Alcoholic Liver Disease and Its Relationship with Metabolic Syndrome

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Abstract

Alcoholic liver disease (ALD), which occurs from chronic excessive drinking, progresses from initial alcoholic fatty liver to more advanced type such as alcoholic hepatitis, liver fibrosis, or liver cirrhosis when habitual drinking continues. In general, chance of liver cirrhosis increases after 20 years of chronic heavy drinking, but liver cirrhosis can occur in women after a shorter period of habitual drinking at a lower amount of alcohol. Alcoholic liver cirrhosis accounts for approximately 20% of all liver cirrhosis cases. The key treatment is abstinence or substantial cutting down on drinking; the prognosis is poor if the patient continues drinking after being diagnosed with liver cirrhosis.

Factors that exert adverse effects on the progression of ALD include gender difference, presence of hepatitis virus, immunologic abnormality, genetic polymorphism of alcohol-metabolizing enzymes, and complication of obesity or overweight. Recently, particular attention has been paid to obesity and overweight as risk factors in the progression of ALD.

Conditions such as visceral fat accumulation, obesity, and diabetes mellitus underlie the pathologic factor of metabolic syndrome (MetS). In liver, MetS may accompany fatty liver or steatohepatitis, with possible progression to liver cirrhosis in some cases. Caution is required for patients with MetS who have a high alcohol intake because alcohol consumption further accelerates the progression of liver lesions.

Key words Alcoholic liver disease, Metabolic syndrome, Obesity, NAFLD/NASH

Introduction

There are many types of liver disease, but alcoholic liver disease (ALD) is unique in the way that it occurs when the patient habitually consumes excessive amounts of alcohol through his or her own volition. Because alcoholic beverages are popular as a lifestyle habit globally and have been established as part of everyday life, ALD that occurs as a result of excessive alcohol is an important lifestyle-related disease that is prevalent throughout the world. According to a WHO estimate, alcohol intake ranks third following hypertension and smoking, as a global disease burden. Organ damage caused by alcohol can occur not only in the liver but also in many other organs including gastrointestinal tract, pancreas, circulatory organs, cranial nerves, and blood, which is why the medical and social impact is great.

This paper provides basic information on ALD and also discusses metabolic syndrome (MetS) which is the focus of a specific health screening/guidance program that begun in April 2008 in Japan as well as the influence of alcohol intake.

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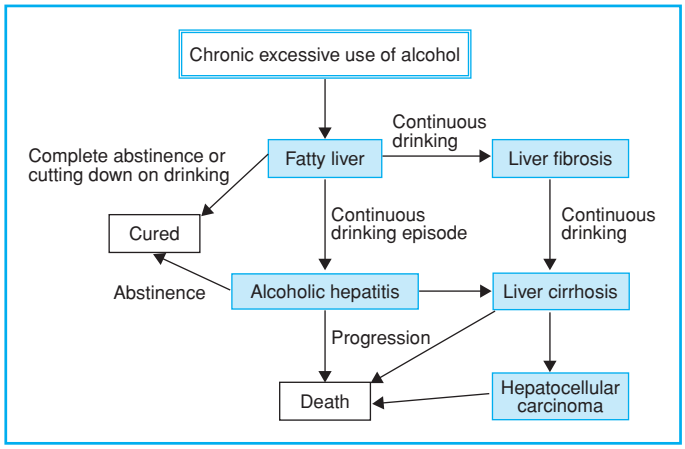

Fig. 1 Types of alcoholic liver diseases and progression processes

Major Types of ALD and Their Characteristic Features in Japan (Fig. 1)

The disease initially caused by chronic excessive alcohol consumption is fatty liver disease. It is said that more than half of regular drinkers (those who drink alcoholic beverages equivalent of 60 g of ethanol or more per day, 5 or more days a week, which corresponds to roughly 0.5 L of Japanese sake, 3 half-litter bottles of beer, 6 shots of whisky, or 5 glasses of wine or more per day) eventually develop fatty liver. Fatty liver is a condition in which triglyceride accumulates in hepatocyte, causing the enlargement of hepatocyte and disturbances of blood circulation within the sinusoids, causing adverse effects on various metabolic processes within the cells. In recent years, changes in dietary habits to European/American styles have caused increases in fat intake among Japanese people. Combined with excessive alcohol intake and overnutrition, it is causing more advanced fatty liver among people. Signs and symptoms found in patients with fatty liver are usually no worse than hepatomegaly with abdominal fullness and malaise, and even asymptomatic cases are not rare.

When patients with alcoholic fatty liver abruptly increase their alcohol consumption and remains that way (continuous drinking episode), 10–20% of them develop alcoholic hepatitis (**Fig. 1**). Clinical manifestations of alcoholic hepatitis include upper abdominal pain, jaundice, fever, vomiting, and diarrhea. When progressed, pneumonia, renal failure, gastrointestinal bleeding, and other conditions occur, frequently accompanied by withdrawal syndrome. At this point, prognosis is poor.

Common histopathologic findings include hepatocyte necrosis, infiltration of polymorphonuclear leukocytes, ballooning of hepatocytes, cholestasis, and peri-cellular fibrosis. Laboratory tests commonly reveal hyperbilirubinemia, aspartate aminotransferase (AST)-dominant transaminase elevation (increased AST/alanine aminotransferase (ALT) ratio), marked increase in γ-glutamyl transpeptidase (GTP), polymorphonuclear leukocytosis, hypertriglyceridemia, and hyperuricemia.

Unlike in European or North American countries, it is not rare in Japan that patients with alcoholic fatty liver have relatively mild symptoms with no serious clinical conditions. Yet, when such people continue to drink alcoholic beverages regularly (in the amount equivalent to 60 g/day or more of ethanol), they are likely to develop liver fibrosis, which then progresses to alcoholic liver fibrosis and, consequently, to liver cirrhosis. Alcoholic liver cirrhosis reportedly occurs in 10–30% of alcoholics. Our own case studies showed that cirrhosis occurred frequently among heavy drinkers who have at least 20 years of drinking history at the consumption level of 0.9 L/day or more of *sake* (100–120 g/day or more as ethanol). Among women, however, we found cases of liver cirrhosis with only 12 to 15 years of habitual drinking at the 2/3 of the said level. The recent nationwide survey we con-

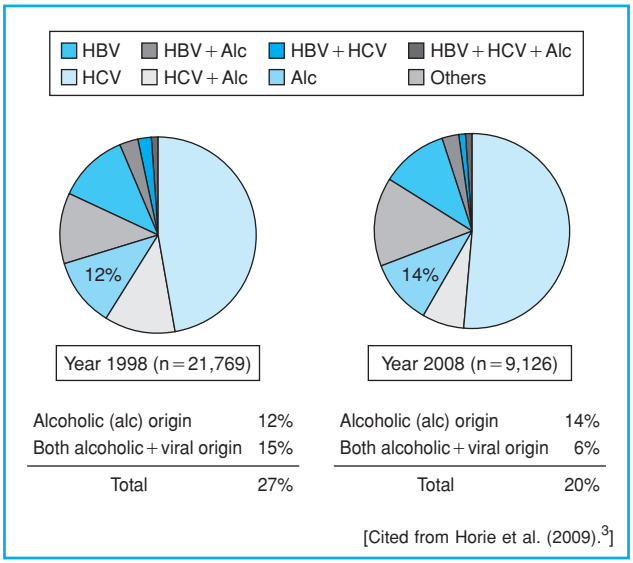

Fig. 2 Proportion of liver cirrhosis that are of alcoholic origin

ducted has revealed that alcoholic liver cirrhosis is frequent among those with 30 years or more of habitual drinking at the consumption level of 0.9 L/day or more of *sake* while women tend to develop liver cirrhosis after about 20 years of habitual drinking at the 2/3 of the same amount.[1] A case where an alcoholic liver cirrhosis patient developed hepatocellular carcinoma without complication of viral hepatitis has also been reported.

According to a recent survey, alcoholic liver cirrhosis accounts for approximately 20% of all liver cirrhosis cases (**Fig. 2**).[2,3] The prognosis of alcoholic liver cirrhosis varies widely, depending on whether or not abstinence is continued after diagnosis was established. In our experience, the survival rate (at 4.4 years after the diagnosis) was 35% in patients who continued to drink, whereas it was 88% in those who abstained from alcohol. This clearly shows the importance of abstinence in ALD treatment.

Key Points of ALD Treatment

The most important issue in the ALD treatment is abstinence and its continuation. In particular, most patients with liver cirrhosis are addicted to alcohol and therefore have difficulty cutting down on their drinking; if any drinking, even in a small amount, is permitted, they are likely to return to heavy drinking. Thus, it is often difficult to have them maintain abstinence.

Fatty liver improves after about 4 weeks of abstinence, often showing reduction of hepatomegaly. Hospitalization is necessary in patients with alcoholic hepatitis or liver fibrosis accompanied by abdominal pain, fever, and jaundice. The prognosis is poor for patients with severe alcoholic hepatitis, often requiring multidisciplinary therapy (including the use of an artificial liver-support system).

Patients with non-compensatory liver cirrhosis should be hospitalized and receive the same treatment as liver cirrhosis of other pathogenesis. Additionally, they should be subjected to alcohol abstinence education for the purpose of transitioning to the compensatory phase. Alcoholics are unable to restrain themselves from drinking once they start, and therefore they require lifestyle guidance to reach the state of complete abstinence from alcohol. In contrast, if the patients are not alcoholic and are fully aware of the fact that their disease is derived from their excessive drinking, then, providing guidance to cut down on drinking may be deemed sufficient, allowing about 0.18 L/day of *sake* with 2 days of abstinence per week.

In patients with liver cirrhosis or when there is a complication of hepatitis virus infection, complete abstinence from alcohol is required.

Table 1 Factors involved in the development and progression of alcoholic liver disease

Primary factors
Alcohol metabolism and acetaldehyde
Oxidative stress/lipid peroxidation
Endotoxin/cytokine (e.g., TNF-α)
Impaired microcirculation
Hypoxic state
Immune reaction
Secondary factors
Nutritional factors (hypo-protein, lipid, iron, vitamin deficiency)
Overweight/obesity
Gender difference
Genetic polymorphism of alcohol metabolism-related enzymes (ADH, ALDH, CYP2E1)

[Cited from Ishii (2003).[5]]

Factors Affecting the Development and Progression of ALD: Focusing on the effects of nutritional factors and obesity/overweight on the progression of ALD (Table 1)

With regard to the developmental mechanisms of ALD, until the 1950s alcohol itself was believed to have no direct toxicity. It had been advocated that the undernutrition commonly seen in heavy drinkers (nutritional deficiency of protein, vitamins, etc.) was mainly responsible for hepatic impairment, which was preventable by administration of choline and methionine. However, after 1963, new methods of alcohol administration were developed, which showed that steady administration of alcohol could produce experimental alcoholic liver lesions even under sufficient nutrition in rats, hamadryas baboons, and human volunteers. Thus, it has been proved that the direct effect of alcohol intake is responsible for a series of liver lesions beginning from fatty liver to liver cirrhosis.[4]

Subsequently, substantial research on the developmental mechanisms of ALD has been conducted to date. Currently, the mechanisms of ALD are considered from two different aspects; primary factors, and secondary factors that modify the progression of the pathologic condition (**Table 1**).[5] For more details, readers are advised to refer to other literature.[4,5]

In this section, among various nutritional factors involved in the progression of ALD, first the effects of quantitative changes in fat will be described. Then, the influence of overweight/obesity on the progression of ALD will be discussed.

It has been known that increasing the amount of fat intake during alcohol consumption also raises the amount of triglyceride in the liver accordingly. Because alcohol inhibits the oxidation of fatty acids in liver mitochondria and also facilitates the triglyceride synthesis from fatty acids, it should be noted that the consumption of both fat and alcohol during a meal augments the severity of fatty liver in proportion to the amount of fat intake.[4]

It is said that 10 to 30% of people who continue heavy drinking for a long period actually develop liver cirrhosis, while many drinkers only develop fatty liver, alcoholic hepatitis, or liver fibrosis without ever developing liver cirrhosis. Possible background factors responsible for this discrepancy include gender difference, presence of obesity or overweight, complication from hepatic viral infection, influences of gene polymorphisms of alcohol/acetaldehyde metabolizing enzymes, and immune abnormality. This paper will specifically discuss overweight/obesity as modifying factors of ALD in relation to MetS that has recently attracted a great deal of attention or in relation to nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH).

Upon examining the liver biopsies from 152 alcoholics, Iturriaga et al.[6] pointed out that the period of drinking, age, and body weight are important factors that are correlated with the his-

tologic stages. In particular, they emphasized that ALD advances as percent overweight increases and regarded obesity as a risk factor in the progression of ALD.

In a clinical study covering a much larger population conducted in France, Naveau et al.[7] performed liver biopsies in 1,604 alcoholics and analyzed the correlation between their histopathologic features and the risk factors of ALD progression (age, gender, alcohol consumption per day during the past 5 years, duration of habitual drinking, and percent obesity). They reported that obesity and overweight each served as independent risk factors for fatty liver (402 cases), alcoholic hepatitis (119 cases), and liver cirrhosis (608 cases) among various types of ALD; the liver lesions in those patients were 2.5, 3, and 2.5 times more likely to progress to more advanced state compared to those who were not obese or overweight.

In addition, Ruhl et al.[8] extracted data on alcohol intake and overweight status as factors related to fatty liver from the National Health and Nutrition Examination Survey that covered 13,580 adults, in order to investigate the relation of these factors to the elevation of AST and ALT levels. Their study found that alcohol intake of 1–2 drinks per day (12–24 g of alcohol on average) resulted in high frequencies of abnormal AST and ALT levels in obese or overweight people in comparison with people of normal weight. As shown in these studies, the incidence of ALD accompanied by obesity is on the increase recently, and it has become more apparent that the excessive nutrition is deeply involved in the progression of various pathologic conditions (fatty liver, hepatitis, liver fibrosis, and liver cirrhosis) of ALD.

The mechanism of involvement of excessive nutrition in ALD has not been fully clarified. However, it has been suggested that in ALD patients with obesity a large amount of free fatty acids derived from visceral fat enter the liver, which induces cytochrome P4502E1 (CYP2E1) in hepatic microsomes, resulting in the production of highly reactive free radicals and lipid peroxides that exert cytotoxicity.[9] Since alcohol itself, as is known widely, induces CYP2E1, it is possible that active oxygen species derived from alcohol are also increased, causing increased cytotoxicity in an additive or synergistic fashion. Furthermore, it is also possible that increased inflammatory cytokines such as TNF-α, MCP-1, and interleukins by both alcohol and obesity may act to reinforce the cytotoxicity.[10]

Relationship between NAFLD/NASH and Liver Injury in Metabolic Syndrome (MetS)

The concept of MetS was first proposed by WHO in 1990. In April 2005, the MetS diagnostic criteria for Japanese people were issued after discussions by eight related academic societies in Japan. In general, a diagnosis of MetS is based on a waist circumference exceeding the reference value in combination with abnormalities in at least two of the three items, namely blood glucose, blood pressure, and blood lipid. Obesity, visceral fat accumulation, and insulin resistance are present in the background of MetS. Since liver lesions can accompany fatty liver, necrotizing inflammation of the parenchyma, and fibrosis, MetS and NAFLD/NASH are considered to be closely correlated and that NAFLD and NASH represent certain phenotypes of MetS in the liver.

However, not all liver lesions in MetS develop into NAFLD or NASH. One explanation for this is that a diagnosis of NAFLD or NASH requires no alcohol intake (or 20 g/day or less of alcohol), while some MetS patients are drinkers. In the USA in particular, it is said that a half to 2/3 of the current population are overweight or obese. Given these circumstances, it is likely that the combination of obesity-related fatty liver and alcoholic fatty liver is increasing.[8]

It is a well-known fact that liver lesions in obese or overweight persons demonstrate findings similar to those in ALD. Therefore, it is quite possible that liver lesions in obese patients who have high levels of alcohol intake may progress additively and synergistically with the effects of alcohol.

On the other hand, the frequency of hepatic dysfunction in nondrinkers who are considered to have MetS upon health examination is reported to be about 20%. Considering the fact that the frequency of hepatic dysfunction in nondrinkers who are determined to have no MetS is about 4%, the obtained odds ratio is 5.6, suggesting that people with MetS can be regarded as future NASH patients.[11]

In future, it is necessary to further clarify the situation of drinkers and nondrinkers among people with MetS. More detailed analysis is also

desirable concerning the actual drinking habits in patients with NAFLD and NASH.

Guidance for People with MetS

Alcohol exerts a variety of effects on energy metabolism, lipid metabolism, and carbohydrate metabolism, serving as a source of energy and as an agent with various pharmacologic properties. Therefore, providing drinking guidance would likely be an important aspect in the MetS treatment.

According to previous reports, alcohol does not have substantial adverse effects on MetS, whereas the benefits of alcohol on the living body, including the anti-atherosclerotic effect, elevated levels of high-density lipoprotein cholesterol, and the blood pressure-lowering effect, have been suggested.[12,13] However, it is noteworthy that such effects vary widely according to the level of alcohol consumption. The benefits of alcohol are found only when a small amount is consumed. When the serum triglyceride and blood glucose levels are well controlled, alcohol exerts its benefits at a dose of 20–30 g/day or less in men and 10–20 g/day or less in women. It is reported that higher levels of alcohol intake causes elevation in the triglyceride and blood glucose levels and blood pressure in proportion to the increase in the intake. Furthermore, by no means the above mentioned drinking levels should be recommended to the people with no drinking habit.

The main points of providing drinking guidance for specific cases are described below.[14]

People who must not drink alcohol

Drinking should be prohibited in alcoholics, patients with advanced alcoholic organ damage (e.g., liver cirrhosis, chronic pancreatitis, cardiomyopathy), pregnant women, minors, and certain other cases.

Cautions for people with obesity or such tendency

One gram of alcohol has an energy value of 7.1 kcal. In addition, some alcoholic beverages may contain carbohydrates and small amounts of protein and amino acids. Fermented liquors such as beer, *sake*, and sweet wine are common examples of such beverages. These drinks have higher calories than distilled liquors with the same alcoholic content. For instance, a medium bottle (500 mL) of beer and a double shot (60 mL) of whiskey contain an almost equal amount of alcohol (20 g). However, there is a great difference between the two in calories (beer 210 kcal, whiskey 140 kcal), and this difference increases as the amount increases. When providing health guidance, this issue should be borne in mind.[14]

Problems of drinking in diabetic patients

Although alcohol exerts various effects on glucose metabolism, the clinical problem of alcohol intake in patients with diabetes mellitus is an increased risk of disordered dietary habits resulting from chronic alcohol consumption. It has been shown that regular drinking above the level of 0.5–1 g/day of alcohol per 1 kg of body weight (equivalent of 30–60 g/day in a person weighing 60 kg) negatively affect blood glucose control.

Furthermore, even greater caution is necessary for diabetic patients who are taking a hypoglycemic drug because chronic alcohol consumption induces a drug-metabolizing enzyme (CYP2E1) in hepatic microsomes and elevates the metabolic rate of sulfonylurea drugs to shorten the drug efficacy period. Additionally, when a diabetic patient takes a hypoglycemic drug in intoxicated condition without an adequate meal, the competitive metabolism of the drug and alcohol can prolong the pharmacologic effect, leading to hypoglycemic episode. For specific cautions in diabetic patients with hypertension or hyperlipidemia, please refer to other literature.[14]

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Special notice (message of condolence)

We wish to dedicate this paper to the memory of Dr. Hiromasa Ishii, who passed away on May 31, 2010, while the paper was in press.