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Alcohol-related disease

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ABSTRACT

Alcohol, the most consumed drug in the world, is responsible for millions of deaths and a significant of disability-adjusted life years. Alcohol-related liver disease is the most recognized disease related to heavy ethanol consumption, the pathophysiology of wich we will cover extensively. However, pancreatitis, dilated cardiomyopathy, alcohol-related neurological diseases and other topics will be reviewed with detailed pathophysiological mechanisms and unifying concepts. Abstinence is the most effective treatment for alcohol-related disease, and an international effort should be made to promote a marked reduction in alcohol consumption.

INTRODUCTION

With circa 2.3 billion drinkers worldwide, alcohol is the most consumed drug in the world[1]. Its harmful use has been responsible for 3.3 million deaths yearly[2] and up to 8.9% and 6.8% of disability-adjusted life years in men and women, respectively[1,2]. Effective measures such as taxation and advertisement control have reduced alcohol-related mortality[3].

Beyond liver cirrhosis, the most well-established relationship with heavy alcohol consumption, many other organs are affected and may occur independently or associated with alcohol-related liver disease (ALD) (Table 1). This review will describe the pathophysiological, clinical and epidemiological aspects of alcohol-induced organ damage (Figure 1).

Table 1. Summary of drinking patterns and alcohol-related disease.

Definitions of drinking consumption	Light: ≤3 drinks/week Moderate: Women: 4-7 drinks/week; Men: 4-14 drinks/week Heavy: Women: ≥8 drinks/week; Man: ≥15 drinks/week Binge: Women: ≥4 drinks on occasion; Men: ≥5 drinks on occasion
Liver	Steatotic liver disease, fibrosis, cirrhosis, acute steatohepatitis, hepatocellular carcinoma
Central nervous system	Cerebellar degeneration, Wernicke encephalopathy, Korsakoff syndrome, Dementia, Seizures, Peripheral neuropathy, Marchiava-Bignami disease, cerebral atrophy with cognitive decline
Cardiovascular	Dilated cardiomyopathy, arrhythmias, hypertension, stroke, peripheral artery disease, coronary artery disease.
Pancreas	Acute and chronic pancreatitis, Diabetes mellitus type 3b, carcinoma.
Metabolic	Malnutrition, obesity, osteoporosis, sarcopenia, gout.
Infectious	Pneumonia, more prone to complications (and acute respiratory distress syndrome), the majority of which caused by *S. pneumoniae*.
Hematological	Iron-deficient, hemolytic and sideroblastic anemia, Sieve's syndrome, Leukopenia, Thrombocytopenia, Myelodysplastic Syndromes, Lymphoma, Myeloma.
Other	ARDS risk, IgA Nephropathy, falls and motor vehicle accidents with potential life-threatening fractures and cerebral contusions. Gastritis, esophagitis, and an increased risk of gastrointestinal bleeding, esophago-gastric cancer

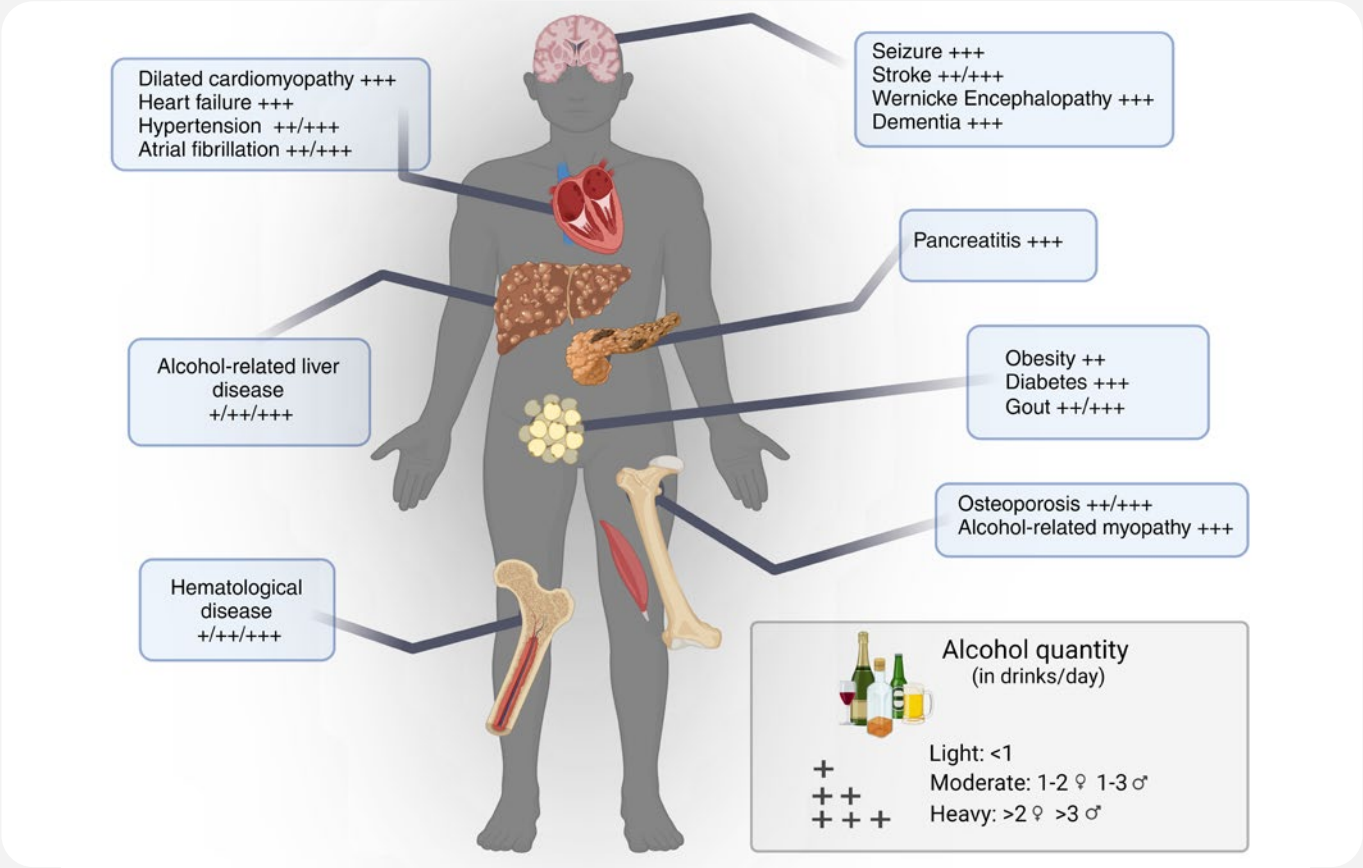

Figure 1. Alcohol-related multi-organ disease with respective impact of the quantity of alcohol consumption.

LIVER DISEASE

Introduction

ALD encompasses a spectrum of states related to alcohol-induced liver damage in patients with alcohol use disorder (AUD), ranging from simple steatosis to steatohepatitis, alcohol-related hepatitis (AH) and cirrhosis, culminating in hepatocellular carcinoma (HCC) (Figure 2).

Epidemiology

Although different patterns of alcohol consumption influence the rate of incidence and prevalence of ALD[1,4], their relationship is clear: incidence[5], hospital admissions and mortality due to ALD increase with higher levels of alcohol consumption[6], regarding steatohepatitis, cirrhosis, HCC and acute alcohol-related hepatitis, available epidemiological data varies between disease types and geographical location. While in the USA, mortality due to alcohol-related cirrhosis is 5.7/100 000 inhabitants (inhab), in Europe, it varies from 3-5.5/100 000 inhab[7,8].

In Latin America, alcohol is also the leading cause of liver cirrhosis, however, with varying rates of mortality, ranging from 3.9/100 000 inhab in Colombia to 20.1/100 000 inhab in Peru[8,9].

In these last three regions, ALD accounts for 60% of cirrhosis related cases[5] and globally for circa 50% of cirrhosis related deaths[6].

The Asia-Pacific region is heterogeneous due to the economic development in recent decades in some countries, while in others, religious practices remain a strong influence on alcohol consumption. For instance, in China and India, the yearly alcohol consumption per capita (ACPC) is circa 7-10 times higher (ACPC China 7.2 L, APCP India 5.6 L) than in countries such as Indonesia (0.8 L) or Bangladesh (0.0 L).[10]

Data for alcohol-related hepatitis is not as vast, but alarming, with high mortality in its severe forms[6,10], accounting for 0.8% of admissions in the USA[1]. Its incidence is probably increasing, with the contribution of the recent global pandemic, especially among young women[11,12].

Genetic and epigenetic factors

There is a multitude of data highlighting the role of genetic variability in developing ALD. In fact, only 10-20% of adults with AUD will develop ALD[3].

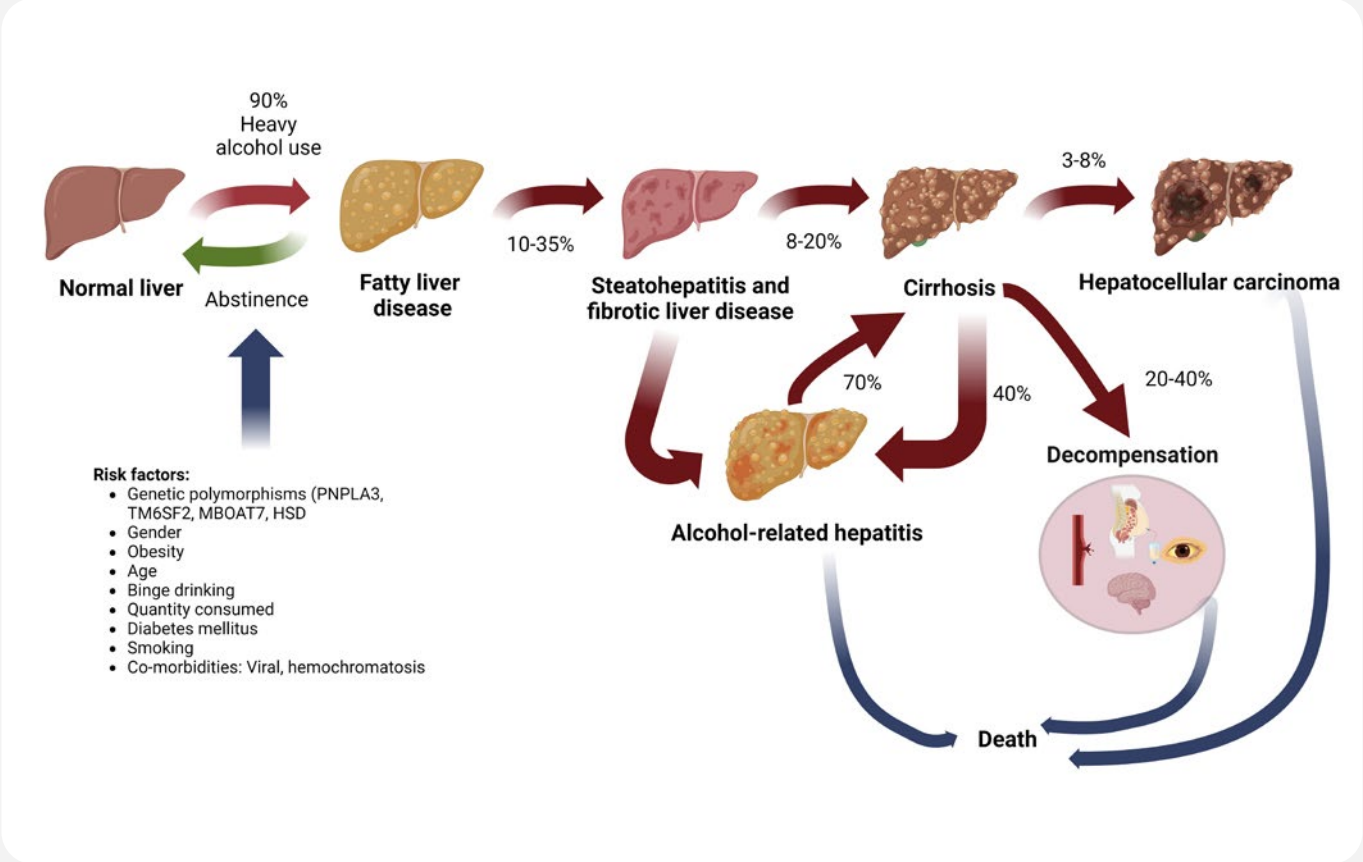

Figure 2. The natural history of alcohol-related liver disease.

Monozygotic twins show a greater concordance for ALD-cirrhosis than dizygotic twins[3,13].

The genes that are thought to play a major role in ALD progression are involved in the pathways of ethanol and lipid metabolism, and mediation of the inflammatory response. Patatin-like phospholipase domain-containing protein 3 (PNPLA3) (rs738409 in PNPLA3) is an enzyme responsible for lipid metabolism in hepatocytes, and Genome Wide Association Studies (GWAS) have implicated it in developing cirrhosis, HCC and metabolic dysfunction-associated steatotic liver disease (MASLD) in multiple populations[13-14]. The population-attributable risk for progression to cirrhosis with the risk allele in PNPLA3 was 26.6%[14,15]. This implies that although genetic risk plays an important role, in most cases, environmental and host-mediated risk factors modifiers are involved.

In the last decade, GWAS studies in European cohorts of ALD cirrhosis have detected other variants, such as in membrane bound O-acyltransferase domain-containing 7 (MBOAT7) and in TM6SF2[14]. Variants in TM6SF2[13,16] impair very-low-density lipoprotein metabolism17 and contribute to hepatic lipid trapping[16], whereas MBOAT7[13,18] is associated with the transfer of fatty acid between phospholipids and lysophospholipids, driving inflammation[16]. Various pathological variants in alcohol dehydrogenase (ADH) have also been identified in GWAS[13]. Inflammatory and fibrosis cytokines and chemokines, such as TNF-α[16] , the IL-20 family[19,20], the inflammasome[21] and CYP2E1[18,22,23] are associated with cirrhosis, AH and HCC development/progression. The involvement of CYP2E1 in alcohol metabolism and the development of ALD and alcohol-related HCC is discussed in detail in another chapter of this edition. More recently, a risk score based on three genetic risk variants and diabetes status stratified heavy drinkers based on their risk of cirrhosis, allowing for earlier preventative interventions[24].

Pathophysiology of alcohol-related liver disease

Ethanol exerts an influence on lipid metabolism, the redox system, organelle function, apoptosis/necroptosis, inflammation, fibrogenesis and epigenetics[18,21,22,25,26]. These processes interact synergistically and lead to steatohepatitis, cirrhosis and hepatocarcinoma[18,25].

Ethanol metabolism, steatosis, and inflammation

Ethanol is metabolized through two major pathways: ADH/Aldehyde Dehydrogenase (ALDH) and CYP2E1[22,25,26]. Ethanol is metabolized by ADH/generating acetaldehyde, which is further converted into acetate by ALDH, generating NADPH in the process[27]. Acetate, after binding to coenzyme A generates acetyl Co-A, can be used to generate energy in the Krebs cycle or for fatty acids synthesis[27].

NADPH shifts hepatocyte metabolism to fatty acid synthesis by inhibiting the Krebs cycle, leading to intrahepatic fat accumulation[25]. Fatty acids are either oxidized for energy use or esterified into triglyceride vesicles and released as VLDL[27,28,29] under normal circumstances, but this process changes with excessive alcohol consumption[27].

Fatty acid oxidation is markedly affected by excessive alcohol use: ethanol depolarizes mitochondria membranes, leading to defective beta-oxidation[27]. Excessive Malonyl-CoA, produced with increased ethanol consumption, also inhibits fatty acid transport to mitochondria[27]. Promoters of beta oxidation, such as PPARα, that increase gene expression related to the transport and oxidation of fatty acids are also inhibited directly by ethanol or adducts that result from its metabolism[27]. Fatty acid production increases with higher alcohol intake, and de novo lipogenesis is also amplified through enzyme induction by the SRKP2 gene, directly upregulated by ethanol[27].

The ADH/ALDH pathway leads to fatty acid accumulation, as depicted by steatosis, and produces other excess byproducts, such as aldehyde, acetaldehyde, lipid hydroperoxides, reactive aldehydes[26] malonyl-CoA, acetyl-CoA[27]. These interact with ROS that are generated by the Microsomal Ethanol Oxidizing System (MEOS) involving CYP2E1, inducible by alcohol consumption[18,25,26]. ROS, such as hydrogen peroxide, hydroxyethyl and hydroxyl radicals, superoxide anions[25,26], are generated by ethanol metabolism via CYP2E1[18,25,26]. Antioxidant defense systems, such as glutathione[22], are depleted by alcohol consumption[22,26], leading to ROS-mediated damage: inhibition of beta oxidation[27] mitochondrial damage, leating to hepatocyte death[26]. The major ethanol metabolism pathways interact in the pathophysiology of ALD when the excessive fatty acids and reactive aldehyde species, as mentioned above, react with ROS, forming lipid peroxides[25,26], which consequently produce lipid peroxide-DNA and acetaldehyde-DNA adducts that are highly carcinogenic, and promote inflammation and oxidative stress[22]. The reactive aldehyde species also react with lipid peroxides and produce acetaldehyde-lipid peroxide adducts that elicit immunogenic responses[18,26]. This leads to apoptosis and necrosis of hepatocytes[20,29], which releases danger-associated molecular patterns (DAMPs) that perpetuate hepatocyte injury[30].

All of the mentioned contribute to the inflammatory process in ALD development and progression. However, there is widespread immune system dysfunction, such as a reduction in natural killer cell activity, defective Kupfer cells (KC) clearance, dendritic cell suppression and T-cell apoptosis[25]. Concomitantly, there is also neutrophil infiltration and pro-inflammatory cytokines and gene activation and upregulation[25,31]. This probably shifts to an aberrant immune response to pathogens such as danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). There is a subsequent activation of a pro-inflammatory cascade, marked by elevated IL-1ß, IL-18, IL-6, TNFα, caspase-1, and activation of inflammasomes and toll-like receptors (TLRs)[28], perpetuating hepatocyte death and DAMPs generation[28].

One of the best-documented pathways of these inflammatory cascades involves lipopolysaccharide (LPS), the prototype for PAMPs. LPS is recognized by TLR4 from KC and leads to upregulation of nuclear factor kappa B (NFκB), mounting of an interferon response, and increased production of TNFα and ROS[32]. The excess fatty acids caused by chronic ethanol consumption increase the sensitivity of TLR4, which may amplify these inflammatory pathways[32]. Moreover, ethanol consumption, in particular, binge drinking, leads to increased intestinal permeability[27,28], which facilitates the translocation of pro-inflammatory agents.

These pro-inflammatory mediators subsequently stimulate hepatic stellate cell (HSC) activation and promote fibrogenesis that is characterized by excessive accumulation of collagen and other extracellular matrix proteins[33]. Activated HSCs, or myofibroblasts, are the major source of the increased production of extracellular matrix proteins, along with portal fibroblasts and bone marrow-derived myofibroblasts.

There are distinctive mechanisms playing a role in the development of alcohol-related liver fibrosis. Alcohol elevates LPS levels in the liver that directly and indirectly activate HSCs via TLR4[34]. LPS can also activate TLR4 signaling in hepatic sinusoidal endothelial cells, resulting in dysregulation of angiogenesis and subsequent promotion of fibrogenesis[34,35]. Furthermore, acetaldehyde directly targets HSCs and upregulates the expression of collagens in these cells[36]. Alcohol also suppresses the antifibrotic effects of NK cells and IFN γ, thus promoting fibrosis[37]. All these processes lead to hepatocyte destruction and scarring of the parenchyma.

Portal hypertension

Portal pressure is a result of blood flow and vascular resistance[31,38]. Increases in one or both components lead to portal hypertension (PH), which is defined as portal pressure >5 mmHg[31,38]. Vascular resistance depends on blood viscosity, liver fibrosis, depletion of intrahepatic vasodilatory agents and microthrombi in portal sinusoids[31,38]. All of them are a byproduct of the widespread inflammatory process, ROS production, hepatocyte dysfunction, and fibrogenesis described above. This leads to increased vascular tone, starting in perivenular fibrosis in the central veins and progressing to destruction of the vascular architecture[38].

In the context of liver cirrhosis, there is an initial elevation in portal venous pressure attributed to heightened resistance in the hepatic circulation. This resistance stems from both mechanical factors, involving the distortion of liver microvascular architecture, and dynamic factors, linked to endothelial dysfunction. Endothelial dysfunction results in a reduced presence of endogenous vasodilators, particularly nitric oxide (NO), and an augmented release of vasoconstrictors such as prostanoids, endothelins, and angiotensin, ultimately leading to an increased hepatic vascular tone. In the subsequent stages, the escalation of portal pressure prompts the development of portosystemic collaterals. These collateral vessels arise from the dilation of existing vascular conduits due to increased portal pressure and angiogenesis mediated by vascular endothelial growth factor. The subsequent increase in blood flow due to splanchnic vasodilation[31,38] is further augmented with translocation for intestinal bacteria and PAMPs[31]. The ensuing systemic vasodilation results in effective hypovolemia, triggering expansion of plasma volume and an increase in cardiac output. This hyperkinetic circulation further amplifies blood flow to splanchnic organs, contributing to an additional elevation in portal pressure[31,38].

Natural history of alcohol-related liver disease and management

Around 85-90% of heavy drinkers develop steatosis[39], typically macrovesicular, and 33% of those will progress to steatohepatitis. Although both may progress to cirrhosis, the risk is twice higher with steatohepatitis[40]. ALD, if not exacerbated by AH, follows a relatively stable clinical course until the development of decompensated cirrhosis, which is characterized by the development of ascites, hepatic encephalopathy, or variceal bleeding[31,41]. Treatment of these conditions is not the scope of this review, and there are specific guidelines for its management[41,42]. Alcohol abstinence is the cornerstone of therapy. In patients with PH due to alcohol consumption, abstinence reduces portal pressure and decreases the risk of decompensation and mortality[43,44]. PH is the lead driver of cirrhosis-related complications. Determination of portal pressure in a compensated cirrhosis phase through hepatic venous pressure gradient (HVPG) measurement, the gold standard, or by way of noninvasive tests, such as transient liver elastography and simple blood tests, helps to stratify patients at risk for decompensation and assess which have clinically significant PH[45]. Beta-blockers prevent decompensating events in patients with PH[45].

In addition to PH-related complications, acute liver injury, such as observed in AH, can present itself or progress to acute-on-chronic liver failure (ACLF), a syndrome of multi-organ failure superimposed on cirrhosis with mortality reaching 50%[31,46].

Alcohol-related Hepatitis (AH)

AH is an exacerbation of ALD with a clear relationship with ethanol consumption[30,47]. Its severe forms may reach a mortality of 50% within 3 months[6]. Contrasting the chronic processes described, here, there is a shift to a more acute inflammatory response to PAMPs, leading to the infiltration of neutrophils and hepatocyte destruction throughout the liver[30]. A recent review looked at potential inflammatory markers that could be associated with increased inflammation in AH[48,49], although not enough to create a unifying concept about triggers for the acute shift in the inflammatory response[49]. In a retrospective clinical study, the amount of alcohol intake was not able to differentiate between moderate AH and severe AH[48]. It can present in up to several weeks of ethanol abstinence[50] with jaundice, abdominal pain, fever, weight loss and signs of hepatic failure, and diagnosis is firmly established with a biopsy[6] that shows features of steatohepatitis, megamitochondriae, Mallory-Denk bodies, neutrophil infiltration, and bilirubinostasis[46,51].

Treatment includes glucocorticoids depending on disease severity (MELD score) and may be an indication for early transplant referral[2].

Hepatocellular carcinoma

HCC usually, but not always[52], requires a cirrhotic liver to emerge. The pathways described above, such as DNA adduct formation, lipid peroxidation, acetaldehyde-lipid peroxide adducts, protein nitrification, HSC activation, ROS production, are highly carcinogenic[22,26,28,45]. Acetaldehyde also inhibits DNA repair[6]. Genotoxicity, along with altered epigenetic expression, leads to chromosomal instability and oncogene expression[6,13,18]. Examples of these include NFkB induction of antiapoptotic genes[28], loss of imprinting and downregulation of cell differentiation genes[28]. HCC management is discussed in dedicated guidelines[53,54].

CENTRAL NERVOUS SYSTEM (CNS) DISEASE

About 50% of chronic alcohol users develop alcohol-related neurological diseases[55]. A recent study identified the presence of ALD in 37% of patients with Wernicke encephalopathy (WE)[56]. Similar mechanisms that occur in ALD are involved in the pathophysiology of neurological disease. Alcohol consumption affects, directly and indirectly, the neuroimmune system[57,58-59]. Widespread inflammation happens in microglia, astrocytes and neurons[58,59], with processes such as the production of ROS[57-59], and the amplification of the inflammatory cascade through TLR receptors that are also expressed throughout the CNS[60]. Alcohol consumption also influences gene expression[61], leading to the upregulation of pro-inflammatory genes such as NFkB. Macroscopically and over time, neuroinflammation manifests itself as widespread cerebral atrophy[57,59].

A particular example of alcohol-induced damage in the CNS is its effect on GABA levels. Synaptic dysfunction occurs due to increases in GABAergic activity[57] with consequent upregulation of NMDA receptors occurs[57]. These processes, combined with thiamine deficiency caused by malnutrition in patients with AUD, are the pathophysiological basis for cerebellar degeneration and alcohol withdrawal[57].

Cerebellar degeneration is characterized by lower limb ataxia and dysarthria that tend to occur mainly with chronic consumption[55,57]; nevertheless, these symptoms have been described after binge drinking[57]. Advanced cases may also present with upper limb ataxia[57]. The clinical diagnosis may be aided with imaging showing vermian atrophy[55,57].

Wernicke encephalopathy is dependent on thiamine deficiency, which is common in AUD. It develops over days to weeks and presents ocular abnormalities (nystagmus and/or ophthalmoplegia), mental status changes and ataxia. Neuroimaging shows changes in the thalamus, mammillary bodies, periaqueductal gray matter, oculomotor regions of the midbrain and the pons. Up to 80% of WE progress to Korsakoff Syndrome[55], which is characterized by confabulation due to retrograde and anterograde amnesia[62]. Treatment and prevention of these conditions is based on thiamine administration[55,62,63].

Alcohol-related dementia is a manifestation of the continuous damage of chronic excessive alcohol consumption (>36 g daily) through the pathophysiological mechanisms described above[59]. These may be aggravated by thiamine deficiency, but may also occur independently[55]. The particular damage to the prefrontal cortex and limbic systems[55,59], as well as the loss of cognitive flexibility[59], lead to the manifestations of this type of dementia. Contrasting with other types, alcohol-related dementia has no specific clinical profile, and patients may partially recover with abstinence[62].

Peripheral neuropathy is present in up to 90% of patients with AUD[55] and is caused mainly by the direct toxic effects of ethanol on nerve cells[62]. It presents in a stocking glove distribution and may aggravate cerebellar ataxia in late phases due to sensorimotor involvement[55,62].

Marchiava-Bignami Disease is a rare, demyelinating form of alcohol-related neurological disease[55] with a characteristic degeneration of the corpus callosum shown on imaging[64]. It presents with a wide array of neurological symptoms that may involve higher cortical functions[64] and may easily be mistaken for dementia. Thiamine deficiency may play a role in its pathophysiology. Treatment encompasses thiamine supplementation and ethanol abstinence[64].

Although treatment remains largely abstinence and thiamine supplementation, the documentation of cumulative doses might help distinguish and anticipate disease.

CARDIOVASCULAR DISEASE

There are two main considerations when analyzing the interaction between ethanol and the cardiovascular system: alcohol-induced cardiomyopathy and arrhythmias[65,66,67].

Concerning cardiomyopathy, the heart is the second most common organ to be affected by ethanol toxicity after the liver[65], with a prevalence estimated between 20-30% in AUD patients[65,67]. Ethanol directly causes ion channel dysfunction, sarcomeric disruption, NFkB upregulation, decrease of cardiomyocyte regeneration and protein synthesis[65,68]. Acetaldehyde induced protein-adducts create additional immunological heart damage[65], contributing to interstitial fibrosis[69].

The dose thought to cause ACM ranges between 60-90 g/day for 5-10 years[66], presenting with a classical heart failure syndrome with pulmonary and peripheral congestion[67]. This amount of excessive alcohol consumption, together with left ventricular dilation and reduced ejection fraction, is readily diagnosed using a transthoracic echocardiogram after exclusion of other causes[70,71]. The treatment is similar to other dilated cardiomyopathies, involving standard heart failure therapy and management of congestion with diuretics[67]. Abstinence from ethanol allows for recovery in most cases[65].

Heavy drinking is associated with an increased risk of developing atrial fibrillation (AF) in a dose-dependent manner, increasing up to 8% with each excessive daily drink[68,72], and with binge drinking episodes[67,68]. In the

latter, AF presents circa 12-36 hours after alcohol intoxication[68,73]. Abstinence might reduce AF recurrence[73].
The shortening of the effective refractory period, slowing of intra-atrial conduction, and induction of atrial fibrosis have also been documented[67,68].
Supraventricular and ventricular arrhythmias are also associated with alcohol binge drinking, albeit less frequently[68,73,74].

PANCREATIC, ENDOCRINOLOGIC AND METABOLIC DISEASE

Between 30-50% of cases of acute pancreatitis (AP) are alcohol-related[75,76], representing the main cause of chronic pancreatitis[76,77]. Ethanol leads to the premature activation of zymogens in pancreatic acinar cells, thereby initiating the inflammatory process[78]. AP severity increases when alcohol-related AP is combined with other aetiologies such as hyperlipidemia[79]. Its presentation does not differ from the others with the classical belt-like abdominal pain, nausea, vomiting and elevated serum amylase and lipase[76].
A daily intake of 60-80 g is a clear threshold for the development of chronic pancreatitis[67,77], and can coexist with ALD[80,81]. It is a disease that affects mainly men, but prevalence among women has increased over time[77,82].
Its pathophysiology is complex, involving recurrent cycles of pancreatitis flares-regeneration (necrosis-fibrosis process), promoting scar tissue formation, pancreatic parenchyma destruction and ductular distortion and direct toxic effect on acinar, ductular and stellate cells[77,83]. Genetic polymorphisms in transport channels also play a role in chronic pancreatitis progression[77,81-83].
Chronic pancreatitis presents with recurrent pain in a patient with a history of pancreatitis, followed by steatorrhea and diabetes mellitus (DM)[76,77,82]. The diagnosis consists of a typical clinical history and imaging (CT/MR) findings of pancreatic calcifications or characteristic pancreatic ductal changes. Medical treatment is centered on alcohol discontinuation, analgesic agents, pancreatic enzymes and antioxidants[82].
DM follows the same relationship as cardiovascular disease. Widespread data shows that light to moderate alcohol intake does reduce DM incidence, while higher amounts may increase it[84-88]. To further strengthen this evidence, moderate alcohol intake is also associated with increased insulin sensitivity in non-diabetic patients[89,90].
A recent meta-analysis of prospective cohort studies[85] found that alcohol intake >57 g/d was associated with an increased risk of DM in men, a number similar to the one associated with the development of CP. Sex discrepancy might be associated with the transporter mutations described previously, which are more prevalent in men[82,85].

MALNUTRITION AND OBESITY

Alcoholic beverages are rich in calories, and ethanol is the second most caloric dense energy source that humans consume[91]. Similar to the argument of sweetened beverages, calories coming from alcoholic beverages can significantly increase daily energy intake and thus contribute to the development of obesity. Alcohol stimulates food intake by inhibiting leptin and glucagon-like peptide 1[92] and its metabolization to acetaldehyde and acetate facilitates readily available energy substrates, inhibiting fat mobilization[93].
There is low-quality data associating weight loss with abstinence from previous moderate drinkers and weight gain from stable heavy drinkers at 5 years[94,95]. The latter association is counterintuitive since heavy drinking is often associated with malnutrition. However, five years may not suffice to observe alcohol-induced malnutrition. Other cross-sectional data associates heavy drinking habits with obesity[92], but it remains challenging to correlate this single variable (alcohol intake) with so many others that account for weight gain. Observational longitudinal evidence is conflicting[92,96]. There is some (short-term) experimental evidence that suggests no relationship: the addition of 270 mL of red wine for 6 weeks resulted in no change in weight in a group of men[92,95].
Alcohol consumption and obesity act synergistically, accelerating the progression of chronic liver disease[97]. Obesity, along with other components of metabolic syndrome, exerts a major role in the development of MASLD[97]. Excessive caloric intake and alcohol[98] both lead to lipolysis in the adipose tissue and consequently increased fat deposition in the liver parenchyma, potentiated by insulin resistance[97]. The hepatic parenchymal damage happens through immunologically mediated pathways similar to ALD, such as organelle dysfunction and oxidative stress[99]. For instance, diabetes and obesity induce CYP2E1, thereby amplifying alcohol-mediated damage[98]. Gut microbiome in MASLD leads to ethanol synthesis, increasing intestinal permeability and PAMPs translocation[99].
A particularly harmful combination is obesity and binge drinking[100]. A high-fat diet and binge ethanol consumption simulate the same inflammatory profile as in alcohol-related hepatitis[100] in mice. Both MASLD and ALD share the same genetic background, such as the aforementioned PNPLA3, TM6SF2 and MBOAT7, as well as other common genes are involved in MASLD progression[98,99].

In epidemiological studies, it is evident that cirrhosis, liver cancer and liver-related death are more prevalent in patients with an excessive alcohol consumption with concomitant metabolic syndrome or risk factors[101].
Another robust association is the one between ALD and malnutrition. It is associated with a higher rate of decompensation of cirrhosis[102-104]. Data for AUD is not as extensive. Although alcoholic beverages are rich in calories and their consumption inhibits leptin, in a disease state such as ALD decreased food intake, malabsorption and a hypermetabolic state are common[102,104].
Appetite is reduced due to early satiety, also influenced by ascites, persistent elevated levels of TNF-alpha and dysgeusia caused by zinc deficiency[102]. Less palatable food because of salt restriction might also play a role in malnutrition in cirrhotic patients[104].
Cirrhosis induces a hypermetabolic state, documented by calorimetry[104], through several processes. These include: saturation of the MEOS system that utilizes significantly more ATP, low-grade endotoxemia that induces a state of persistent low-grade inflammation, thermal loss with ascites and altered macro- and micronutrient balance culminating in a negative nitrogen balance, gluconeogenesis through proteolysis, progression of steatosis and multiple vitamin and ionic deficiencies[102,104].
Portosystemic shunts might aggravate malnutrition by bypassing the first pass of many nutrients and toxic substances through the liver[104].
The prevalence of malnutrition in patients with cirrhosis lies between 20-60%[103,104], and nearly every patient with AH presents with malnutrition[2,93,105].
Adequate and long-term supplementation are measures that need to be taken as soon as cirrhosis is diagnosed. This evidence is further corroborated by associated sarcopenia and osteoporosis, as described below.

BONE AND MUSCLE DISEASE

Alcohol has a myriad of direct and indirect effects on bone metabolism. In in vitro studies, excessive consumption shows altered levels of osteoprotegerin, insulin-like growth factor 1, receptor activator of nuclear factor-κB (NF-κB; RANK), and its ligand (RANKL), decrease in osteogenesis, increase in adipogenesis and activation of senescence pathways in osteoblast transformation of mesenchymal stem cells into adipocytes[106,107].
Indirect effects account for lifestyle habits related to AUD, such as malnutrition leading to ion deficiencies, as well as reduced sunlight exposure contributing to decreased levels of vitamin D[94,106,107]. Besides osteoporosis, excessive alcohol intake is associated with frequent falls, accidents and fractures[94].
Despite this evidence, prospective observational studies show a J-curve relationship between ethanol intake and development of osteoporosis. Alcohol consumption is positively correlated with increased bone mineral density (BMD) in postmenopausal women in up to 29 g/d and in men in up to 55 g/d[106,107]. However, excessive intake, such as 4 daily drinks, is associated with lower BMD, cortical thickness and osteopenia[106,107]. Moreover, abstinence for as little as 90 days is linked to an increase in femoral BMD[106].
Although sarcopenia is commonly found in patients with AUD, particularly if associated with cirrhosis, the direct effect of heavy alcohol consumption on muscle has not been widely explored.
In vitro, ethanol impairs skeletal muscle protein synthesis[108]; however, meta-analyses fail to establish that relationship, also, in part, because of different methodological aspects, such as diverse cutoffs to define sarcopenia[108,109]. A recent cross-sectional study found an association between moderate alcohol consumption and lower muscle mass in men but did not manage to establish an association with sarcopenia[110]. Sarcopenia occurs in up to 70% of patients with cirrhosis[111], and because of the hypermetabolic mechanisms described above, sarcopenia propagates and perpetuates a cachexia[111,112]. The impact of sarcopenia in cirrhosis is significant to the point that a MELD-Sarcopenia score has been developed and showed an improved prediction of mortality in patients with lower MELD scores[113].

INFECTIOUS DISEASE

AUD patients have an increased risk of infection and sepsis[114-116]. This is due to widespread immune dysfunction/paresis, intestinal dysbiosis, increased risk of aspiration and defective mucociliary function[114]. The best available literature concerns pneumonia and respiratory sepsis. Ethanol use is associated with an increased risk of community-acquired pneumonia, as well as more virulent microorganisms, parapneumonic effusion and empyema[116].

HAEMATOLOGICAL DISEASE

Alcohol causes hematopoiesis dysfunction in the three blood cell lineages[117]. Acetaldehyde adducts interfere with cell replication[117]. Excessive consumption may culminate in one or more cytopenias or pancytopenia, which may also be associated with malnutrition states[118] and hypersplenism[119]. The factors predicting which and how many cell lineages affected are not clearly described.

Leukopenia is mainly expressed through neutropenia. Excessive ethanol intake, mainly in a pattern of chronic consumption plus binge, leads to the depletion of granulocyte precursors by mobilization to the peripheral circulation, while inhibiting their differentiation[120]. Furthermore, neutrophils are dysfunctional with chronic excessive alcohol consumption. Thereby, granulocyte-colony stimulating factor has been proposed as a potential therapy in severe infections frequently detected in AUD or AH patients[120].

Anaemia can occur by various mechanisms that may coexist in AUD. Although alcohol consumption downregulates hepcidin, leading to potential iron overload, anaemia is frequent in ALD[121].

Ethanol damages erythroid precursors and leads to sideroblastic anaemia. In patients with AUD, nutritional deficiencies (B complex vitamins, folate and iron), gastrointestinal blood loss and forms of hemolytic anaemia can also be found[121,117]. The latter, spur cell anaemia, usually occurs in cirrhosis due to impaired cholesterol metabolism[121], with hemolysis happening because of a fragile membrane once erythrocytes meet splenic macrophages. A particular form of hemolytic anaemia in ALD is Zieve's Syndrome, consisting of a triad of jaundice, hyperlipidaemia and hemolytic anemia[122], which might correlate temporarily with AP[123] or AH[124].

Finally, alcohol interferes in platelet function and production, leading to thrombocytopenia[125]. Ethanol directly impairs megakaryocyte maturation[117] and decreases in platelet count are observed circa 4 h after ethanol solution infusions[125]. Furthermore, ALD may lead to lower levels of thrombopoietin[125]. Data regarding the prevalence of ethanol-induced thrombocytopenia is scarce; however, it is estimated to be frequent and is detected in up to 25% of hospitalized AUD patients[125].

CONCLUSIONS

Abstinence is the most effective way to stop and reverse alcohol-induced organ damage. Urgent strategies to decrease societal stigma and governmental approaches such as taxation and better labelling of alcohol content are required. International academic societies in alcohol research should aim to reach a consensus regarding a standardized measure of alcohol consumption to improve and homogenize research. Healthcare services and professionals must improve pathways of referral to addiction care and specialized therapy.

Conflict of Interest

The authors deny any conflict of interest.

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