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Alcoholic Liver Disease and Alcohol in Non-Alcoholic Liver Disease: Does it Matter?

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Abstract

Alcoholic Liver Disease (ALD) is still a major problem in Western and Asian countries. The long-term impact of ALD might further lead to liver disease complications, such as liver cirrhosis and liver cancer. The safe limit amount of alcohol might be different between Western and Asian countries as the genetic factor might also become an important role in the liver disease progression.

It is well-known that alcohol consumption would have synergistic liver injury effect together with chronic viral hepatitis infection. However, in non-alcoholic fatty liver disease (NAFLD), mild to moderate alcohol consumption might have a beneficial effect as it might protect the liver.

Further studies will be needed to confirm the beneficial effect of mild to moderate alcohol consumption for protecting the liver as the liver disease progression in many countries might have different influenced factors, especially in chronic viral hepatitis infection due to different genetic polymorphism and different virus genotype distribution. Obesity, which is now becoming one of the biggest problems in NAFLD patients, it would also give a different prognosis in liver disease progression between Western and Asian countries because of different type of food habits and lifestyle.

Alcohol consumption issue would become the emerging controversies issue in the near future as NAFLD is now becoming an emerging disease despite chronic viral hepatitis infection.

Keywords: Alcoholic liver disease; Liver cancer; Alcohol consumption; Viral hepatitis

Introduction

Alcoholism is still become a major problem either in Western countries or Asian countries, which responsible for 493.300 deaths and 14.544.000 disability adjusted life years (DALYs). Based on studies, mortality rate is higher in men compared to women, which the range of age between 35 to 64 years old. Alcoholic liver disease (ALD) is a spectrum from alcoholic steatosis, steatohepatitis, and liver cirrhosis which also can further lead to the liver cancer development. There are several limit of alcohol amount intake and the length of the consumption itself that can lead to the development of alcohol steatohepatitis until the development of liver cirrhosis based on literatures. Its prevalence around 20% among subjects who undergo liver biopsy and probably higher in hospitalized alcoholic liver patients [1-3].

The change of the lifestyle among young generation might be one of the important factors for the development of alcoholic liver disease. Based on an epidemiological study, looking at male-female differences in drinking and drinking related problems, the sociocultural influence also can be an important role in alcoholic liver disease development [4].

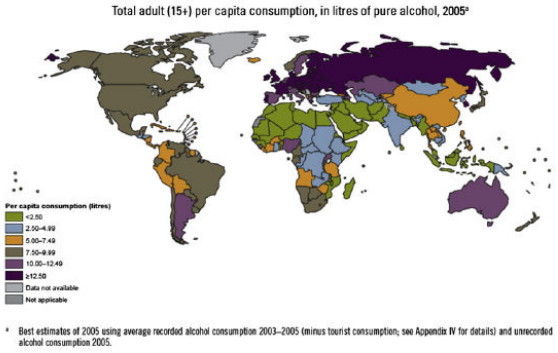

Figure 1: Adapted from: Schwartz an Reinus. Clin Liver Dis 2012 (16): 659-666.

Recently, there has been new paradigm about mild to moderate amount of alcohol consumption, where it is postulated that there might be an advantage for protecting the liver from liver disease progression. However, the impact of mild and moderate drinking in patients with chronic hepatitis viral infection is still become a controversy issue. On the other side, the liver condition improvement in the spectrum of the disease like Non-Alcoholic Fatty Liver Disease

(NAFLD) has been shown with mild to moderate alcohol consumption [5].

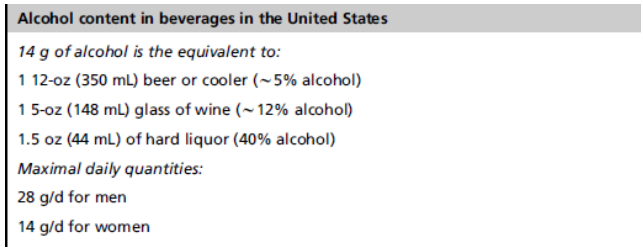

Figure 2: Adapted from: Schwartz an Reinus. Clin Liver Dis 2012 (16): 659-666.

Pathogenesis of ALD

Based on previous studies, it has been well-known that alcohol intake will disrupt or injured the mitochondria by increasing the ratio of reduced nicotinamide adenine dinucleotide/oxidized nicotinamide adenine dinucleotide in hepatocytes, even though this pathogenesis is still not clear enough to be understood. As we know that alcohol is metabolized in the liver through the pathways: 1. by the enzyme alcohol dehydrogenase (ADH), 2. by cytohrome P-4502E1 (CYP2E1); and 3. by mitochondrial catalase. ADH is the most important factor which is also present in gastric mucosa; therefore the lower ADH activity will lead to the development of alcoholic liver disease. The first two enzymes will convert alcohol to acetaldehyde, which has role in the progression of liver injury. Acetaldehyde is thought to have a direct toxic effect on cells by the formation of protein adducts by binding to cysteine residue. These modified proteins may then evoke an immune response and the production of autoantibodies perpetuating an inflammatory response. Alcohol exposure also will stimulate lipogenesis and inhibits fatty acid oxidation. The increase of fatty acid synthesis will lead to the steatosis condition. Through its metabolite, acetaldehyde, alcohol consumption also could directly increase transcription of sterol regulatory element-binding protein 1c (SREBP-1c), a transcription factor that promotes fatty acid synthesis via up-regulation of lipogenic genes. The hepatic steatosis itself will further lead to steatohepatitis, where the reactive oxygen species generated and liver injury will progress. Alcohol consumption also increases gut permeability and the bacterial translocation which will contribute to the increase of LPS levels. The LPS will interact with TLR-4 which lead to production of oxidative stress and proinflammatory cytokines that cause hepatocellular damage [2,6].

Some evidence showed that alcoholism is a complex genetic disease where there have been two genes identified such as ADH1B and ALDH2 that play important role in alcohol metabolism in the liver [7].

Diagnosis of ALD

The diagnosis of ALD can be made based on the appropriate history of amount alcohol intake, physical examination and laboratory data [8].

Physical examination usually reveals a malnourished patient with fever, low blood pressure and tachycardia. The stigmata of advanced chronic liver disease might be easily found such as jaundice and ascites and a significant number of patients have hepatic encephalopathy. The liver is usually enlarged and tender. A minority patients will have an audible bruit in the right upper quadrant [8,9].

Laboratory tests are important for the diagnosis. The AST is greater than the ALT, and the total and direct bilirubin levels are usually elevated, with bilirubin level can be more than 15 mg/dL in severe cases. Other markers such as carbohydrate deficient transferring (CDT) and gamma glutamyl transpeptidase (GGT) are more reliable markers to detect previous alcohol consumption. The sensitivity for detection of daily ethanol consumption >50g of CDT (69%), and GGT (73%) are higher than those of AST (50%) and ALT (35%). However, the level of GGT can be influenced also by body mass index (BMI) and sex. Serum sodium and albumin are low, while INR is elevated. White blood cell (WBC) count is elevated, occasionally to >15.000/mm^3 [8,9].

Ultrasound examination of the abdomen is reliable to exclude biliary tract obstruction. Other examination such as liver biopsy provides a sensitive method of evaluating the severity and the degree of liver fibrosis. Whether liver biopsy is needed to be performed in all patients is still controversial. However, liver biopsy might be very useful to confirm the diagnosis, to evaluate the impact of co-existing disease (viral hepatitis), and to rule out other diagnosis. In more advanced disease, liver biopsy should be probably be performed by transjugular route to avoid the risk of hemorrhage [8,9].

Most of non-invasive markers showed a good correlation with the severity of liver damage or injury but good performance is only when it comes to the advanced stage of liver damage. Transient elastography also has a good performance to detect the severity of liver fibrosis, however it should be interpreted with other clinical and laboratory data as there are many factors might influenced the results itself [9].

Alcohol and Chronic Hepatitis B Virus (HBV) Infection

There is still lack of data about interaction between alcohol consumption and chronic HBV infection, especially in Asia. Until now, HBV infection is still become a major problem in developing countries. There are many different prognoses in CHB patients since they will be detected in different stages as well as different liver disease condition. Alcohol consumption might give synergistic injury and will further lead to the development of liver fibrosis and cirrhosis. Study in mice showed that chronic alcohol consumption led to increased levels of HBV surface antigen and viral replication compared with control that did not consume alcohol. Nomura et al found that the prevalence of abnormal liver function test in HBV carriers was increased in patients with light (<59 g/d) and heavy (≥ 60 g/d) alcohol consumption compared with non-drinkers. Another study also showed that alcohol consumption rapidly accelerated fibrosis and the development of cirrhosis in 777 patients with HBV infection [5,10].

Alcohol and Chronic Hepatitis C Virus (HCV) Infection

Chronic HCV infection is the leading cause of advanced liver disease in Western countries. Studies have shown that alcohol consumption results in synergistic liver injury. The liver fibrosis progression has been postulated by several mechanisms such as alcohol's effect on HCV viral replication, HCV-related cytotoxicity, hepatic oxidative stress, and immune modulation. Perlemuter et al found that alcohol consumption increased lipid peroxidation and enhanced production of the cytokines tumor necrosis factor-α and

hepatic transforming growth factor-β, which are associated with increased reactive oxidative species generation and further lead to liver fibrosis stimulation [5,10].

There have been many studies showing that different limit amount of alcohol intake can lead to liver fibrosis, cirrhosis and even hepatocellular carcinoma. It has been well-understood that even small amount of alcohol intake (<30 g/d) can promote liver fibrogenesis. The problem with average daily alcohol consumption was not significantly associated with the liver disease progression, so it can be concluded that there was no safe limit amount of alcohol consumption in HCV patients. However, a multivariate study looking at liver fibrosis model found that alcohol consumption was not an independent predictor of fibrosis, and it showed that factors such as age, serum alanine aminotransferase, and histologic inflammation were independent predictors of fibrosis. This model suggested the possible of immunologic or genetic variable are more important than the alcohol intake itself [5,10].

Alcohol and Non-Alcoholic Fatty Liver Disease (NAFLD)

Non-alcoholic fatty liver disease (NAFLD) is an emerging spectrum of disease which is range from simple steatosis, steatohepatitis, and liver cirrhosis. The metabolic syndrome which is the risk factor for the development of NAFLD has also become one part of the disease together with NAFLD. The absence of alcohol intake or minimal alcohol intake has become necessary to confirm the diagnosis of NAFLD [10].

The different amount of alcohol intake in NAFLD patients might have different impact compared to patients with chronic viral hepatitis infection. Even though alcohol intake seems to be an important risk factor for liver fibrosis progression in non-alcoholic steatohepatitis (NASH), there was evidence that alcohol consumption impact is really dose-dependent in NAFLD patients. Alcohol consumption has been shown to be an additive risk factor for liver disease progression in obese fatty liver patients. However, recent studies have shown that light to moderate drinking (<20 g/d and 40 g/d) did not have any impact on the severity of steatosis and steatohepatitis and it might become a protective factor against NAFLD progression. This protective effect has been showed from most of Japanese studies with odds ratio 0.47, 0.824, and 0.754 [5]. Recent study from NASH Clinical Research Network (CRN) group showed that modest alcohol consumption was associated with lesser degree of severity in NAFLD patients (OR 0.56, 95% CI 0.39-0.84, p=0.002) [11].

Alcohol, Viral Hepatitis Infection, Metabolic Syndrome and Liver Cancer

There have been evidence showing that a synergistic interaction on hepatocellular carcinoma (HCC)/liver cancer was observed between alcohol consumption and diabetes (OR 4.2; 95% CI, 2.6-5.8), and between heavy alcohol consumption and viral hepatitis (OR 5.5; 95% CI, 3.9-7.0). It was concluded that heavy alcohol consumption, diabetes, and viral hepatitis were found to exert independent and synergistic effects on risk of HCC. A prospective control-study found that the risk of HCC increased 6-fold for patients with lifetime alcohol exposure, 5-fold with greater than 20 pack-years of smoking, and 4-fold with body mass index (BMI) greater than 30. Another study showed the significant synergy between heavy alcohol consumption, hepatitis virus infection, and diabetes mellitus. Synergistic interactions on additive model were observed between heavy alcohol consumption and chronic hepatitis virus infection (OR 53.9; 95% CI, 7.0-415.7), and diabetes mellitus (OR 9.9; 95% CI, 2.5-39.3) [5,10,12,13].

Update on Management and Alcohol Issue As A Protective Agent

The main management of alcoholism and ALD is the abstinence, and the malnutrition evaluation. Based on studies, there are specific medications that have been used for alcoholic steatohepatitis treatment such as corticosteroids, pentoxifylline, anti-TNF agents, and N-acetylcysteine. However, despite the standard care management, the assessment of the progression of liver disease itself is more important than just giving medication as the patients might develop acute liver failure and liver transplantation might become a better choice. The problem with the donor and the waitlisted make majority of the patients would have died prior to this goal [3,14].

The recent paradigm showing that alcohol intake might be a protective agent to the liver. There have been studies about a constituent of the red wine which is well known as resveratrol suspected to have a beneficial effect for cardiovascular and cancer prevention. Resveratrol (3,5,4'-trihydroxystillbene) was first isolated from the roots of white hellebore in 1940, and later in 1963, from the roots of Polygonum cuspidatum, a plant used in traditional Chinese and Japanese medicine. Resveratrol was shown to inhibit the deposition of cholesterol and triglycerides in the livers of rats, and to decrease the rate of hepatic triglyceride synthesis. However, some recent studies failed to detect a significant effect on serum cholesterol or triglyceride concentrations [15,16].

When we learn from cardiovascular study, there was evidence that alcohol has beneficial effects on insulin and triglyceride levels, and also gives experimental cardio protection against ischemic-reperfusion injury in isolated hearts. Western studies have concluded that those who take no alcohol might be disadvantaging themselves by lack of beneficial lifestyle. Another study has shown that the men who are fairly heavy drinkers (≥ 3 drinks per day) had lower blood pressure as compared to those who were not had drink red wine. A meta-analysis showed that consumption of wine but not beer was protective to the cardiovascular diseases. In a randomized animal study, resveratrol significantly lowered serum lipid, hepatic cholesterol and triglyceride levels compared to the control. The overall potential of the antioxidant system was significantly enhanced by the resveratrol as plasma and hepatic thiobarbituric acid relative substances (TBARS) levels were significantly lowered while serum superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) activities were significantly increased in the cholesterol-fed rats. These findings suggest that resveratrol maintains an antioxidant efficacy as well as its anti-hyperlipidemic effect [17-20].

Future Perspective

In the future, further studies will be needed as there are different factors between Asian and Western Countries. Alcohol issue would still become an emerging issue as many studies have given new paradigm and controversies. Despite the alcohol itself, of course, it is more important to focus on viral hepatitis management when it is found incidentally with alcohol history. Light to moderate alcohol consumption with the right management of viral hepatitis infection might be a new cornerstone in the near future.

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