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Gender Difference in Alcoholic Liver Disease

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1. Introduction

Alcoholic liver disease occurs after prolonged heavy drinking, particularly among persons who are physically dependent on alcohol. Alcoholic liver disease is pathologically classified into three forms: fatty liver (hepatic steatosis), alcoholic hepatitis, and cirrhosis. There is considerable overlap among these conditions. The incidence of alcoholic liver disease increases in a dose-dependent manner proportionally to the cumulative alcoholic intake. Alcoholism is increasing among females, owing to a decline in the social stigma attached to drinking and to the ready availability of alcohol in supermarkets. In general, however, males have a greater opportunity for drinking. In the United States, the National Comorbidity Survey estimated that, at some time in their lives, 6.4% of females and 12.5% of males will meet the criteria for alcoholic abuse (Kessler et al., 1994). The Italian longitudinal study on aging showed that 42% of elderly females and 12% of elderly males were lifelong abstainers (Buja et al., 2010). In Japan, based on data from the National Nutrition Survey, heavy drinkers with a daily consumption exceeded 40 g of ethanol per day for females and 60 g of ethanol per day for males were more frequently observed in males (Figure 1). Despite the male predominance for alcoholism, chronic alcohol consumption induces more rapid and more severe liver injury in females than males.

In contrast, the progression of hepatic fibrosis in chronic hepatitis B and C appears to be slower in females than in males (Poynard et al., 1997; Poynard et al., 2003; Rodriguez-Torres et al., 2006; Wright et al., 2003). Hepatic fibrosis is fibrous scarring of the liver in which excessive collagens build up along with the duration and extent of persistence of liver injury. In other words, overproduced collagens are deposited in injured areas instead of destroyed hepatocytes. Moreover, females, especially before menopause, produce antibodies against hepatitis B virus (HBV) surface antigen (HBsAg) and HBV e antigen (HBeAg) at higher frequency than males (Furusyo et al., 1999; Zacharakis et al., 2005). In chronic infection with hepatitis C virus (HCV), the clearance rate of blood HCV RNA appears to be higher in females (Bakr et al., 2006). Most asymptomatic carriers of HCV with persistent normal alanine aminotransferase (ALT) are females and have a good prognosis with a low risk of progression of hepatic fibrosis to the end-stage cirrhosis and its complications such as hepatocellular carcinoma (HCC) (Gholson et al., 1997; Puoti et al., 2002). The menopause is associated with accelerated progression of hepatic fibrosis, and the HCC risk is inversely related to the age at natural menopause (Shimizu, 2003; Shimizu et al., 2007a).

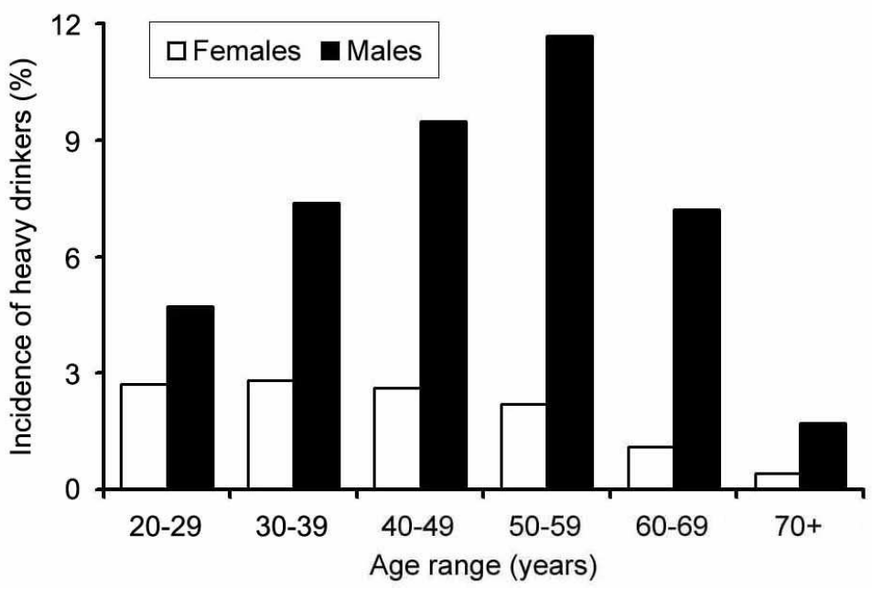

Fig. 1. Incidence of heavy drinkers with a daily consumption exceeded 40 g of ethanol per day for females and 60 g of ethanol per day for males based on data in 2002 from the National Nutrition Survey in Japan.

The "female paradox" observed in patients with alcoholic liver disease in comparison with chronic viral hepatitis is based on susceptibility by females to liver damage from smaller quantities of ethanol.

2. Alcoholic liver disease in females

The amount of alcohol required producing hepatitis or cirrhosis varies among individuals, but as little as 40 g/day (Table 1) for 10 years is associated with an increased incidence of cirrhosis. There is considerable evidence to suggest that females require less total alcohol consumption (20 g ethanol/day) to produce clinically significant liver disease. Indeed, it is reported that the lowest point of weekly alcohol intake that helps to develop liver disease was higher in males (168-324 g) than in females (84-156 g), and that, in the case of heavy drinkers with a weekly consumption of 336-492 g, the relative risk for alcoholic liver disease was 3.7 in males and 7.3 in females, while it was 1.0 in the group with a weekly consumption of 12-72 g (Becker et al., 1996). Thus, safe drinking guidelines recommend that females do not drink more than 20 g ethanol per day, and males not more than 40 g ethanol. A common, reasonable recommendation is not to exceed 70 g of ethanol a week.

Whisky	60 ml	20 g
Wine	200 ml	20 g
Beer	500 ml	20 g

Table 1. Alcohol (ethanol) equivalents.

The incidence of alcoholic liver disease correlates with the national per capita consumption of ethanol derived from sales of beer, wine and spirits (Figure 2). For instance, in France, the

United Kingdom and Germany, the annual per capita (average consumed by each person) ethanol consumption is over 9 litres per person per year, but in Asia such as China and Japan, it is 4 to 6.5 litres per person per year. Ethanol is metabolized by hepatic alcohol dehydrogenase (ADH) and the hepatic microsomal ethanol oxidizing system (MEOS) to acetaldehyde, which is subsequently converted by aldehyde dehydrogenase (ALDH) to acetate. The accumulation of acetaldehyde leads to the clinical syndrome of flushing, nausea and vomiting. Isoenzymes of ALDH with low activities are common among Asian populations and are associated with lower rates of alcoholism. These persons experience a similar flushing syndrome after consuming ethanol. This inhibits Asian populations from taking alcohol and is a negative risk for the development of alcoholic liver disease (Tanaka et al., 1996).

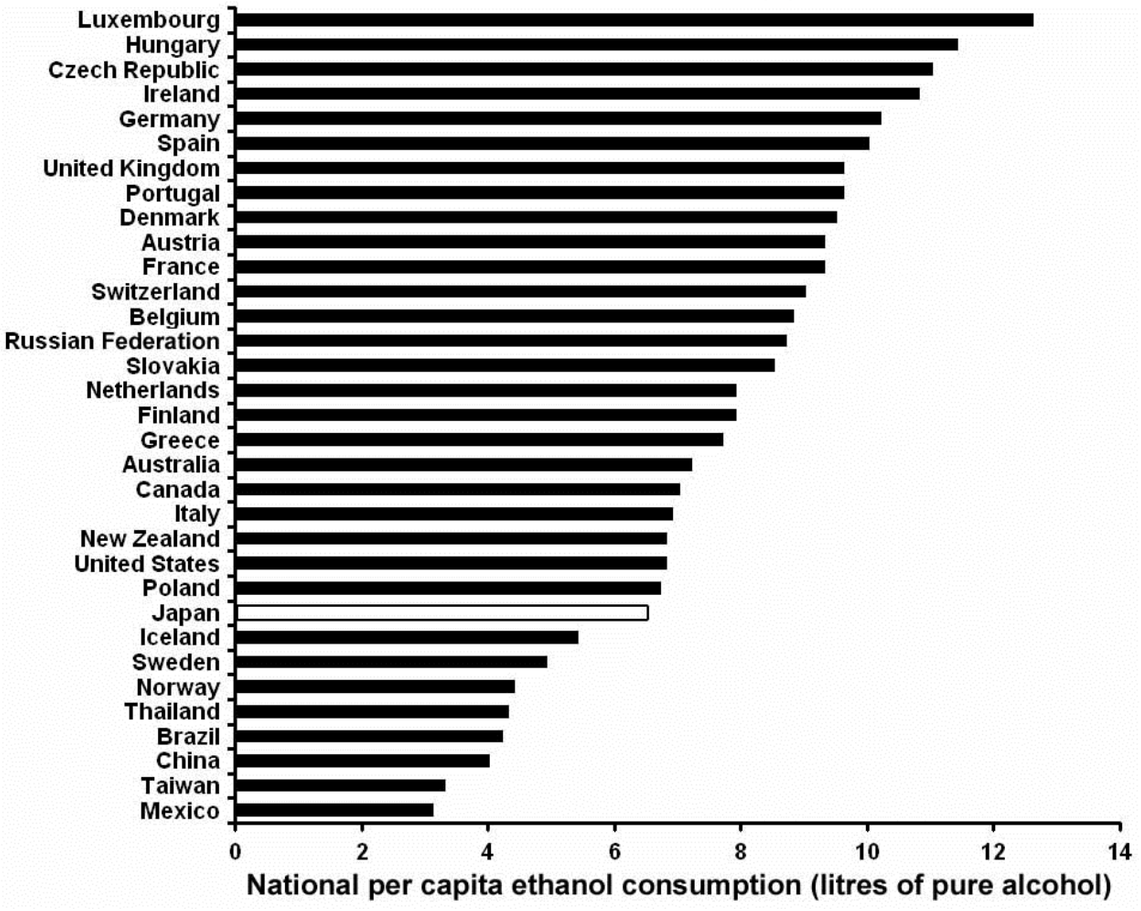

Fig. 2. The annual per capita (average consumed by each person) consumption of ethanol derived from sales of beer, wine and spirits (whisky, brandy, vodka, rum, gin and all other spirits) in the world (National Tax Agency, 2008).

In a study on the sex difference in Japanese patients hospitalized in Tokushima, western Japan, the incidence of alcoholic cirrhosis was 9-fold higher in males than females (Figure 3). However, females develop higher blood ethanol levels following a standard dose, at least in part, because of a smaller mean apparent volume of ethanol distribution. Moreover, sex differences in hepatic metabolism with increased production of acetaldehyde may contribute

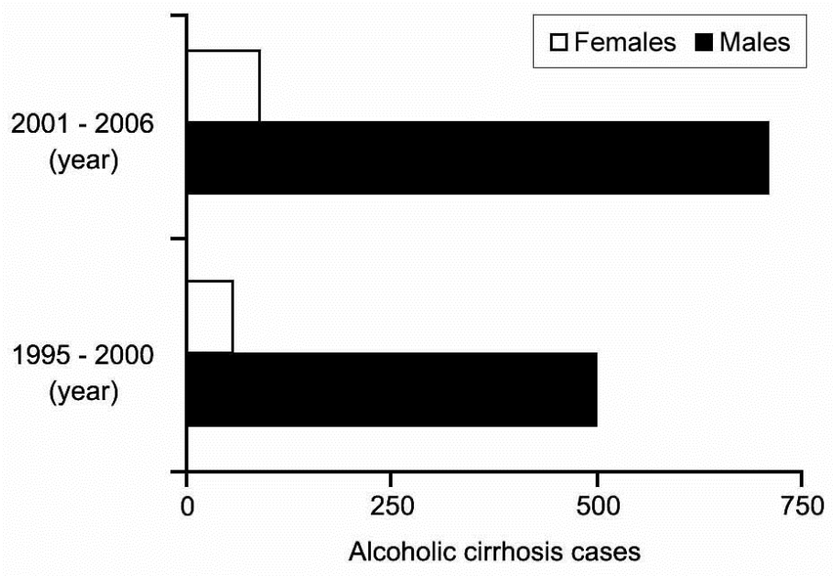

Fig. 3. Male-to-female ratio in Japanese patients with alcoholic cirrhosis. Male-to-female ratio in alcoholic cirrhosis was examined from 1995 to 2000 and from 2001 to 2006 in 1,005 Japanese patients (mean age 59.5 years, 10.4% females) hospitalized in Tokushima, western Japan. The subjects were seronegative for HBsAg and antibody against HCV.

to vulnerability of females to alcohol consumption (Eriksson et al., 1996) (see below), suggesting that chronic alcohol consumption may induce more rapid and more severe liver injury in females than males. Females with alcoholic cirrhosis survive a shorter time than males (Sherlock & Dooley, 2002).

3. Alcoholic liver injury and oxidative stress

3.1 Ethanol hepatotoxicity

Alcoholic liver injury is mainly due to ethanol hepatotoxicity linked to its metabolism by means of the ADH and cytochrome P450 2E1 (CYP2E1) pathways and the resulting production of toxic acetaldehyde (Figure 4). CYP2E1 is the key enzyme of the MEOS, and it is involved in the oxygenation of substrates such as ethanol and fatty acids. Although most ethanol is oxidized by ADH, CYP2E1 assumes a more important role in ethanol oxidation at elevated levels of ethanol or after chronic consumption of ethanol. CYP2E1 has a very high NADPH oxidase activity. NADPH/NADH oxidase is a primary source of reactive oxygen species (ROS) production in non-phagocytic cells such as hepatic stellate cells (HSCs) in the space of Disse (Figure 5). Therefore, excess of ethanol and fatty acids and their metabolism by means of CYP2E1 pathway produce extensively ROS, which cause oxidative stress with lipid peroxidation and membrane damage, leading to cell death. ROS and products of lipid peroxidation activate not only inflammatory cells including neutrophils, macrophages and Kupffer cells (hepatic resident macrophages), but HSCs as well. In the injured liver, HSCs are regarded as the primary target cells for inflammatory and oxidative stimuli, and undergo proliferation and transformation into myofibroblast-like cells. These HSCs are activated cells and are responsible for much of the collagen synthesis observed during hepatic fibrosis to cirrhosis.

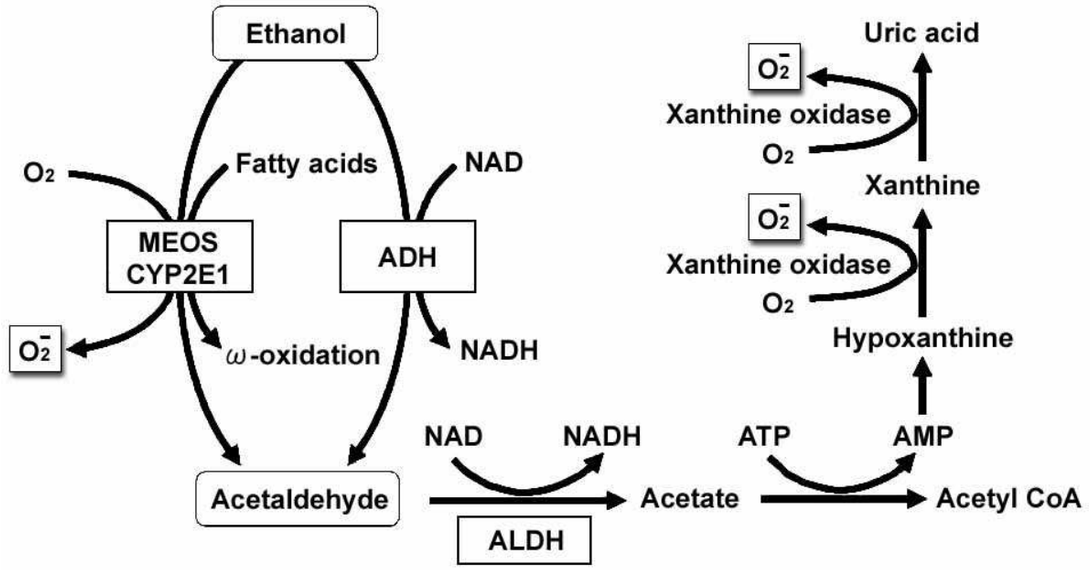

Fig. 4. Ethanol oxidation by alcohol dehydrogenase (ADH) and the hepatic microsomal ethanol oxidizing system (MEOS), which involves cytochrome P450 2E1 (CYP2E1), produces acetaldehyde (Shimizu, 2009). CYP2E1 produces ROS (superoxide, O_2^-). Acetaldehyde is converted by aldehyde dehydrogenase (ALDH) to acetate. Both reactions of ethanol to acetaldehyde and then acetate reduce nicotinamide adenine dinucleotide (NAD) to its reduced form (NADH). Excess NADH causes inhibition of fatty acid oxidation, leading to fat accumulation (hepatic steatosis).

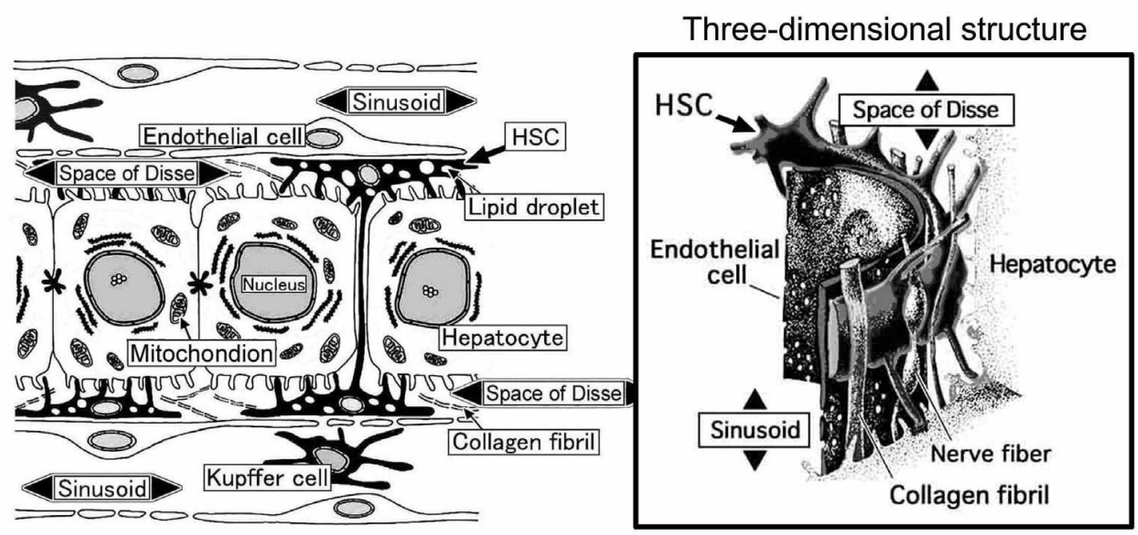

Fig. 5. Schema of the sinusoidal wall of the liver. Schematic representation of hepatic stellate cells (HSCs) was based on the studies by Wake (Wake, 1999). Kupffer cells (hepatic resident macrophages) rest on fenestrated endothelial cells. HSCs are located in the space of Disse in close contact with endothelial cells and hepatocytes, functioning as the primary retinoid storage area. Collagen fibrils course through the space of Disse between endothelial cells and the cords of hepatocytes.

3.2 Excess fatty acids lead to hepatic steatosis

Increased lipid peroxidation and accumulation of end products of lipid peroxidation are commonly observed in alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) based on studies of human alcohol-related liver injury and animal models of diet-induced hepatic steatosis and drug-induced steatohepatitis (Berson et al., 1998; Letteron et al., 1993; Letteron et al., 1996). Fatty liver is the result of the deposition of triglycerides via the accumulation of fatty acids in hepatocytes. In the progression of fatty liver disease, lipid peroxidation products are generated because of impaired β-oxidation of the accumulated fatty acids. The major site for fatty acid β-oxidation (degradation of fatty acids) in the liver is hepatocyte mitochondria (Figure 6). Key mediators of impaired fatty acid β-oxidation include a reduced mitochondrial electron transport (respiratory chain dysfunction). In addition to impaired mitochondrial β-oxidation of fatty acids, an activity of CYP2E1 in the

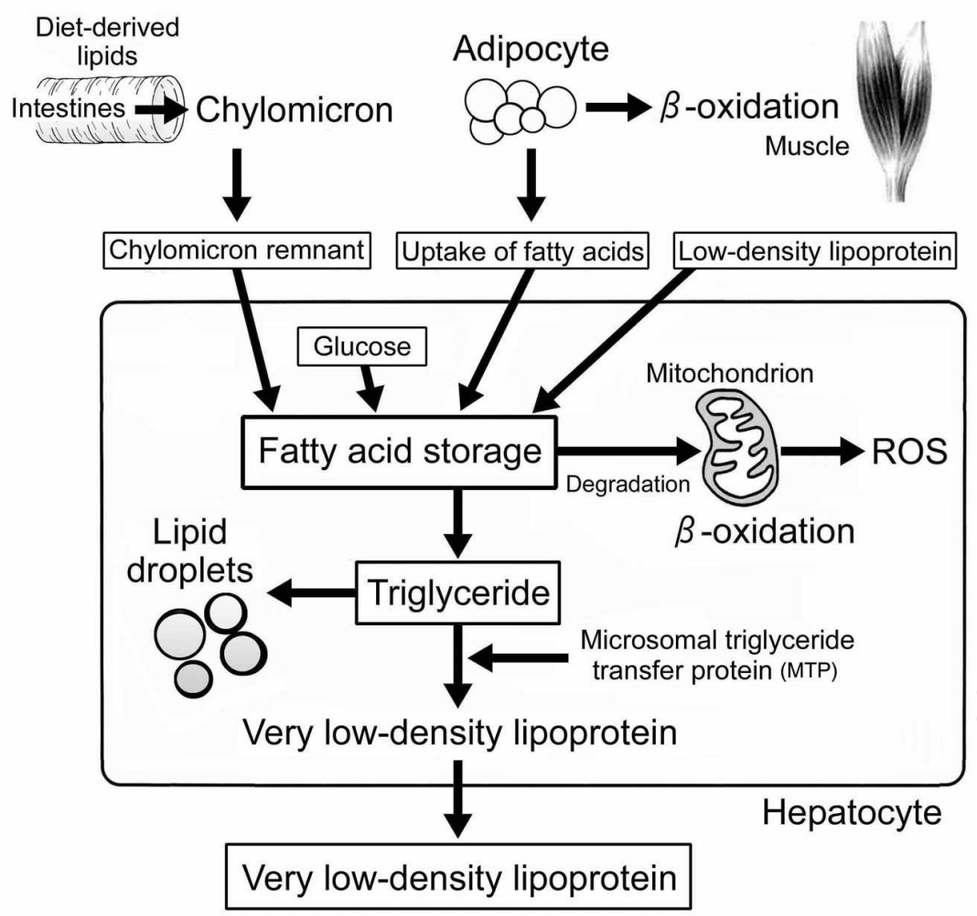

Fig. 6. Increased hepatic uptake of free fatty acids, increased triglyceride synthesis, and impaired transport of very low-density lipoprotein (triglyceride-rich lipoprotein) into the blood mainly contribute to the accumulation of hepatocellular triglycerides. Microsomal trigyceride transfer protein (MTP) is essential for the secretion of very low-density lipoprotein. Excess triglycerides are stored as lipid droplets in hepatocytes, which in turn results in a preferential shift to fatty acid degradation (β-oxidation), leading to the formation of ROS and lipid peroxidation products.

microsomes is increased. Elevated CYP2E1 and mitochondrial defects result in an increase in the ROS formation and lipid peroxidation products. ROS and lipid peroxidation in turn cause further mitochondrial dysfunction and oxidative stress, thus contributing to cell death via ROS-induced DNA injury and membrane lipid peroxidation and discharge of products of lipid peroxidation, malondialdehyde (MDA) and 4-hydroxynonecal (HNE), into the space of Disse. MDA and HNE besides ROS are able to activate inflammatory cells (neutrophils, macrophages and Kupffer cells) and HSCs. Activated inflammatory cells in turn produce chemokines as well as tumor necrosis factor-α (TNF-α) and ROS. Chemokines such as monocytes chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) attract neutrophils, lymphocytes, monocytes, macrophages, and Kupffer cells to inflammatory sites, leading to the persistent liver injury.

3.3 CYP2E1

Oxidation of ethanol through the ADH and CYP2E1 pathways produces acetaldehyde which is also toxic to the hepatocyte mitochondria. Acetaldehyde aggravates oxidative stress by binding to reduced glutathione, an antioxidant, and promoting its leakage, which triggers an inflammatory response of the host. This involves the activation of Kupffer cells and the attraction of inflammatory cells to injured sites. The inflammatory cells in the liver produce transforming growth factor–β (TGF-β) and proinflammatory mediators including TNF-α and ROS, leading to oxidative tress and hepatic fibrosis. Thus, TNF-α mediates not only the early stages of alcoholic liver disease but also the transition to more advanced stages of liver damage.

Reactions of ethanol converted to acetaldehyde and subsequently acetate reduce nicotinamide adenine dinucleotide (NAD) to its reduced form (NADH). Excess NADH causes a number of metabolic disorders, including stimulation of the fatty acid synthesis and inhibition of the Krebs cycle and of its fatty acid oxidation (Lieber, 2004). The stimulation of the fatty acid synthesis and inhibition of fatty acid oxidation favor fat accumulation (hepatic steatosis) and hyperlipidemia.

CYP2E1 activity is elevated in the livers of obese animals (Raucy et al., 1991) and non-alcoholic steatohepatitis (NASH) patients (Weltman et al., 1998) as well as patients with alcoholic liver disease. The role of CYP2E1 in fatty acid metabolism supports the concept of a nutritional role for CYP2E1. Indeed, besides its ethanol-oxidizing activity, CYP2E1 catalyzes fatty acid ω-hydroxylations (microsomal ω-oxidation of fatty acids) and metabolizes ketones. Fatty acids and ketones increase especially in obesity and diabetes, and their excess up-regulates CYP2E1. CYP2E1 leaks ROS as part of its operation, and when increased ROS production exceed the cellular antioxidant defense systems, excess ROS result in oxidative stress with its pathologic consequences. This is true when excess alcohol has to be metabolized, as in alcoholic steatohepatitis, or when CYP2E1 is confronted by an excess of fatty acids and ketones associated with obesity, diabetes, or both, resulting in NASH (Lieber, 2004).

4. Endotoxin in alcoholic liver injury

Alcohol ingestion disrupts gastrointestinal barrier function and subsequently induces the diffusion of luminal bacterial products including bacterial lipopolysaccharides (endotoxins)

into the portal vein. Experiments using animals show direct evidence of increased translocation of endotoxin from the gut lumen into the portal bloodstream caused by ethanol (Mathurin et al., 2000). Acute ethanol ingestion, especially at high concentrations, facilitates the absorption of endotoxin from rat small intestine via an increase in intestinal permeability, which may play an important role in endotoxemia observed in alcoholic liver injury (Tamai et al., 2000). Increased endotoxin levels in the portal blood are essential for initiation and progression of alcoholic liver disease (Bode & Bode, 2005).

Bacterial translocation from the gastrointestinal tract, namely spillover endotoxemia, is important in the relationship between endotoxin and hepatotoxicity in the reticuloendothelial system such as monocytes-macrophages and Kupffer cells. Gut-derived endotoxin activates Kupffer cells, which produce proinflammatory mediators such as TNF-α and ROS. The ability of Kupffer cells to eliminate and detoxify various exogenous and endogenous substances including endotoxin is an important physiological regulatory function (Figure 7).

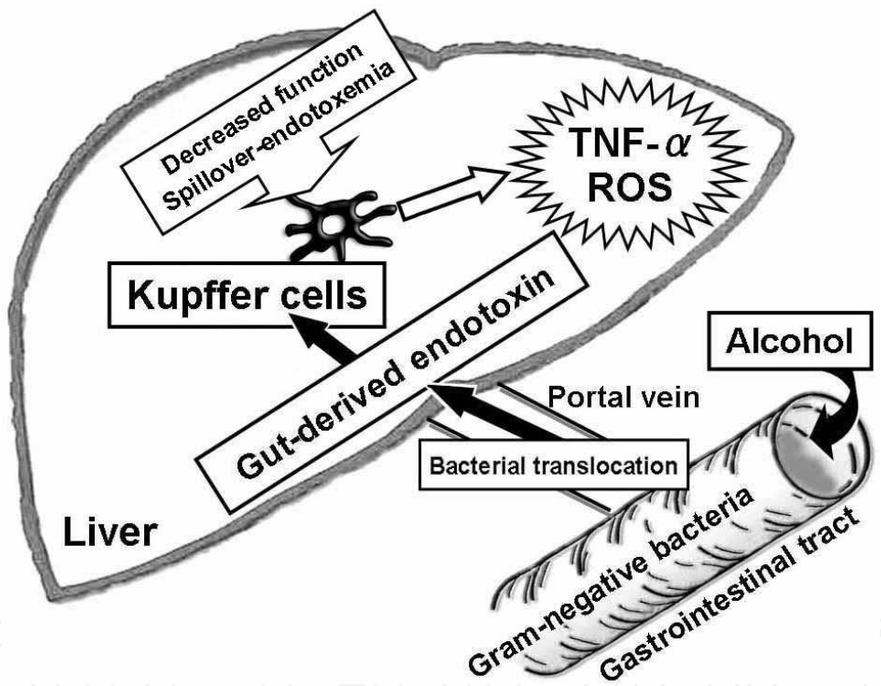

Fig. 7. Activation of Kupffer cells by gut-derived endotoxin plays a pivotal role in alcoholic liver injury (Shimizu, 2009). Following chronic alcohol ingestion, endotoxin, also called lipopolysaccharide, released from intestinal gram-negative bacteria moves from gastrointestinal tract (gut) into the liver via the portal bloodstream.

Like chronic ethanol feeding, TNF-α cytotoxicity is also with alteration of mitochondrial function. The mitochondria of TNF-α-exposed cells overproduce ROS derived from the respiratory chain. The mitochondria themselves then become the targets of ROS, thus setting up a cycle of injury (Nagata et al., 2007). In addition to ROS production, TNF-α prompts the opening of the mitochondrial permeability transition (MPT). The MPT is the regulatable opening of a large and non-specific pore across the outer and inner mitochondrial membrane. Ethanol may also increase the susceptibility of MPT induction by TNF-α at the

mitochondrial level, possibly through an increase in ROS production caused by respiratory chain dysfunction and/or CYP2E1 (Pastorino & Hoek, 2000).

Ethanol-induced oxidative stress is the result of the combined impairment of antioxidant defense and the ROS production by the mitochondrial electron transport chain, the ethanol-induced CYP2E1 and activated phagocyte such as macrophages and Kupffer cells (Albano, 2006). Indirectly, chronic ethanol ingestion may augment oxidative stress by decreasing antioxidant defenses such as reducing glutathione peroxidase and glutathione homeostasis (Figure 8).

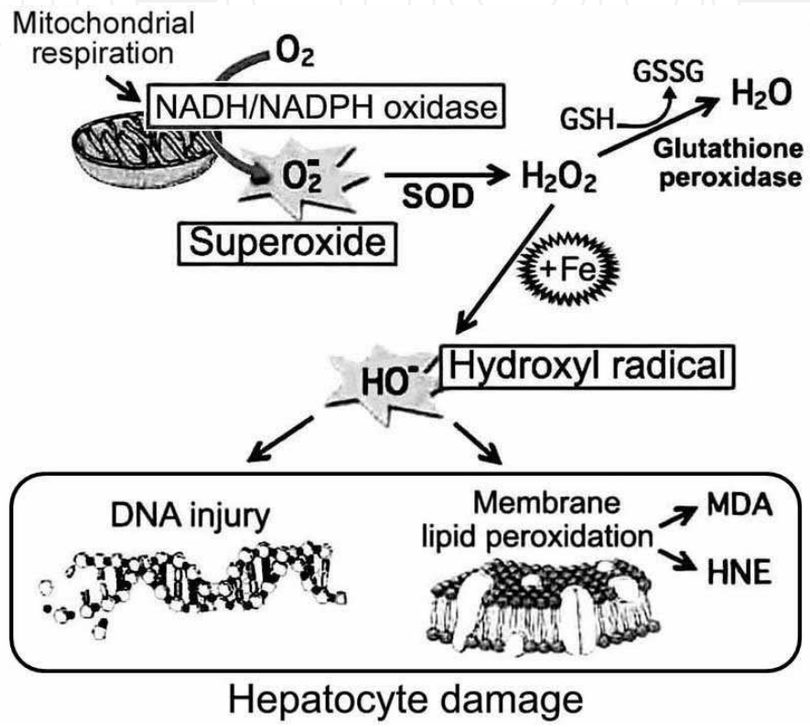

Fig. 8. Oxidative stress and hepatocyte damage (Shimizu and Ito, 2007). A primary source of reactive oxygen species (ROS) production is mitochondrial NADPH/NADH oxidase. Hydrogen peroxide (H_2O_2) is converted to a highly reactive ROS, the hydroxyl radical, in the presence of transition metals such as iron (+Fe) and copper. The hydroxyl radical induces DNA cleavage and lipid peroxidation in the structure of membrane phospholipids, leading to cell death and discharge of products of lipid peroxidation, malondialdehyde (MDA) and 4-hydroxynonenal (HNE) into the space of Disse. Cells have comprehensive antioxidant protective systems, including SOD, glutathione peroxidase and glutathione (GSH). Upon oxidation, GSH forms glutathione disulfide (GSSG).

5. Sex difference of ADH and CYP2E1 via growth hormone and estrogens

5.1 Gastric ADH in females

After an equivalent dose of alcohol, females have higher blood ethanol levels than males (Nolen-Hoeksema, 2004). There are multiple explanations for this. First, females are generally smaller than males so the same dose of alcohol leads to higher blood alcohol levels

for females than males. Second, female body water content is smaller than male per kilogram of body weight. Thus, a dose of ethanol is distributed in a smaller volume of water in females than in males, leading to somewhat higher concentrations of ethanol in female blood (Frezza et al., 1990).

Third, the first pass metabolism of alcohol in the stomach may lead to higher blood alcohol levels in females than males. In the stomach, alcohol is metabolized with the enzyme gastric ADH. The stomach thus acts as a barrier against the penetration of alcohol into the body, by retaining and breaking down part of the alcohol (Nolen-Hoeksema, 2004). Gastric ADH activity is lower in females than in males; one study found that for a given alcohol dose, male ADH levels were two times higher than female levels, and in turn, female blood alcohol levels were higher than those of males (Frezza et al., 1990).

This sex difference in metabolism of alcohol appears to hold for younger adults but not older adults. ADH activity decreases with age, particularly for males, leading to similar blood alcohol concentrations in older males and females, or even higher concentrations in older males than older females (Nolen-Hoeksema, 2004).

5.2 Growth hormone secretion in females

The profile of growth hormone secretion pattern shows clear sex dimorphism (Ameen & Oscarsson, 2003). In female rats, the growth hormone is continuously secreted, and the hormone levels are always detectable in the circulation, while, in male rats, it is secreted by episodic bursts every 3.5 to 4 hours with low or undetectable levels between peaks (Shapiro et al., 1995). Integrated 24-hour growth hormone secretion (Clasey et al., 2001) and fasting blood growth hormone levels (Figure 9) are higher in women than in men. Growth hormone secretion is stimulated by estrogens (Ameen & Oscarsson, 2003). Oral and high-dose transdermal estrogen administration in menopausal women increases integrated 24-hour growth hormone secretion (Friend et al., 1996).

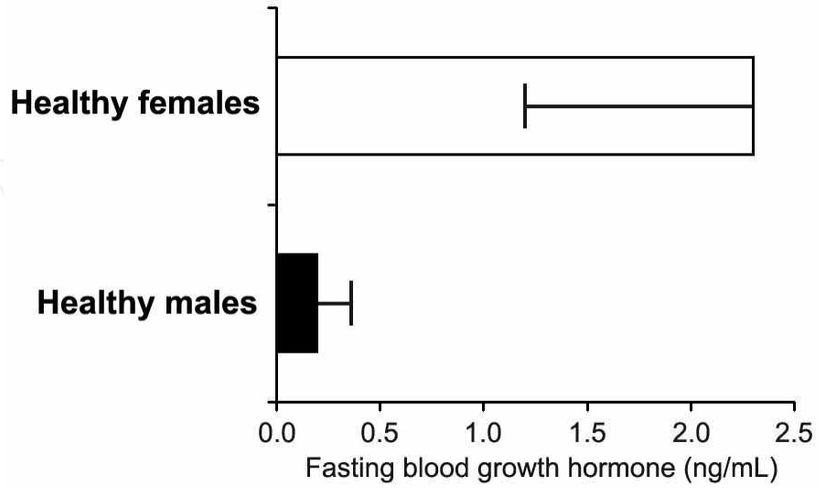

Fig. 9. Fasting mean blood levels of growth hormone in 15 premenopausal women (mean age 41.3 years) and 15 age-matched men (mean age 41.1 years) of healthy non-obese (body mass index ≥ 18.5 to 24.9 kg/m^2) individuals. The subjects had no history of alcohol abuse (defined as an alcohol intake >20 g/day).

Interestingly, growth hormone increases ADH activity in the liver. The steady exposure of hepatocytes in cultures to growth hormone resulting in increased ADH activity resembles the female pattern of growth hormone secretion (Potter et al., 1993). ADH activity is higher in female rats and mice than in their male counterparts (Mezey, 2000). Thus, increased rates of the resulting production of toxic acetaldehyde in females compared with males may be responsible for the known increased susceptibility to alcohol-induced liver injury by females. Females are more likely to progress from alcoholic hepatitis to cirrhosis even if they abstain.

5.3 Endotoxin after ethanol in females

Endotoxin-stimulated monocytes in males produce more TNF-α as compared to females (Bouman et al., 2004). Like Kupffer cells, monocytes stimulated by endotoxin induce proinflammatory cytokines and ROS. In studies using animals, however, the stimulation of Kupffer cells by estrogen increased sensitivity to endotoxin after ethanol (Ikejima et al., 1998). It appears that monocytes-macrophages respond differently to endotoxins compared to Kupffer cells as far as the signaling pathways are concerned (Schultze et al., 1999). The estrogen addition to ethanol ingestion enhanced TNF-α production in Kupffer cells via elevation of the blood endotoxin level and hepatic endotoxin receptor (CD14) expression, resulting in increased inflammatory activity in the liver (Yin et al., 2000). The administration of ethanol in female rats induced the hepatic activity of CYP2E1, and the ethanol-induced CYP2E1 activity was reduced by the treatment with antiestrogen (Jarvelainen et al., 2001). Because activity of cytochrome P-450 (CYP) isoenzymes is regulated by circulating growth hormone, sex differences in growth hormone secretion profiles account for a different expression pattern of hepatic CYP isoenzymes between females and males (Agrawal & Shapiro, 2001).

6. Favorable role of female factors in chronic viral hepatitis

Clinical observations and death statistics support the view that chronic hepatitis C and B appears to progress more rapidly in males than in females (Poynard et al., 1997; Poynard et al., 2003; Rodriguez-Torres et al., 2006; Wright et al., 2003), and that cirrhosis is largely a disease of men and postmenopausal women with the exception of classically autoimmune liver diseases, such as primary biliary cirrhosis and chronic autoimmune hepatitis (Shimizu, 2003). HCV infections are more common than HBV infections in Japan and Western countries, and are recognized as a major causative factor of chronic hepatitis, cirrhosis, and HCC. According to a report of the International Agency for Research on Cancer (Brannstrom et al., 1999), the male:female ratio of the age-standardized incidence per 100,000 of liver cancer worldwide is 2.9 : 1, and in Asia (particularly in China, Japan, and Taiwan), the incidence of liver cancer is high and it accounts for half of all liver cancer cases in the world.

The prevalence of HBsAg is reported to be higher in males than in females throughout the world (Blumberg et al., 1972). In a prospective follow-up study of up to 19 years on HBsAg carriers in Okinawa in Japan, clearance of HBsAg was found more frequently in females (7.8%) than in males (5.8%) (Furusyo et al., 1999). Seroconversion from HBeAg to its antibody (anti-HBe) occurs more frequently in females than in males (Zacharakis et al.,

2005). In chronic HCV infection, the clearance rate of blood HCV RNA appears to be higher in females (Bakr et al., 2006). Demographic data from the United States (Gholson et al., 1997), Europe (France and Italy) (Puoti et al., 2002; Renou et al., 2002), and Japan (Okanoue et al., 2005) show that most HCV carriers with persistently normal ALT (asymptomatic carriers) are females, and have a good prognosis with a low risk of progression to cirrhosis and HCC. The menopause is associated with accelerated progression of hepatic fibrosis, and the HCC risk is inversely related to the age at natural menopause (Shimizu, 2003; Shimizu et al., 2007a). Chronic HCV- and HBV-infected patients of female sex and under 50 years old, namely premenopausal women are least vulnerable to HCC (Shimizu, 2009).

Premenopausal women have lower hepatic iron stores and a decreased production of proinflammatory cytokines such as TNF-α (Clerici et al., 1991; Pfeilschifter et al., 2002; Shimizu et al., 2007b). Iron is essential for life, but is toxic in excess, because it produces ROS that react readily with lipids and DNA, leading to cell death and DNA mutagenesis. An experimental animal study showed that hepatic steatosis spontaneously becomes evident in an aromatase-deficient mouse, which lacks the intrinsic ability to produce estrogen and is impaired with respect to hepatocellular fatty acid β-oxidation. Estrogen replacement reduces hepatic steatosis and restores the impairment in mitochondrial and peroxisomal fatty acid β-oxidation to a wild-type level (Nemoto et al., 2000). In addition, tamoxifen is a well known antiestrogen used in the hormone treatment of estrogen receptor-positive breast cancer, and it has been shown to be associated with an increased risk of developing fatty liver and NASH in such patients (Oien et al., 1999; Van et al., 1996). Estrogens are potent endogenous antioxidant (Lacort et al., 1995; Yoshino et al., 1987), suppresses hepatic fibrosis in animal models, and attenuates induction of redox sensitive transcription factors, hepatocyte apoptosis and HSC activation by inhibiting the generation of ROS and TGF-β in primary cultures (Itagaki et al., 2005; Lu et al., 2004; Shimizu et al., 1999; Yasuda et al., 1999; Zhou et al., 2001). Variant estrogen receptors are expressed in HCC patients and, to a greater extent, in male patients with chronic liver disease than in female patients, even at an early stage of chronic liver disease (Villa et al., 1995; Villa et al., 1998). The occurrence of variant estrogen receptors leads to the loss of estrogen responsiveness. These lines of evidence suggest that the greater progression of hepatic fibrosis and HCC in men and postmenopausal women may be due, at least in part, to both a lower production of estrogen and a lower response to the action of estrogen.

7. Heavy alcohol intake and HCC

Chronic alcohol intake (mostly heavy alcohol use of more than 50 g/day) and alcoholic cirrhosis have long been recognized as a cause of HCC. In alcoholic cirrhosis, the risk of HCC is about 1% per a year. Most HCC cases are in males. There are no clinical or pathological differences compared with HCC complicating chronic HBV and HCV infection. However, it is not certain whether alcohol is a true carcinogen. Several epidemiologic studies among alcoholics show a high prevalence of HBV markers (16%-70%) and HCV markers (10%-20%) as compared with a background prevalence of close to 5% and less than 1%, respectively (Bosch et al., 2004). These prevalences are even higher in HCC cases who are also alcoholics (27% to 81% of HBV markers and 50% to 77% of HCV markers), suggesting a complex interaction between alcohol and viral infections in the etiology of HCC (Di Bisceglie et al., 1998).

Case-control studies have shown that, as a result of the synergy between alcohol intake and HCV infection, the risk of liver cancer is increased approximately 2- to 4-fold among cases drinking more 60-80 g/day of alcohol (Fattovich et al., 2004). The presumed basis for this is that both alcohol and HCV infection independently promote the development of cirrhosis. In a longitudinal cohort study of cirrhotic patients with HCV infection, heavy alcohol intake (>65 g/day) was an independent factor for the development of HCC, increasing the risk approximately 3-fold (Aizawa et al., 2000).

A case-control study also shows a synergism between alcohol drinking and HBV infection on the risk of HCC, increasing the risk approximately 2-fold for HBsAg-positive subject of both sexes who drink more than 60 g/day of ethanol compared with HBsAg-positive non-drinkers (Donato et al., 2006). In a longitudinal cohort study of patients with HBV-related cirrhosis, heavy alcohol intake was associated with a 3-fold increased risk for HCC (Ikeda et al., 1998).

Studies in northern Italy and Greece estimated that the attributable fraction of high levels of alcohol consumption, once adjusted for HBV and HCV status, were 45% in Italy (Donato et al., 1997) and 15% in Greece (Kuper et al., 2000). In low-risk populations, heavy alcohol intake may account for the majority of the HCC cases who are seronegative for HBV and HCV markers.

8. Conclusion

A large body of evidence has been accumulated suggesting that increased oxidative stress is an essential step in the development of hepatic fibrogenesis and carcinogenesis. Environmental and lifestyle risk factors such as HCV and HBV infection and heavy alcohol intake lead to increased oxidative stress, which in general occurs more frequently in males. Moreover, biological female sex factors such as estrogens, hepatic iron storage status, and growth hormone play antioxidative and cytoprotective roles in the functional and morphological modulation of the liver physiopathology. However, it should be noted that females consistently drink less than males and appear to suffer serious negative consequences of alcohol consumption earlier and to a greater degree than males. Specifically, chronic alcohol consumption induces more rapid and more severe liver injury in females than males. The “female paradox” observed in patients with alcoholic liver disease in comparison with chronic viral hepatitis is based on susceptibility by females to liver damage from smaller quantities of ethanol. Being female or male is an important basic human variable that affects health and liver disease throughout the life span. Sex is defined as female or male according to their biological functions, while gender is shaped by environment and experience. Better knowledge of the basic mechanisms underlying the sex-associated differences during hepatic fibrogenesis and carciogenesis may open up new avenues for the prevention and treatment of chronic liver disease.

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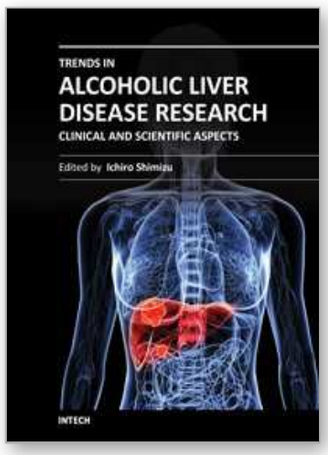

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Alcoholic liver disease occurs after prolonged heavy drinking. Not everyone who drinks alcohol in excess develops serious forms of alcoholic liver disease. It is likely that genetic factors determine this individual susceptibility, and a family history of chronic liver disease may indicate a higher risk. Other factors include being overweight and iron overload. This book presents state-of-the-art information summarizing the current understanding of a range of alcoholic liver diseases. It is hoped that the target readers - hepatologists, clinicians, researchers and academicians - will be afforded new ideas and exposed to subjects well beyond their own scientific disciplines. Additionally, students and those who wish to increase their knowledge will find this book a valuable source of information.

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