases in gut permeability, which longitudinally can result in worse intestinal inflammation.[29] Interestingly, permeability correlated with the location of disease, suggesting that moderate alcohol consumption disrupted intestinal permeability in areas of greater susceptibility (ie, areas previously injured due to inflammation) in a second-hit fashion.[29] Further studies are required to clarify the effect of red wine and small amounts of alcohol use on the risk of IBD relapse. Based on the current evidence, high amounts of alcohol are harmful and associated with worse inflammatory activity and, consequently, relapses.

Alcohol and Inflammatory Bowel Disease Symptoms

The effect that alcohol has on promoting a variety of GI symptoms in patients with IBD has been explored in multiple studies. Beyond previously discussed mechanisms (eg, changes in intestinal microbiome, increased gut permeability, and overt immune activation) that can result in worsening symptoms, many adjuvants seen in alcoholic beverages have been significantly associated with worsening GI symptoms. Sulfur and sulfate, common additives to alcohol, have been associated with mechanisms capable of worsening IBD, including disruption of the mucosal barrier of the gut.[5,30-32] Hydrogen sulfide is known to cause increased epithelial permeability, loss of barrier function, cellular proliferation, and histologic changes in murine colons similar to the changes seen in humans with UC.[5,30-32] A study that examined the impact of dietary factors on UC relapse noted an association between relapse and a high intake of sulfites.[5] Other research has shown a significantly positive correlation between sulfite-containing alcoholic beverages (eg, wines and beers) and increased UC disease activity (n=81; r^2=007; P<.02), although this effect was not seen with the consumption of spirits.[33] In addition to sulfites, sugar also has been proposed as a major stressor in different GI disorders. A Danish cohort study showed a direct association between abdominal pain and blood sugar but not alcohol levels following consumption of alcoholic beverages with high sugar content (Smirnoff Ice or Elephant Beer), highlighting the importance of this additive in alcoholic beverages' related effects.[34]

In a survey of patients with CD, 40% reported worsening of symptoms following alcohol use,[35] although they did not elaborate on the nature of the symptoms or the degree of exacerbation. A similar questionnaire-style study in New Zealand found that 55% of patients with CD reported worsening of symptoms with beer consumption, but also other carbonated beverages such as energy drinks and cola.[36] One study of patients with IBD and IBS assessed the effect of alcohol consumption on symptoms through a questionnaire and found significant worsening of GI symptoms associated with alcohol consumption in patients with inactive IBD when compared with patients with IBS.[3] However, this study found no statistical difference in the overall severity of GI symptoms when compared with the quantity of alcohol consumed and no correlation between the type of alcohol consumed and GI symptoms. Furthermore, retrospective observations corroborated by experimental observations demonstrating worse outcomes of mice infected with *Citrobacter rodentium* following alcohol consumption have confirmed that alcohol may facilitate bacterial infections mechanistically and contribute to worsening IBD outcomes.[1] Notably, alcohol use, directly or indirectly via additives, has been shown to worsen GI-related symptoms regardless of disease relapse or worsening of inflammation.

Alcohol and Inflammatory Bowel Disease Medications

Concerns of alcohol and medication interactions mostly arise from alcohol's hepatic metabolism that involves the microsomal ethanol oxidizing system, particularly cytochrome P450. Chronic ethanol consumption increases the activity of the microsomal ethanol oxidizing system by inducing cytochrome P450, which predisposes patients to alcohol-medication interactions involving this enzyme. Depending on the timing of alcohol ingestion, possible interactions include: (1) delaying the breakdown of medications by direct competition of alcohol for metabolism by cytochrome P450, and (2) accelerating metabolism of medications in the absence of alcohol by upregulating cytochrome activity levels.[37,38] Health care providers should be aware of these mechanisms because many patients with IBD are on a variety of medications related or unrelated to their IBD.

With regard to IBD-specific therapies, a large number of the medications used have the potential to interact with alcohol, including antibiotics, 5-aminosalicylates, immunosuppressants (eg, methotrexate and thiopurine), and biologics. The Table summarizes the available data on interactions from alcohol use and IBD-specific medications. Data regarding the concomitant use of alcohol and antibiotics are controversial. Overall, the major concern of decreased efficacy has not been confirmed in studies assessing the common antibiotic classes used in IBD such as beta-lactam, cephalosporins, or fluoroquinolones, but further studies are needed.[39] An additional concern of combining alcohol and antibiotics is an increase in adverse events, particularly disulfiram-like reactions, which are usually associated with metronidazole or cephalosporin antibiotics.[37] These reactions result from inhibition of aldehyde dehydrogenase, leading to an accumulation of acetaldehyde during ethanol metabolism responsible for a flushing reaction.[37] With mesalamine and 5-aminosalicylates, alcohol has been proposed to influence drug release of modified-release formulations in experimental studies, but data in patients are still lacking.[40] Similarly, concomitant alcohol use has been reported to decrease levels of circulating cyclosporine, often used as salvage therapy in patients with acute severe UC.[41] The effect of heavy alcohol consumption and methotrexate use as it relates to liver damage has been studied extensively. Studies carried out in patients with autoimmune conditions treated with methotrexate confirmed that progression of liver fibrosis

Table. Interactions From Alcohol Use and IBD-Specific Medications

Interaction	Medication	Mechanism
Disulfiram-like reactions	Antibiotics[37,39,47] (eg, metronidazole and cephalosporins)	Inhibition of aldehyde dehydrogenase
Decreased efficacy	5-aminosalicylates[40,48,49]	Interference with modified-release formulations
	Cyclosporine[41]	Reduced drug-circulating levels
Hepatotoxicity	Thiopurines[45]	Glutathione depletion (peliosis hepatis)
	Methotrexate[42-44]	Direct hepatotoxicity via inhibition of DNA and RNA synthesis
	Tumor necrosis factor inhibitors[46,50]	Potential increase in the risk of drug-induced liver injury

IBD, inflammatory bowel disease.

was greater in patients reporting concomitant alcohol use. Therefore, concomitant heavy alcohol consumption and methotrexate use increases the risk of liver damage and should be avoided in that scenario.[42-44] Similar concerns have been raised with azathioprine use; however, the risk of interaction between azathioprine and alcohol is largely theoretical.[45] Lastly, concerns over alcohol and biologic medication use have not been studied extensively. These concerns center around a potential increased risk of drug-induced liver injury that can occur, particularly with tumor necrosis factor–α antagonists, but further studies are needed.[46]

Conclusion

The impact of alcohol consumption on IBD has significant ramifications for disease management. Although alcohol use seems to promote a microbiome that facilitates the development of intestinal inflammation, its role in the development of new-onset IBD has not been confirmed. In patients with established IBD, mild alcohol consumption may have a negligible clinical impact, with sugar and sulfur perhaps more relevant to symptoms and flare-ups than ethanol. Conversely, heavy alcohol use has been associated with worse IBD outcomes and development of inflammation. These effects are notably related to alcohol's modulation of a proinflammatory microbiome and disruption of the intestinal barrier, which, in turn, results in increased gut permeability and immune overactivation. Some alcoholic beverages, however, may have a beneficial impact on inflammatory levels when used in moderation, most notably red wine. With regard to medications, alcohol consumption increases risk due to the unpredictability of its effect on drug delivery. Disulfiram-like reactions with antibiotics, decreased efficacy of 5-aminosalicylates and cyclosporine, and increased hepatotoxicity with methotrexate and azathioprine are important interactions between alcohol and IBD-specific medications. Several factors of the impact of alcohol use and IBD remain unclear. These include the potential long-term suppressive action of red wine on fecal calprotectin levels as well as the unknown interactions with newer biologic agents. In the literature to date, there is a trend toward harmful effects of alcohol use in patients with IBD, but more research is needed to provide recommendations such as complete avoidance vs any potential types or quantity of alcohol that patients with IBD can consume.

Disclosures

The authors do not have any relevant conflicts of interest to disclose.

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