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Alcohol, smoking and the liver disease patient

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A B S T R A C T

Alcohol is an established risk factor for cirrhosis. Current recommendations for a “safe” limit for alcohol consumption are usually set to around 30 g of alcohol per day for men and 20 g per day for women, but evidence is mounting that these cut-offs might be set too high. Also, inter-individual differences in the hepatic sensitivity for alcohol likely play into the risk of development of cirrhosis. In patients with concomitant liver diseases, a synergistic effect on fibrosis progression and high consumption of alcohol is evident. The role of low to moderate consumption is less clear.

Alcohol can also lead to a specific inflammatory state in the liver, alcoholic hepatitis (AH). Treatment of severe AH consists of corticosteroids, which are at best moderately effective, and new treatments are needed.

Liver transplantation is an option in severe alcoholic liver disease, although selection of patients that are at a very low risk of post-transplantation alcohol consumption is paramount. There is some evidence to suggest an increased risk for fibrosis progression and development of hepatocellular carcinoma specifically for smoking.

1. Introduction

Practising gastroenterologists are highly likely to come across patients with alcoholic liver disease during one's career. There is a large disease spectrum, including patients with only mild elevation of liver transaminases, to end-stage cirrhotic patients and development of hepatocellular carcinoma. Knowledge of how to best care for these patients are of importance to increase patient survival. This review covers several aspects of alcoholic liver disease, including alcoholic hepatitis and development of hepatocellular carcinoma.

1.1. Epidemiology

Consumption of alcohol might have started as early as 10.000 BCE [1,2], and is today common in most human cultures. 86% of US citizens report any lifetime consumption of alcohol [3], and the mean yearly consumption of alcohol in the US is currently 8.6 L of pure alcohol, compared to 6.2 L per year globally [4]. Alcohol accounts for roughly 85.000 deaths per year in the US [5]. In Europe, alcohol is estimated to be responsible for around 6.5% of all deaths, and globally 5.9% of mortality can be attributed to alcohol [4]. Alcoholic liver disease (ALD) can be defined as different stages of liver damage due to consumption of alcohol, and is a major cause of cirrhosis [6].

1.2. Pathophysiology

Alcohol is mainly metabolised into acetaldehyde by intestinal and hepatic alcohol dehydrogenase, but can also be oxidized by microsomal CYP2E1 [7–9]. The CYP2E1 system normally accounts for a smaller proportion of alcohol oxidation, but is inducible by its substrates and can be highly upregulated in persons who consume high quantities of alcohol [8,10]. Induction of CYP2E1 leads to increased production of reactive oxygen species and DNA damage, thought to increase the risk of cancer development [11]. Independent of pathway, the intermediate product of ethanol metabolism, acetaldehyde, is highly reactive and carcinogenic [12], and thought to be a main contributor to alcoholic liver disease [13]. Acetaldehyde is further metabolised into acetate, which is then broken down into water and carbon dioxide.

Enzymes involved in ethanol metabolism are highly expressed in hepatocytes, which can explain why the most harmful effect of

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ethanol is seen in the liver. A more extensive review of the pathophysiological mechanisms in alcoholic liver disease was recently published [13].

1.3. Alcoholic liver disease with cirrhosis

Alcohol accounts for up to 50% of all deaths in liver cirrhosis globally [4], with this figure being 60–80% in Europe [14]. Conversely, 1% of all alcohol-attributed deaths are attributed to alcoholic liver disease, including cirrhosis [15]. Alcoholic liver disease is also a major cause for liver transplantation world-wide, and is the second most common indication for liver transplantation in Europe and the third in the US [16,17].

1.3.1. Risk modifiers

Although approximately 90% of persons who consume more than 60 g of alcohol per day, roughly equivalent to five to six units of alcohol depending on the definition of a unit, develop steatosis [18], significant fibrosis or cirrhosis is only seen in up to 30% of this population [19–21]. In contrast, a low to moderate consumption of alcohol, usually defined as below 20 g per day in women and 30 g per day in men is currently considered safe in most countries [22,23], although a more restrictive approach is currently advocated in some countries, including the UK where the recommended maximum intake for men is now two drinks per day [23]. Importantly, data from meta-analyses suggests that the risk for cirrhosis is present already for persons consuming more than 25 g of alcohol per day [24], and another study found that an increased risk for liver-related mortality can also be found in persons consuming between 12 and 24 g of alcohol per day, corresponding to 1–2 drinks per day [25].

Nevertheless, it is obvious that there are inter-individual differences on the risk of developing severe ALD including cirrhosis. These include environmental and genetic differences, many of which are currently unknown.

Environmental factors include binge-drinking, usually defined as consuming more than five units of alcohol at the same occasion for men and four for women. Binge-drinking has been associated with a higher risk of both ALD and mortality [26] and drinking outside of meals was in the landmark Dionysos study associated with a 2.7-fold increased risk for ALD compared to drinking only at mealtimes [22].

Some epidemiological evidence suggests that persons that primarily drink wine might be at a lower risk for development of cirrhosis compared to patients that drink spirits or beer independent of the quantity of consumption [27,28]. However, caution must be taken when interpreting the results of these studies. Persons that drink wine might be at a lower risk for cirrhosis due to other factors, including a lower risk of increasing the level of alcohol consumption (and thus de facto drinking more) [29], as well as other factors such as smoking, use of narcotics and differences in binge-drinking.

Of genetic risk modifiers, the most obvious one is gender. Women are at a higher risk for developing ALD given the same exposure to alcohol, which can partly be explained by differences in gastric alcohol dehydrogenase and a higher proportion of body fat leading to higher serum concentrations of ethanol [30]. In a twin study of more than 15 000 male twins, presence of alcoholic cirrhosis was three times more common in monozygotic twins compared to dizygotic twins [31], which can be considered a strong indication for genetic risk modification on fibrosis progression in ALD. Recently, several genome-wide association studies have identified a strong association between mutations in the PNPLA3, TM6SF2 and MBOAT7 genes [32–35] with ALD and alcoholic cirrhosis. These finding are promising for understanding the pathophysiology behind severe ALD, however none are to date used in clinical practice.

1.4. Alcoholic hepatitis

Alcoholic hepatitis (AH) is a complication of long-standing ingestion of ethanol [36]. The diagnosis of AH can be difficult to differentiate against acute-on-chonic liver failure, and the gold-standard diagnosis of AH is liver biopsy although it is rarely performed due to risk of bleeding and infection. If needed, a transjugular approach is considered safest [36]. Histologically, AH is defined as ballooning degradation of hepatocytes, parenchymal inflammation and steatosis, with or without fibrosis. Cirrhosis might be present, but is not mandatory for the diagnosis of AH. Patients with alcoholic hepatitis usually present after an extended period of binge-drinking, and at presentation jaundice, fever and abdominal pain are common attributes. It is vital to rule out acute-on-chronic liver failure and precipitating bacterial infections [36]. After this, staging of disease into severe and non-severe AH is appropriate as cases with severe AH have a high mortality of around 30–40% six months after presentation [37], and should be considered for treatment with corticosteroids, unless contraindications such as uncontrolled infection is present. Cases with non-severe AH have a good prognosis without pharmacotherapy, and treatment consists of abstinence and proper nutrition.

There are several scoring systems to identify cases with severe AH, including the Maddrey score [37] the Glasgow alcoholic hepatitis score [38] and the MELD score [39], as presented in Table 1.

The most important factor for all forms of AH is cessation of alcohol consumption, as recidivism is associated with a pessimistic prognosis including increased mortality [40]. Following diagnosis of severe AH, pharmacotherapy should be initiated in selected patients. Initial results with corticosteroids indicated a survival benefit [37], and this has been the mainstay of therapy since more than 40 years [41,42]. However, results from the large STOPAH trial in UK in which more than 1000 patients with severe AH were randomized to receive therapy with either prednisolone-placebo, prednisolone-pentoxifylline, pentoxifylline-placebo or placebo-placebo has somewhat challenged this, as no clear overall survival benefit was seen after 28 days or one year for patients on prednisolone treatment compared to placebo [43]. Nevertheless, mortality in the prednisolone-treated groups was relatively increased due to a higher proportion of patients that developed bacterial infections. Thus, some patients might indeed benefit from prednisolone treatment, but strong vigilance for detection of bacterial infections is needed, and these should as stated above be actively screened for before initiation and during therapy.

Importantly, one week after initiation of steroid treatment,

Table 1
Scoring systems used to define severe alcoholic hepatitis.

Scoring system	Parameters included	Cut-off for treatment initiation	Link to calculator
Maddrey score	Patient PT, lab PT, Bilirubin	32 or higher	https://www.mdcalc.com/maddreys-discriminant-function-alcoholic-hepatitis
Glasgow alcoholic hepatitis score	Age, WBC, urea, Bilirubin, patient PT, lab PT (or INR)	9 or more	http://www.gastrotraining.com/calculators/glasgow-alcoholic-hepatitis-score
MELD	Dialysis, creatinine, bilirubin, INR, sodium	18 or higher	https://www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older

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