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Review Article

Effects of Ethanol on the Digestive System: A Narrative Review

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Abstract

Alcohol consumption is responsible for approximately 6% of all deaths and 5.1% of the global disease burden. The most common alcohol-related causes of death include liver cirrhosis (50% of cases), pancreatitis (25%), and esophageal cancer (22%). In this review, we provide an overview of ethanol metabolism and highlight the major diseases caused by alcohol consumption in the liver and gastrointestinal tract. Due to its central metabolic role, the liver is particularly susceptible to ethanol, which is known to cause a wide spectrum of conditions, including steatosis, steatohepatitis, alcohol-associated hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma). The gastrointestinal tract is often one of the first areas to show signs of damage from excessive alcohol consumption. Chronic alcohol abuse is a well-established risk factor for both acute and chronic pancreatitis, as well as pancreatic cancer. Approximately 70% of acute pancreatitis cases and 30% of chronic pancreatitis cases are attributable to alcohol abuse. Epidemiological studies have consistently demonstrated a positive correlation between alcohol intake and the prevalence of gallstones. Moreover, alcohol is an important risk factor for gastroenteropancreatic cancer, as ethanol metabolism produces acetaldehyde, a potent carcinogen for humans. In conclusion, chronic ethanol intake, through one of its main metabolic products, acetaldehyde, causes pathological changes in the gastrointestinal tract, liver, pancreas, and gallbladder. Even moderate amounts of alcohol may increase the risk of cancers, such as colorectal cancer. Therefore, if there is clinical suspicion of excessive alcohol intake in a patient with persistent digestive symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea, and bloody stools), immediate medical evaluation is essential. Referral to specialized centers with expertise in alcohol use disorder is a key management option for patients with established alcohol use disorder.

Introduction

The impact of excessive alcohol intake on human health is dramatic. Recent data show that alcohol consumption is responsible for approximately 6% of all deaths (3.3 million people) and 5.1% of the global disease burden.[1] In addition to its addictive properties, alcohol consumption can lead to roughly 200 different diseases, including 14 different types of cancer.[1] More than 50% of all alcohol-related deaths in both males and females are due to gastrointestinal diseases. The most common alcohol-associated causes of death are liver cirrhosis (50% of cases), pancreatitis (25%), and esophageal cancer (22%).[1] These data indicate that about 50% of deaths are due to end-stage cirrhosis, and approximately 500,000 annual deaths in Europe are related to alcohol misuse.[1] The knowledge of digestive system damage caused by alcohol abuse, coupled with significant unmet needs in managing patients with established alcohol use disorder, represents an area in practical gastroenterology that requires thorough appraisal. Indeed, in the last decade, very few reviews have been published on this topic.[2–5] Therefore, this narrative review aimed to provide a summary of ethanol metabolism and highlight the main diseases caused by alcohol consumption on the digestive system (Fig. 1).

Liver

Alcohol is absorbed in the upper digestive tract (20% in the stom-

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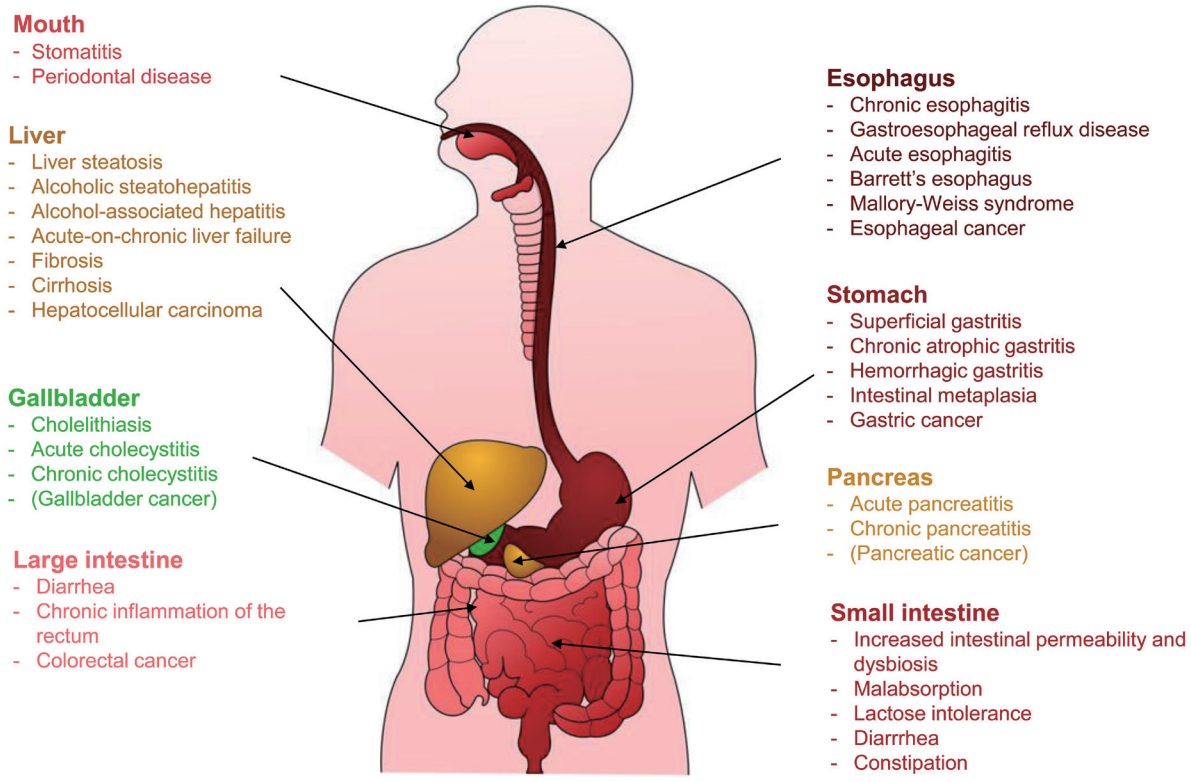

Fig. 1. Acute and chronic pathological effects of ethanol on the digestive system. Brackets indicate an increased risk of developing cancer, although the relationship is not yet fully established.

ach and 75% in the first part of the small intestine), with the remaining 5% absorbed in the small intestine and colon.[6,7] In fasting conditions, absorption is almost complete within one hour after intake: alcohol levels peak after 30–45 m and cannot be reliably measured 4–6 h after intake. If the alcoholic beverage is ingested with food (particularly fatty foods), the alcohol peak is delayed by 2–6 h.[6,7] One endogenous factor that modulates ethanol absorption through the gastric mucosa is alcohol dehydrogenase (ADH). Approximately 10% of ingested ethanol is metabolized by gastric ADH,[8,9] thus preventing it from entering systemic circulation ("first-pass metabolism [FPM]"). The intake of similar doses of ethanol (corrected for body weight) can lead women to have higher blood alcohol levels than men. This difference is due to both lower body water content and reduced FPM (due to decreased gastric ADH activity).[8,9] These factors increase ethanol bioavailability and contribute to the greater susceptibility of females to alcohol-related damage. Furthermore, anatomical changes (such as gastric resection) or histological modifications (e.g., metaplasia) of the antral parietal cells can affect alcohol bioavailability. Certain drugs (e.g., acetylsalicylic acid and proton pump inhibitors) can inhibit gastric ADH activity, particularly if low doses of alcohol are consumed.[9] Through the portal system, approximately 90% of absorbed alcohol reaches the liver, the primary site of its metabolism, where ethanol is metabolized to acetaldehyde via liver ADH. Acetaldehyde is a highly reactive and toxic compound that is further metabolized by the enzyme aldehyde dehydrogenase (ALDH) and the coenzyme NAD in both the cytoplasm and mitochondria. The resulting product is acetyl-CoA, which is further processed to acetate, eventually being degraded to carbon dioxide and water (Fig. 2).[6,7] A small percentage of alcohol escapes the liver and is eliminated via exhaled air, urine, and sweat. Additionally, a small, unmodified amount of alcohol targets other tissues, particularly those with a high lipid content (e.g., the central nervous system). The saturation of the ALDH system leads to the accumulation of acetaldehyde, which can form covalent bonds with cellular proteins by interacting with sulfhydryl or amino groups, resulting in the production of protein adducts (acetaldehyde + cellular pro-

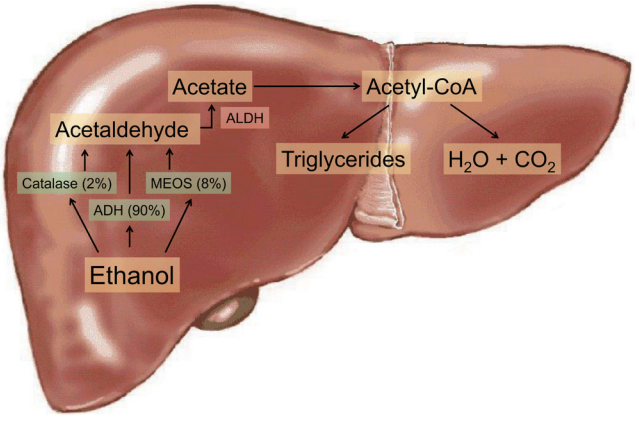

Fig. 2. Diagrams illustrating the various pathways of alcohol metabolism in the liver. The first step of alcohol metabolism occurs in the liver via the alcohol dehydrogenase enzyme. The subsequent phases involve other key enzymes that form intermediate and final metabolites, such as acetate and acetyl-coenzyme A (acetyl-CoA). ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; MEOS, microsomal ethanol oxidation system.

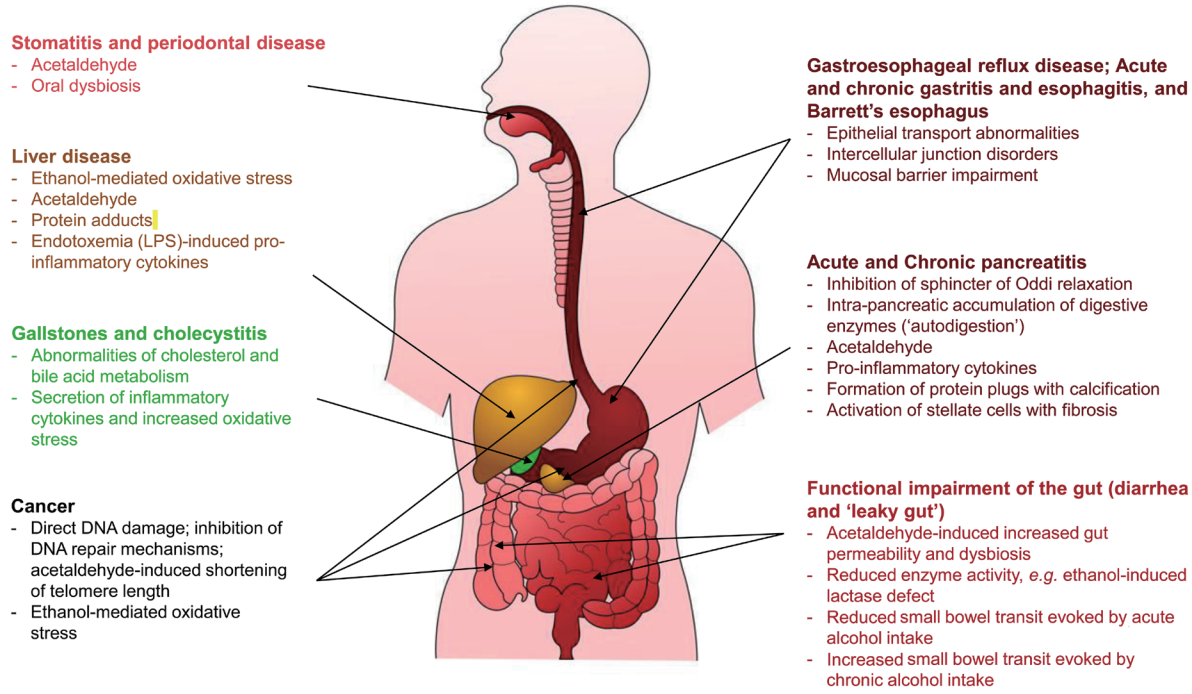

Fig. 3. Main molecular mechanisms and related clinical conditions of alcohol-induced digestive system damage. LPS, lipopolysaccharide.

teins). These adducts, which are detected in the liver and serum of individuals with alcohol use disorder, are highly reactive and immunogenic substances.[10,11] Moreover, acetaldehyde can alter the fatty acid composition of membrane phospholipids, reducing micro-viscosity and increasing rigidity.[10] Additionally, acetaldehyde interferes with the Krebs cycle and oxidative phosphorylation at the mitochondrial level, leading to reduced oxidation of fatty acids and intracellular accumulation of these compounds, contributing to hepatic steatosis.

The mechanisms underlying alcohol-induced liver damage are influenced by the dose and duration of abuse, as well as genetic, environmental, immunological, infectious, and nutritional factors.[12,13] The Dionysos study demonstrated that the increased risk of developing alcoholic liver disease and cirrhosis occurs with >30 g/day of alcohol consumption for at least 10 years.[14] Beyond this threshold, the risk increases linearly with higher alcohol intake. Although this analysis did not detect gender-related differences, other studies suggest that women are more vulnerable, showing increased risk with much lower doses (>20 g/day) of alcohol consumption. Additionally, the Dionysos survey highlighted the importance of alcohol consumption patterns: individuals who consume alcohol between meals have a three- to five-fold higher incidence of alcoholic liver disease and cirrhosis compared to those who drink only during meals.[14] Furthermore, the role of the type of alcoholic beverage consumed remains controversial.

As previously mentioned, the damage resulting from the direct toxic action of alcohol and its metabolites is largely modulated by various cofactors, such as gene polymorphisms, gender, nutritional status, immunological response, and potential associations with other liver-damaging agents, including viruses and toxins.[12,13,15] In particular, some isoforms of enzymes involved in alcohol metabolism predispose individuals to liver damage. Population-based epidemiological studies have shown that polymorphisms of genes encoding ADH isoform 2, aldehyde dehydrogenase isoform 2, and allele 2 of ADH isoform 2 are associated with increased liver damage, even with the same amount of alcohol consumption.[12,13,15,16] Recently, gene polymorphisms related to lipid metabolism have been identified in the patatin-like phospholipase domain-containing 3 gene, which increases the risk of alcohol-related liver disease and/or hepatocellular carcinoma (HCC).[13] In addition, women have higher blood alcohol levels than men after consuming similar doses of alcohol (adjusted for body weight). This difference is attributed to lower body water content and reduced FPM due to decreased gastric ADH enzyme activity.[12,13,15,16] These factors increase ethanol bioavailability and make females more susceptible to alcohol-induced liver damage. Moreover, the gut-liver axis is a novel concept in alcohol-related damage.[17–19] Specifically, chronic excessive alcohol consumption can increase intestinal permeability, allowing endotoxins produced by gut bacteria to pass into the bloodstream (Fig. 3).[20] Once in the liver, lipopolysaccharide and pathogen-associated molecular patterns stimulate Kupffer cells to produce cytokines, such as tumor necrosis factor-alpha, interleukin-6, and transforming growth factor-beta, which play a crucial role in the development of alcohol-induced liver damage.[17–19]

Excessive alcohol consumption results in a wide spectrum of liver diseases,[13,21,22] collectively known as alcohol-associated liver disease, which includes liver steatosis, alcoholic steatohepatitis (ASH), alcohol-associated hepatitis (which can cause acute-on-chronic liver failure), fibrosis, and cirrhosis. The latter is characterized by severe complications, such as HCC.

The liver steatosis is the most common histopathological manifestation of alcohol-related metabolic damage, observed in 60–100% of individuals with excessive alcohol intake.[13,22] It is a benign, non-progressive condition that is generally reversible with cessation of alcohol intake. The ASH affects 10–35% of patients who misuse alcohol. Approximately 10% of ASH cases regress after discontinuation, while 50% progress to advanced fibrosis or cirrhosis with continued excessive alcohol use. The acute alcohol-

associated hepatitis is a progressive inflammatory syndrome typically associated with high levels of alcohol consumption (60–80 g/day for males and 20–40 g/day for females).[13,22,23] The fibrosis and cirrhosis occur in <10% of patients. The minimum acceptable ethanol consumption for liver health is estimated to be 2.6 g/day. Above this threshold, the relative risk of cirrhosis-related morbidity and mortality begins to increase. Meta-analytic evaluations suggest that the risk of developing fibrosis begins with daily consumption of 12 g/day for females and 24 g/day for males.[9,14,15,24] It has recently been suggested that Kupffer cells play a key role in fibrogenesis by being stimulated by alcohol to produce cytokines (particularly transforming growth factor-beta), which in turn stimulate stellate (Ito) cells to produce collagen. Cirrhosis typically develops after 10–15 years of excessive alcohol use and correlates with the overall dose consumed. Cirrhosis often progresses from the steatosis/fibrosis stage of alcohol-related damage without recurrent episodes of the acute alcohol-associated hepatitis. Transient elastography is a commonly used non-invasive method to assess liver stiffness, which can help identify patients with alcohol-induced fibrosis.[25] HCC is strongly associated with liver cirrhosis.[26] In cirrhotic patients, the annual incidence of HCC ranges from 1.5% to 5%. Several cofactors increase the risk of developing HCC, including hepatitis B and C virus infections, excess iron deposition in the liver, male sex, advanced age (as a marker of long-term disease), patatin-like phospholipase domain-containing 3 genetic polymorphisms, and advanced liver disease.[27]

Gastrointestinal tract

The digestive system is often one of the first to be affected by excessive alcohol consumption. The resulting damage can be either reversible or irreversible, depending on the frequency and mode of alcohol intake. From the oral cavity to the large intestine, alcohol can have profound toxic effects, resulting in various lesions throughout the gastrointestinal tract.[28]

Chronic alcohol consumption can lead to significant damage in the oral cavity. This includes stomatitis, often a result of nutritional deficiencies, and periodontal disease due to alterations in the oral microbiota. Changes in the bacterial environment can exacerbate gum disease and other oral health problems, highlighting the need for proper oral hygiene and dietary supplements for patients with chronic alcohol use.[29]

Alcohol can also cause substantial damage to the esophagus, both through direct toxicity to the mucosal lining and via alterations in esophageal motility and peristalsis.[28] The pathophysiological mechanisms by which alcohol damages the epithelium include epithelial transport abnormalities, intercellular junction disruptions, and impairment of the mucosal barrier. Additionally, alcohol reduces lower esophageal sphincter pressure and affects both esophageal motility and gastric emptying.[2–5,28] These changes increase the risk of developing gastroesophageal reflux disease, acute and chronic esophagitis, and Barrett's esophagus, a known precancerous condition. Excessive alcohol intake is also associated with a pro-emetic effect, which can lead to Mallory-Weiss syndrome, characterized by tears in the mucosal layer at the esophagogastric junction. Studies indicate that about 80% of patients with Mallory-Weiss syndrome had consumed large amounts of alcohol before the onset of symptoms.[2–5,28] Moreover, the stomach is also highly susceptible to damage from excessive alcohol consumption. The same mechanisms that cause esophageal damage can affect the stomach, leading to superficial gastritis, chronic atrophic gastritis, and, in the long term, intestinal metaplasia, a precursor to gastric cancer. Ethanol slows gastric emptying and increases gastric acid secretion, which can result in acute hemorrhagic gastritis.[2–5] In addition to a wide array of symptoms, irritation and inflammation of the gastric mucosa are associated with an increased risk of peptic ulcer disease.[2–5,28]

Furthermore, acute and chronic alcohol intake can also severely damage the intestinal mucosal barrier, leading to increased intestinal permeability—a condition known as 'leaky gut.' This results in the passage of macromolecules through the intestinal wall, contributing to dysbiosis, or an imbalance in the diversity and richness of gut microbiota.[17–19] This condition can exacerbate mucosal damage and impair nutrient absorption, leading to deficiencies in vital vitamins such as thiamine, ascorbic acid, and folic acid. Additionally, alcohol disrupts carbohydrate and lipid metabolism and reduces the activity of enzymes such as lactase and sucrase, promoting intolerances, including lactose intolerance. There is also significant evidence that alcohol alters intestinal motility. The effect of alcohol on small bowel motility varies depending on whether the consumption is acute or chronic. Acute alcohol administration inhibits small bowel transit, while chronic consumption of large doses accelerates small bowel transit.[2–5,30] Although ethanol primarily reaches the large intestine through the bloodstream, it still exerts harmful effects. Acetaldehyde, a toxic metabolite of ethanol, accumulates in the colon due to reduced activity of the ADH enzyme. The increased presence of acetaldehyde contributes to alcohol-related diarrhea. Chronic alcohol use also alters the morphology of the rectum. Histological examination of rectal biopsies from patients with chronic alcohol use disorder reveals significant abnormalities in the crypts, chronic inflammation, and epithelial cell proliferation. These changes can act as precursors to neoplastic processes, increasing the risk of colorectal cancer.[3–5,30,31]

Pancreas

The relationship between alcohol consumption and pancreatic diseases has been a subject of considerable research and clinical interest.[32,33] Chronic alcohol misuse is a well-established risk factor for the development of pancreatic diseases, ranging from acute to chronic pancreatitis and pancreatic cancer. In particular, pancreatitis is a common consequence of chronic alcohol consumption. It is estimated that approximately 70% of acute and 30% of chronic pancreatitis cases are attributable to alcohol misuse. As recently indicated by Rasineni *et al*., the pathophysiology of alcohol-induced pancreatitis is multifactorial and involves both direct toxic effects of alcohol and its metabolites on pancreatic cells, as well as indirect mechanisms mediated through the activation of inflammatory and fibrotic pathways.[34]

Acute pancreatitis (AP)

AP is a painful and potentially life-threatening condition characterized by inflammation of the pancreas. While various factors contribute to its onset, excessive alcohol consumption remains a significant risk factor. In Europe, approximately 10–50% of AP cases are attributed to alcohol consumption.[32] A systematic review and meta-analysis found that the relationship between alcohol consumption and the risk of pancreatitis is nonlinear. Beyond 40 g per day, alcohol consumption becomes detrimental, increasing the risk of AP.[35] Indeed, more than 80 g of alcohol intake per day for at least six to twelve years significantly increases the risk of developing symptomatic pancreatitis. The pathophysiology of AP involves a number of mechanisms. Alcohol consumption inhibits acinar cell secretion, leading to intra-pancreatic accumulation of digestive en-

zymes, causing auto-digestion and pancreatic tissue damage. Alcohol also promotes the production of pro-inflammatory cytokines, which exacerbate pancreatic inflammation. Alterations in cell permeability and increased cell necrosis further contribute to pancreatic injury. Hyperlipidemia, mainly sustained by elevated triglyceride levels, can also occur during acute alcohol intoxication, thereby aggravating the inflammatory response. One specific condition that may occur in alcoholic pancreatitis is Zieve's syndrome. This is characterized by a triad of hyperlipidemia (leading to milky serum), hemolytic anemia, and jaundice. Zieve's syndrome confers a more severe outcome to the clinical course of alcoholic AP.[33]

Chronic pancreatitis

Chronic pancreatitis is a prolonged inflammatory condition of the pancreas that results in permanent damage and fibrosis of exocrine and endocrine pancreatic tissues. One of the primary risk factors for developing chronic pancreatitis is chronic and excessive alcohol consumption. The relationship between alcohol intake and chronic pancreatitis is multifaceted, involving direct toxic effects of alcohol and its metabolites, along with indirect effects through interactions with genetic and lifestyle factors.[36,37] Chronic alcohol consumption results in the secretion of protein-rich pancreatic juice, which precipitates and forms plugs in the pancreatic ducts.[33] Over time, these protein plugs become calcified, giving rise to stones that cause ductal obstruction, worsening acinar damage and fibrosis throughout the pancreas. Furthermore, ethanol plays a significant role in the pathogenesis by inhibiting the sphincter of Oddi relaxation. This sphincter impairment contributes to stone formation in the gallbladder and biliary tract, which increases the risk of acute (or chronic) biliary pancreatitis and the development of chronic obstructive pancreatitis, thereby enhancing pancreatic fibrosis. Chronic inflammation and prolonged injury to the pancreas lead to major remodeling of pancreatic tissue, with massive fibrosis that ultimately exacerbates ductal obstruction and causes a progressive deterioration of pancreatic structure and function, reaching exocrine and endocrine insufficiency (usually when 80–90% of the pancreatic parenchyma is compromised). The loss of exocrine function can lead to malabsorption and nutritional deficiencies, while the loss of endocrine function can result in diabetes mellitus.[38] Genetic factors can modulate the susceptibility of individuals to alcohol-induced pancreatitis. For example, variants in genes encoding trypsin inhibitors or proteins involved in cellular junctions can increase the risk of developing chronic pancreatitis in heavy drinkers. Smoking, which often co-occurs with heavy drinking, can synergistically increase the risk and accelerate the progression to pancreatic damage.[36–38]

Gallbladder

Diseases affecting the gallbladder encompass a wide spectrum, ranging from asymptomatic gallstones to acute and chronic cholecystitis.[39] While the etiology of gallbladder disease is multifactorial, emerging evidence suggests a significant association between alcohol consumption and the development of these conditions, although the underlying mechanisms remain incompletely understood.[40]

Epidemiological studies have consistently demonstrated a positive correlation between alcohol intake and the prevalence of gallstones.[40] Indeed, alcohol can affect bile composition and secretion, leading to alterations in cholesterol and bile salt metabolism, which are key factors in the formation of gallstones.[41] Moreover, heavy alcohol intake is often accompanied by poor dietary habits and obesity, both of which are known risk factors for gallstone development.[42]

Moreover, chronic and excessive alcohol consumption is a known risk factor for gallbladder inflammation, which can lead to the development of both acute and chronic cholecystitis.[41] Alcohol can exacerbate inflammation within the gallbladder by promoting the secretion of inflammatory cytokines and increasing oxidative stress. Furthermore, alcohol abuse can lead to the formation of gallstones, which can obstruct the cystic duct and contribute to the development of cholecystitis.[43]

Gastrointestinal tumors

Alcohol is an important risk factor for gastrointestinal tumors. Indeed, ethanol metabolism produces acetaldehyde, which is considered a Group 1 carcinogen in humans by the International Agency for Research on Cancer. The main processes involved in acetaldehyde-induced carcinogenesis include the following aspects: (i) direct damage to DNA strands; (ii) inhibition of DNA repair mechanisms; and (iii) shortening of telomere length. Moreover, it is well known that alcohol metabolism produces reactive oxygen species and increases oxidative stress, which affect genome stability.[44,45]

Regarding esophageal squamous cell carcinoma, the most common type of esophageal cancer, alcohol is a well-established risk factor acting synergistically with cigarette smoking. In the USA, alcohol-related squamous cell carcinoma accounts for 72.4% of cases. In this context, the local production of acetaldehyde by opportunistic bacteria in the mouth and esophagus has been claimed to play an important role.[46,47] A very large study in the US demonstrated an association between heavy drinking (five or more drinks per day) and the risk of gastric cancer. In a national survey from 1999 to 2010, the risk of gastric cancer was significantly increased (OR 3.13, 95% CI: 1.15–8.64) in heavy drinkers.[48] Pancreatic adenocarcinoma represents a very severe form of cancer, with a five-year survival rate of about 9%. The most important risk factors are smoking, diabetes, chronic pancreatitis, and obesity. There is limited evidence of a relationship between heavy drinking and pancreatic cancer. However, the association between alcohol consumption and tobacco smoking seems to play a role in the cumulative risk of pancreatic cancer.[49]

Although the relationship between alcohol consumption and gallbladder cancer is less well-defined, some studies have suggested a potential link.[31,50] Indeed, chronic alcohol consumption seems to be associated with an increased risk of gallbladder cancer. Alcohol metabolism in the liver can lead to the formation of harmful by-products and oxidative stress, which may contribute to carcinogenesis in the gallbladder. Additionally, heavy alcohol intake is often associated with other risk factors for gallbladder cancer, such as obesity, diabetes, and a high-fat diet. Chronic inflammation of the gallbladder, which can result from alcohol-induced gallstone formation or chronic cholecystitis, may also play a role in the development of gallbladder cancer.[51] Both moderate and heavy drinking are associated with a statistically significant increase in the incidence of colorectal cancer, but not in mortality. A recent meta-analysis explored a possible carcinogenic mechanism of alcohol in the pathogenesis of colorectal cancer and found that DNA methylation induced by alcohol plays an important role.[52]

Discussion

Excessive alcohol intake can affect the entire digestive system, leading to a wide range of inflammatory and non-inflammatory

(direct toxic) changes, which result in various clinical phenotypes. The detrimental effects of chronic alcohol consumption can involve any segment of the gastrointestinal tract, from the oral cavity to the rectum. The nature and extent of the damage largely depend on the amount and frequency of alcohol intake.[31] Gender differences (e.g., reduced FPM in women) and the interaction of alcohol with other drugs may play a crucial role in interfering with ethanol metabolism. In addition, acetaldehyde and the role of alcohol-related endotoxemia can trigger liver damage through the release of a wide array of cytokines, which provoke cellular necrosis and acute hepatitis. As a result, several trials with antioxidants, antimicrobial agents, and anti-inflammatory drugs have been designed to target these mechanisms and mitigate alcohol-induced liver damage.[23] Interventions aimed at reducing alcohol consumption, along with early detection and management of pancreatic injury, are crucial to prevent the progression from acute insult to chronic pancreatitis and its associated complications, such as diabetes and pancreatic cancer. Notably, it is important to emphasize that even low levels of alcohol consumption increase the risk of cancer in the digestive system, including in the gallbladder.[51] In this context, liver cirrhosis, pancreatitis, and esophageal cancer remain the most frequent alcohol-associated causes of death. This narrative review does not allow for drawing definitive conclusions about the actual impact and outcomes of alcohol-related digestive clinical phenotypes. In-depth studies on this critical topic are therefore eagerly awaited.

Conclusions

It is recommended that individuals maintain minimal alcohol intake (i.e., social drinking, which is up to one drink per day for women and up to two drinks per day for men) and seek immediate medical evaluation if they are suspected of excessive alcohol intake and experience persistent digestive symptoms (e.g., abdominal pain, nausea, vomiting, diarrhea, and bloody stools). Patients with alcohol use disorder should seek professional support, including counseling, medication, and self-help groups.

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Conflict of interest

Fabio Caputo received honoraria for lectures, advisory board participation, or consultancies from Laboratorio Farmaceutico CT Sanremo. Roberto De Giorgio has been in the editorial board of *Journal of Translational Gastroenterology* since March 2023. All other authors declare no conflict of interests with any financial organization regarding the material discussed in the manuscript.

Author contributions

Giving substantial contributions to the conception or the design of the manuscript (FC, RDG), acquisition, analysis, and interpretation of the data (FC, MG, AC (A Casabianca), LL, AC (A Costanzini), GC), drafting the manuscript (FC, MG, AC (A Casabianca), LL, AC (A Costanzini), GC, GZ, RDG), and critically revision (FC, MG, AC (A Casabianca), RDG). All authors read and approved the final version of the manuscript. All authors contributed equally to the manuscript and approved the final version of the manuscript.

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