

# Alcohol and Obesity: A Dangerous Association for Fatty Liver Disease

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## Key Words

Alcoholic liver disease · Nonalcoholic fatty liver disease · Metabolic syndrome · Obesity · Synergism

## Abstract

Alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD) are the most frequent chronic liver disorders, and their advanced forms – alcoholic steatohepatitis and nonalcoholic steatohepatitis – are the most frequent conditions leading to liver cirrhosis and hepatocellular carcinoma worldwide. NAFLD is considered as the hepatic manifestation of the metabolic syndrome. With the pandemic rise of obesity, the incidence of NAFLD is also further increasing, and considering the life style in modern societies, there is a significant overlap of (risk factors causing) NAFLD and (alcohol consumption predisposing for) ALD at least in Western countries. Epidemiological studies propose a causative link between chronic alcohol consumption and progressive liver disease in obese individuals. Furthermore, experimental studies indicate combined pathological effects of alcohol and obesity or fatty acid levels, respectively, on hepatocellular lipid accumulation and injury as well as hepatic inflammation, fibrosis and cancerogenesis. Notably, these combined pathological effects are in part additive but partly even synergistic. And importantly, alcohol does already exhibit synergistic pathological effects with obesity at moderate doses. This indicates significant differences in the dose threshold for hepatotoxic alcohol effects in lean and obese subjects and herewith also has important implications for

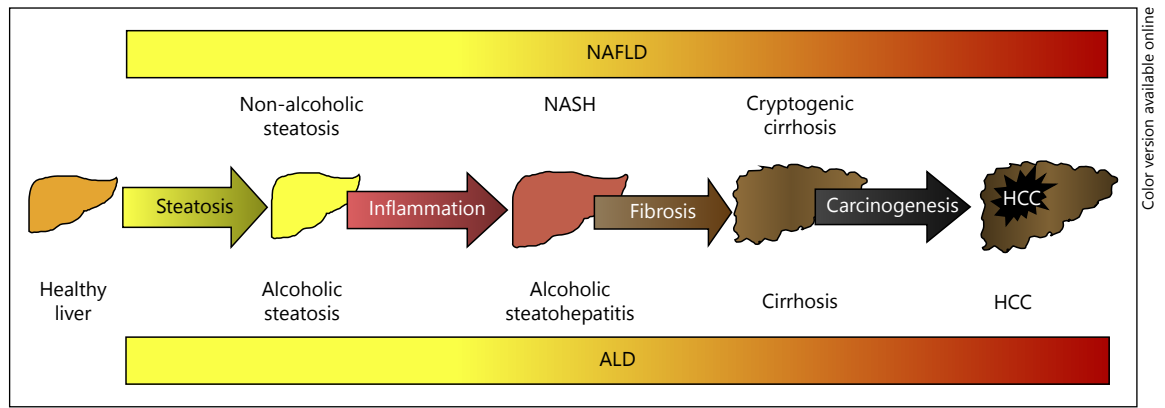
recommendations for ‘safe’ alcohol consumption. The purpose of this brief review is to update the knowledge on the combined effects of alcohol and obesity on the development and progression of liver disease. Undoubtedly, alcohol and the metabolic syndrome appear as a dangerous mix, and there are important interactive effects of either condition with regard to crucial triggers of liver injury.

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## Introduction

Chronic and excessive alcohol consumption can lead to the development of alcoholic liver disease (ALD), which is a critical health problem in many countries [1]. The spectrum of liver injury ranges from steatosis and steatohepatitis to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Hepatocellular lipid accumulation is the first pathological step of ALD. Alcohol is predominantly metabolized in hepatocytes, and in the oxidation of ethanol to acetaldehyde, NAD is reduced to NADH, which promotes fatty acid synthesis while counteracting lipid catabolism, thus leading to fat accumulation in hepatocytes [2, 3].

More recently, the pathophysiological significance of hepatic lipid accumulation in the absence of significant alcohol consumption is increasingly recognized. Today, nonalcoholic fatty liver disease (NAFLD) is considered the most common cause of liver enzyme elevations in Western countries [4]. In most cases, NAFLD is associ-



**Fig. 1.** ALD and NAFLD have very similar pathophysiological steps of disease progression, that is, hepatic steatosis, inflammation and fibrosis. Progressive hepatic fibrosis may ultimately lead to cirrhosis, the major risk factor for HCC.

ated with (components of) the metabolic syndrome, that is, central obesity and insulin resistance with resulting diabetes type 2, dyslipidemia and hypertension. Therefore, NAFLD is regarded as the hepatic manifestation of the metabolic syndrome. Very similar as in ALD, NAFLD encompasses a wide range of pathological conditions from mild hepatic steatosis to steatohepatitis (a syndrome named non-alcoholic steatohepatitis (NASH)) with significant necroinflammation and progressive fibrosis. In its advanced form, NASH is believed to account for a large fraction, if not entirely for what was previously termed ‘cryptogenic cirrhosis’ and also progresses to HCC in a significant number of cases [5, 6]. Also, hepatocellular fat accumulation is the first pathological step in NAFLD (fig. 1). The metabolic syndrome is associated with increased levels of circulating free fatty acids (FFA) [7] and the rate of hepatic FFA uptake is not regulated. Therefore, hepatic uptake of FFA is proportional to plasma FFA concentrations and the predominant reason for hepatocellular fat accumulation in NAFLD [8].

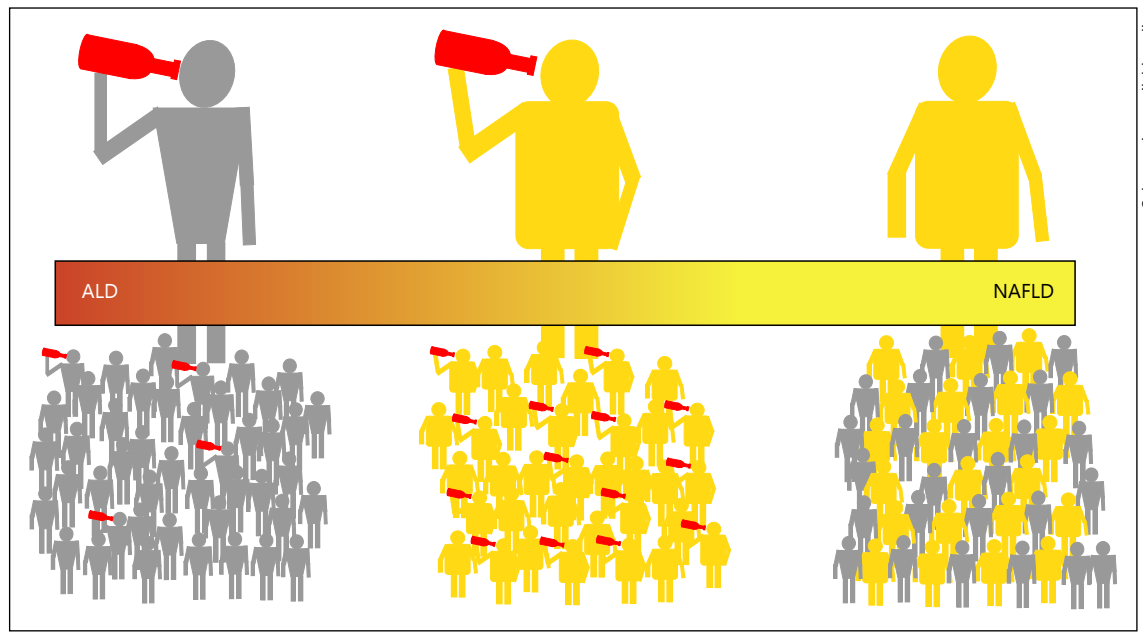
### Epidemiology of Alcoholic and Non-Alcoholic Fatty Liver Disease

NAFLD reveals a drastically rising prevalence due to a lifestyle favoring the development of the metabolic syndrome, and today more than half of the adult population in most Western countries has already been found to be overweight. Furthermore, regardless of the precise definition of safe margins for the dose of daily alcohol consumption, certainly, a 2-digit percentage of the population in Western countries chronically consumes alcohol

in amounts that predispose for ALD. Therefore, based on statistical numbers, there is a considerable overlap of individuals with both (components of) metabolic syndrome and chronic alcohol consumption. In addition, it has to be considered that in modern societies, people frequently drink alcohol with high caloric foods. Therefore, the overlap of obese and alcohol-drinking individuals is even larger than pure statistics would predict and it may constitute even the vast majority of cases (fig. 2). Certainly, a critical question is the definition of safe margins for the dose alcohol consumption. Dosis facit venenum, and certainly, this is also true for alcohol intake. However, the dose threshold of alcohol for its hepatotoxic effects depends on a variety of factors including ethnicity and gender [9]. Guidelines from the European Association for the Study of the Liver and the American Association for the Study of the Liver recommend <30 g of alcohol per day in man and <20 g of alcohol per day in women [9, 10]. Also, the Asian Pacific for the Study of the Liver guideline defines different levels of daily alcohol consumption for men and women (<20 and 10 g, respectively) as ‘safe’. So far, body weight and obesity are not considered in guidelines. In fact, existing cutoff levels are used to differentiate ALD from NAFLD in most clinical trials.

### Combined Effects of Alcohol and Obesity on the Development and Progression of Liver Disease

Actually, it appears likely and plausible that the combination of 2 pathological mechanisms causes more harm than either of the 2 factors alone. Thus, it has been shown that pre-existing liver diseases such as hepatitis C infection



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**Fig. 2.** High frequency and high overlap of chronic alcohol consumption and obesity. A significant percentage of the population in Western countries chronically drinks alcohol in amounts that predispose for ALD (symbolized by a red wine bottle). Furthermore, in many industrialized nations, almost half of the adult pop-

ulation are overweight or obese (symbolized by yellow color), and the majority of these individuals have NAFLD. Very frequently, excess alcohol and calorie intake coincide and therefore the frequency of risky alcohol consumption in obese is even higher than in the general population (symbolized by grey color).

deteriorate with chronic alcohol ingestion [11, 12]. Likewise, obesity and diabetes are independent risk factors for liver fibrosis in patients with chronic viral hepatitis infection [13, 14]. A combined effect on the progression and development of liver injury seems even more probable in the case of alcohol and obesity since ALD and NAFLD reveal astonishing histopathological similarities [15].

Indeed, several epidemiological studies suggest a strong causative link between the consumption of alcohol and progressive liver disease in individuals with high fat intake and/or diabetes. Combined effects appear to affect all pathophysiological steps of disease development and progression, starting with hepatic steatosis. The DIONYSOS study was one of the first epidemiological studies clearly showing combined effect of alcohol consumption and elevated body weight on hepatic steatosis in a large cohort of subjects in Northern Italy [16]. The prevalence of hepatic steatosis determined by ultrasonography was increased in subjects with a daily intake of >60 g of alcohol to 46% and in obese persons to 76% compared to lean controls that revealed hepatic steatosis only in 16% of cases. Still, in obese individuals drinking >60 g alcohol per day, steatosis was found in even 95% of individuals [16].

Also, with regards to hepatocellular injury and inflammation, a strong causative link has been found between alcohol consumption and obesity [17, 18]. Of note, the likelihood of hepatic injury was higher at increasing body weight even when the levels of alcohol consumption were as low 28 g alcohol per day [17]. Loomba et al. [19] found that the odds for elevated serum transaminase levels increased with higher body mass index (BMI) as well as each alcohol drinking level in a study with 2,364 individuals in the US. OR was approximately 3 in obese people with no or only one drink per day and approximately 2 in lean individuals consuming 40 g alcohol per day or more. However, OR was nearly 9 in obese individuals drinking >40 g alcohol per day, showing a clear synergistic effect of alcohol and obesity on hepatocellular injury.

Alcohol and obesity also appear as a critical association for hepatic fibrosis and development of cirrhosis. In subjects with heavy alcohol consumption, obesity is an independent risk factor for the development of both acute alcohol-induced hepatitis and cirrhosis [20, 21]. Moreover, Ekstedt et al. [22] found an accelerated progression of fibrosis in patients with NAFLD who drank moderate (up to 140 g/week) amounts of alcohol. Liu et al. [23] analyzed more than 1 million middle aged women in the

UK. Here, alcohol consumption of >150 g/week was found to increase the relative risk for cirrhosis approximately 3-fold while obesity (BMI >30) in individuals drinking <70 g alcohol/week did not significantly affect the risk for cirrhosis. However, in obese women drinking >150 g of alcohol/week, the relative cirrhosis risk increased more than 6 fold.

Lastly, there are strong epidemiological data showing a combined effect of alcohol and obesity on the risk of developing HCC. Ascha et al. [24] found an increasing risk for HCC in patients with underlying NASH who consumed alcohol in moderate amounts. In another study, Loomba et al. [25] analyzed the relative HCC risk in 23,712 Taiwanese residents. In this study, chronic alcohol consumption (>4 times per week for >1 year) did not significantly affect HCC risk but obesity increased the risk by approximately 2 fold. Noteworthy, obesity and chronic alcohol consumption together led to a 7-fold increase of HCC risk in this large study [25] indicating a clear synergistic effect.

### **Animal Models of Combined Effects of Alcohol and High Fat on Development and Progression of Liver Disease**

Experimental studies have shown that obesity or feeding a high fat diet (HFD), respectively, in combination with alcohol application accelerate hepatic steatosis, inflammation and fibrosis in mice and rats. These experimental models also revealed mechanistic insights on how alcohol and obesity caused synergistic harm.

Carmiel-Haggai et al. [26] showed that short-term binge alcohol exposure increased apoptosis and liver injury in obese rats compared to lean controls. In a study by Xu et al. [27], moderate obesity induced by intragastric overfeeding of a HFD and alcohol intake caused synergistic steatohepatitis in an alcohol dose-dependent manner. This was associated with increased fibrosis, induction of inducible nitric oxide synthetase and reactive nitrogen species, that is, nitrosative stress. Wang et al. [28] combined a genetic model for NASH, the leptin-deficient, insulin-resistant Zucker rat by feeding ethanol containing Lieber-DeCarli diet and identified cytochrome P-4502E1 induction and the generation of carcinogenic DNA lesions as exacerbating pathological forces. Purohit et al. [29] found that combined consumption of alcohol and a HFD significantly increased *SREBP-1* and *FAS* gene expressions in mice. Wang et al. [30] investigated the effect of a rather low intake of ethanol

(16% of total calories) on the progression of a HFD-induced NASH model in Sprague–Dawley rats. They observed an increased number of inflammatory foci and apoptosis due to the additional intake of ethanol, suggesting that even moderate alcohol intake can augment hepatic inflammation and apoptosis in rodents with underlying NASH.

Also, we established an experimental murine model where we combined feeding a HFD, which results in (modest) weight gain with chronic alcohol administration in the drinking water resembling so-called ‘social drinking’ [31]. Under these experimental conditions, alcohol and HFD caused additive effects on hepatic steatosis and inflammation, while effects on hepatic fibrosis were clearly synergistic. The pronounced effect on hepatic fibrosis indicates that this phenomenon was not simply a result of timely preceding pathological effects but that alcohol and HFD cause (metabolic) changes that promote fibrogenesis via mechanisms independent of steatosis and inflammation.

### **An in vitro Model of Combined Effects of Alcohol and Free Fatty on Hepatocytes**

More recently, we have developed an in vitro model to study the combined effects of alcohol and FFA on primary human hepatocytes [32]. To induce intracellular lipid accumulation, cells were incubated with FFA complexed to albumin [33]. Subsequently, steatotic and control hepatocytes were incubated with up to 50 mM alcohol. This alcohol concentration on its own revealed only minimal effects but significantly enhanced oleate-induced lipogenesis and cellular triglyceride content compared to control cells. Similarly, lipid peroxidation, oxidative stress and pro-inflammatory gene expression were synergistically induced by alcohol and steatosis. Of note, the joint pathological effect of alcohol and cellular triglyceride content were caused by synergistic induction of CYP2E1 activity in our in vitro model. Generally, this cytochrome P450 is known for its detrimental effects in ALD through free radical formation and lipid peroxidation [34, 35]. Therefore, pharmacological inhibition of CYP2E1 has emerged as strategy for treatment of alcohol-induced liver injury [34, 36]. Also, several studies identified the induction of cytochrome P4502E1 as a critical pathological factor in NAFLD. This cytochrome metabolized both fatty acids and ethanol. When these substances are chronically present in large amounts, they induce the activity of this enzyme which is associated with the release

of free radicals. This reaction can cause lipid peroxidation and liver injury, and *in vitro* data indicate that these mechanisms are even synergistically enhanced in the presence of both alcohol and excessive FFA.

Notably, alcohol and cellular steatosis also induced autophagy in a synergistic manner in hepatocytes *in vitro*, and this was also mediated via CYP2E1 [32]. Further induction of autophagy ameliorated the joint effects of alcohol and oleic acid on hepatocellular lipid accumulation and inflammatory gene expression while inhibition of autophagy further enhanced the dual pathological effects.

Autophagy is a highly conserved intracellular catabolic pathway for the degradation of long-lived proteins and cytoplasmic organelles. The effects of ethanol on autophagy are complex and only partly understood but it is becoming clear that autophagy serves a protective function against alcohol-induced liver injury [37, 38]. Similarly, there is increasing evidence that autophagy also inhibits NAFLD progression [39–41].

Certainly, the clinical relevancy of our *in vitro* findings in hepatocytes has to be verified. Still, the CYP2E1-mediated joint effects of alcohol- and oleate-induced steatosis on autophagy indicate that alcohol induces not only pathological but also protective mechanisms in steatotic hepatocytes via CYP2E1. Therefore, the manipulation of CYP2E1 may be a double-edged sword and warrant the exercise of caution in the pharmacological use of CYP2E1 inhibitors for the treatment of ALD in obese individuals. Furthermore, one may speculate whether individual factors tipping the balance on the one or the other side of detrimental or beneficial joint effects of alcohol and FFA account at least in part for the high variation in the clinical course of ALD. Only slight differences in the ratio of individual beneficial and detrimental factors may decide whether moderate alcohol consumption is protective or is causing harm in (non-alcoholic) fatty livers. Actually, there are some studies suggesting that moderate alcohol consumption might even be protective for patients with NAFLD [42, 43]. Light to moderate alcohol consumption can lead to an improvement in peripheral insulin resistance, and herewith, may also have a protective effect against the development of diabetes and hepatic steatosis [44–47]. However, these studies have to be reflected on with great caution. The border between safe or eventually even beneficial alcohol consumption on the one side and dangerous and deleterious levels on the other side is extremely narrow and depends also on several confounding variables which are only incompletely understood. Furthermore, one needs to be cautious because even if a certain level of drinking might

protect against fatty liver disease, it may be harmful for other organs and tissues and may also increase the risk of certain cancers, such as breast or colorectal cancer [48, 49].

### **Extrahepatic Mechanisms Affecting Disease Progression in ALD and NAFLD**

It has to be noted that both ALD and NAFLD occur in the context of a systemic disease, that is, (components of) the metabolic syndrome and chronic alcoholism. Therefore, in addition to the liver, several other organs and biological functions can be affected. These pathological alterations can directly or indirectly promote inflammation and fibrosis in fatty liver [50]. For instance, alcohol and obesity/diabetes lead to quantitative and qualitative changes of the microbiome and an impaired intestinal barrier, and these mechanisms are known to promote hepatic inflammation, fibrosis and cancerogenesis [51, 52]. One further example is (visceral) adipose tissue, in which secretion of adipokines is altered by both obesity and alcohol. Adiponectin, which is known to be hepatoprotective and anti-fibrotic, is reduced in individuals with obesity or chronic alcohol consumption [53–55]. In contrast, both chronic alcohol intake and obesity induce the expression of the profibrogenic adipokine leptin in adipose tissue [56, 57]. There are several more extrahepatic systemic processes and biological functions affected by both alcohol and the metabolic syndrome, making the relationship between ALD and NAFLD extremely complex. Accordingly, the mechanisms responsible for accelerated disease progression if both conditions coincide are most likely related to multiple factors.

### **Confounding Dietary Factors Affecting Disease Progression in ALD and NAFLD**

Experimental and epidemiological studies clearly indicate that in addition to the quantity, the type of dietary fat also critically affects the pathogenesis of ALD [58, 59] and NAFLD [60, 61]. For instance, *in vitro* studies clearly show that saturated FFA cause more apoptosis in hepatocytes than unsaturated FFA [62, 63]. Besides lipids, quantity and quality of carbohydrates consumption have been shown to affect hepatic steatosis, inflammation and fibrosis in experimental models [64, 65]. These findings are of particular relevancy in ALD where malnutrition is a frequently observed problem [66].

Moreover, it becomes more and more evident that not only the amount of consumed alcohol but also the subcategory of alcoholic beverage affects the development and progression liver disease. A recent study found that the ratio of the budget for healthy to that for unhealthy foods were highest for wine drinkers and lowest for beer drinkers [67]. In this study, healthy foods included for instance coffee, and it has been shown by others that coffee consumption has hepatoprotective effects [68, 69]. On the other side, unhealthy foods were considered for instance as soft drinks and saturated fatty acids, that is, dietary components well known to accelerate progression of liver disease [63, 70]. Some studies have also suggested that a high percentage of red wine in the amount of alcohol consumed lowers the relative risk to develop (alcoholic) liver cirrhosis [71]. One explanation for this phenomenon may be resveratrol, a polyphenol in grapes, which is also found in red wines [72]. Several studies have demonstrated the protective effects of resveratrol in experimental models of liver injury in animals [73–75]. More recent studies show that beer also contains substances that protect from liver damage [76]. Furthermore, experimental studies revealed that hop ingredients such as xanthohumol or iso-alpha acids inhibit hepatic steatosis, inflammation, fibrosis and hepatocarcinogenesis [77]. Moreover, these hop ingredients have been shown to beneficially affect the metabolic syndrome [77] and it has been shown already in patients with prediabetes that doses of iso-alpha acids as low as 1.5 mg/kg daily improved insulin resistance and reduced body weight [78]. This dose corresponds to a beer consumption of approximately 1–6 liter depending on the type of beer [79]. This means that with alcohol consumption of approximately 40 g/day in the form of beers with high content of iso-alpha acids, some beneficial effects on insulin resistance

and body weight could be achieved. Together, the available data show that not only the amount of alcohol and calorie intake but also the type of food and alcoholic beverages affect ALD and NAFLD, which further contributes to the complexity of the interaction between alcohol and obesity in (chronic) liver disease.

## Conclusion

Alcoholic and non-alcoholic liver fatty liver disease are the most frequent liver diseases worldwide, and one needs to consider that both conditions overlap in a significant number of patients. There is unequivocal epidemiological and experimental evidence that alcohol and (components of) the metabolic syndrome exhibit combined effects on the development and progression of liver injury, which are in part additive and partly even synergistic. Consequently, these combined effects have a major impact on the dose threshold for hepatotoxic alcohol effects, that is, safety levels for ‘social drinking’ and guideline recommendations for ‘safe’ alcohol consumption. Today, practically all guideline recommendations define different threshold levels for hepatotoxic alcohol in man and woman. Available data strongly suggest that in addition to gender, the presence of overweight and obesity should be considered for defining safe alcohol levels. Obese individuals should adhere to lower amounts of regular alcohol consumption than lean subjects, and those who drink within safe margins should take care to not become overweight.

## Disclosure Statement

Both authors have no conflicts of interest to declare.

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