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Review

Conceptual importance of identifying alcoholic liver disease as a lifestyle disease

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The concept that alcoholic liver disease (ALD) is as a toxic disease does not mirror the exact nature of the disease. ALD should be defined as an alcohol-associated lifestyle disease, the predisposition to which is largely governed by gene–environment interactions, much like other chronic diseases such as diabetes, atherosclerosis, and neurodegenerative diseases. The epidemiology and pathogenesis of ALD need to be re-addressed from this viewpoint. Specifically, the interactions between alcohol and secondary risk factors (high-fat diet, iron, tobacco, medications, female gender) and comorbidities (viral hepatitis, diabetes) are of urgent epidemiological importance. Molecular characterization of the interfaces of these interactions is essential for revelation or acquisition of new pathogenetic, preventive, and therapeutic insights.

Key words: synergism with risk factors, viral hepatitis, diabetes, female gender

Alcohol abuse as a global health problem

Alcohol abuse is no longer a problem of individual nations but constitutes an important global health issue. The best evidence that attests to this conclusion is found in the World Health Report 2002 on risk factors of the World Health Organization (WHO) (http://www.who.int/whr/2002/en/index.html). Annex Tables 15 and 16 of this report have been modified by the National Institute on Alcohol Abuse and Alcoholism to produce Figs. 1A and B in this review. These two figures depict the ten leading risk factors that serve as major burdens of disease in developed countries (Fig. 1A) and developing countries, excluding those with high child and adult mortalities (Fig. 1B). Risk factors are listed with their corresponding effects as the percentage of reduced disability-adjusted life years (equivalent to the percentage loss of healthy life years). According to these data, alcohol is ranked as the third most important risk factor in developed nations worldwide, being responsible for an approximately 9.2% reduction in healthy life years. More importantly, alcohol is the number one risk factor in developing countries without high child or adult mortality (Fig. 1B). These nations include northeastern European, Central and South American, and East Asian countries, and some of these nations are currently beginning to undergo a surge of economic development. Thus, one must conclude that alcohol is and will continue to be a major risk factor of the disease burden around the world. At the present time, when rapid globalization is taking place not only in the areas of communication, finance, and economy but also at social and cultural levels, this trend needs to be seriously considered and addressed by the international community, including Japan. Alcoholic liver disease (ALD) constitutes a major medical consequence of alcohol abuse. Worldwide, cirrhosis claims as many as 150000 lives annually,[1] and alcoholic cirrhosis accounts for 30%–50% of these deaths.[2,3] What is not included in these statistics is the mortality associated with alcoholic hepatitis, a serious outcome of ALD common in the United States and European nations. For this reason, the actual figure of ALD mortality is expected to be higher. In the United States alone, the hospital costs of treating ALD are estimated to be $600 million to $1.8 billion per year,[4] of which 6%–18% is spent in Los Angeles (LA) County, where our Research Center is located.[5] LA County's population is 3.4% of the total U.S. population, so this figure indicates that LA County's burden is two to four times that in the rest of the nation. On the basis of our epidemiology study, we attribute this high incidence at least in part to increasing migration of certain ethnic

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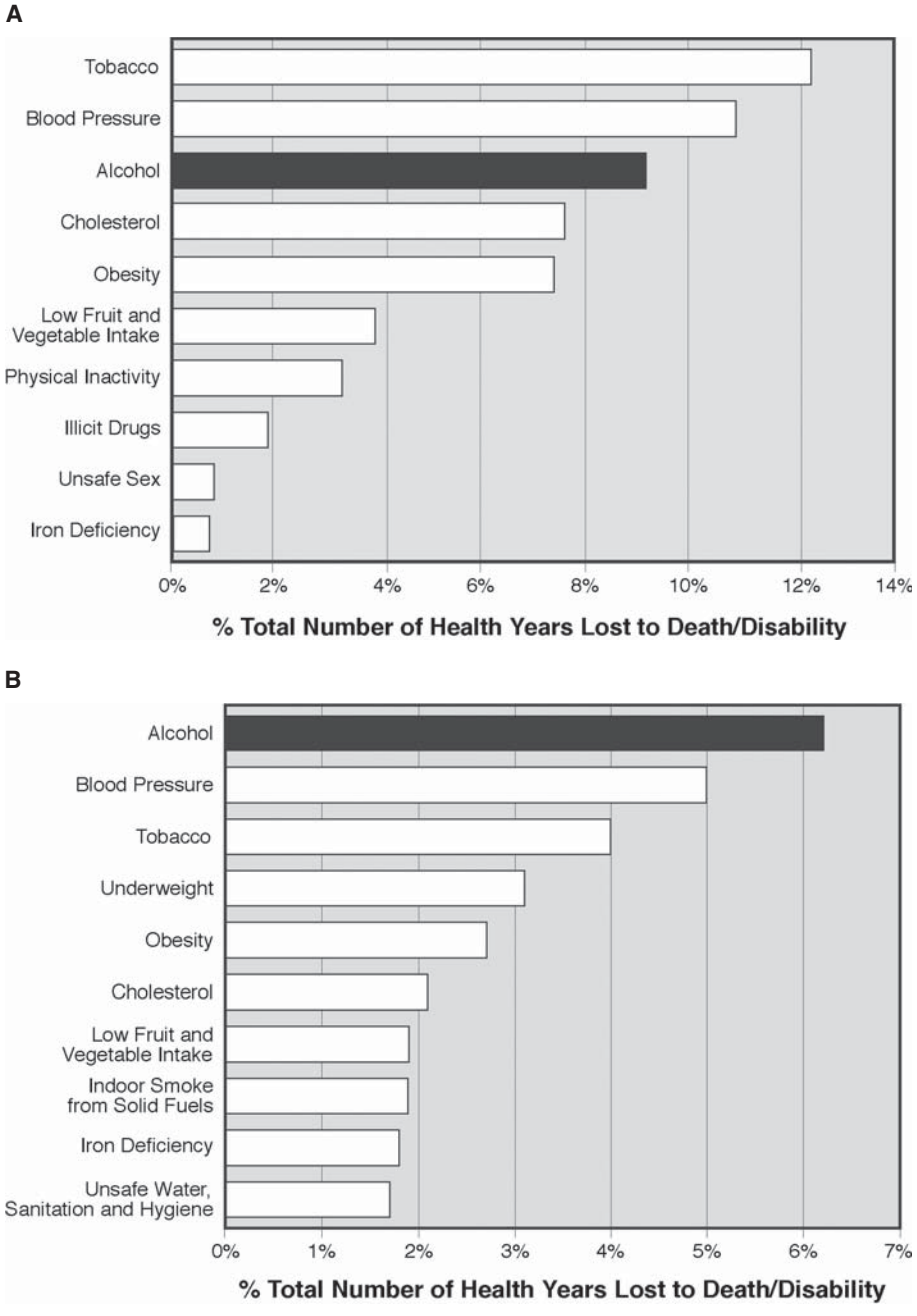

Fig. 1. A Top ten risk factors in developed countries as determined by the percentage of lost healthy years (disability-adjusted life years) per risk factor. Note alcohol is ranked third in the list among other prevalent lifestyle risk factors such as tobacco and obesity. The figure is modified from Annex Table 16 of the 2002 World Health Report. **B** Top ten risk factors in developing countries with low infant and adult mortalities. Note: alcohol is the number one risk factor. Modified from Annex Table 15 of the 2002 World Health Report

groups with a lifestyle conducive to ALD.[5] Another intriguing fact is that ALD is not just a disease of low-income and indigent patients hospitalized in public hospitals but is also prevalent among the middle-income population. In fact, more than 60% of the 3500 annual hospitalizations for ALD in LA County take place in private hospitals.[5] ALD should be considered a hidden disease prevalent in metropolitan areas around the world, as exemplified by the statistics for LA County.

ALD as a lifestyle disease versus toxicity

For the past three decades in particular, the concept that ALD is a hepatic manifestation of alcohol toxicity has been vigorously advocated.[6–8] This toxicity concept is based on the rationale that metabolism of alcohol generates acetaldehyde, an electrophilic metabolite, and long-term abuse causes metabolic changes such as induction of cytochrome P450 2E1 (Cyp2e1), which promote biochemical perturbations resembling those

of hepatotoxicity, including enhanced oxidant stress. However, the hepatotoxicity concept alone fails to explain the absence of a clear dose responsiveness and the definite presence of an individual predisposition to the disease. Although evidence exists that per capita alcohol consumption is correlated with the incidence of cirrhosis in different nations or in a given population,[8,9] critical examination of the data reveals that the relationship is not straightforward. For instance, supporting evidence for a linear relationship between the cumulative dose of alcohol and the incidence of cirrhosis is more heavily influenced by the duration of alcohol drinking than by the alcohol dose, indicating a constant incidence rate of cirrhosis instead of a cumulative dose-related effect. This interpretation is also supported by studies of Sorensen and colleagues,[10,11] who prospectively followed chronic alcoholics who did not initially have cirrhosis and found that they developed cirrhosis at a rate of 2%–3% per year regardless of the preceding duration of drinking, leading to the logical question as to whether ALD is a dose-related or permissive effect.[11] Indeed, a more recent prospective study demonstrates that alcohol has a threshold but not a dose–response effect on mortality from alcoholic cirrhosis in heavy drinkers.[12,13] Another simple and yet long-recognized fact that casts doubt on the dose-responsive hepatotoxic theory is that ALD develops in only a small fraction of heavy drinkers, despite similarly high intakes of alcohol. In studies that carefully eliminate individuals with viral hepatitis infection, the incidence of ALD can be as low as 10%, despite consumption of alcohol exceeding the "threshold" dose.[13] However, this interpretation does not minimize the harmful effects of alcohol on the liver; rather, it reinforces the permissive nature of alcohol effects and the notion that ALD requires coexisting risk factors.

Alcohol's interactions with risk factors

It has long been known that many lifestyle factors are associated with ALD. The list includes smoking,[14–16] a diet high in fat,[17] malnutrition,[18] concomitant medication,[19] and obesity.[20,21] Many of these factors are also listed among the top ten risk factors in the WHO report (Figs. 1A and B). Comorbidities are also important risk factors for ALD, and they include viral hepatitis infection,[22] diabetes,[23,24] autoimmunity,[25] iron disorders,[26] and sleep apnea.[27] Genetic factors are of obvious importance, and the most convincing genetic risk factor for ALD is female gender.[28] Many genes known to be involved in alcohol and lipid metabolism, antioxidant defense, inflammation, and immunity have been examined for an association of their polymorphisms with ALD, as reviewed by Wilfred de Alwis and Day.[29] To

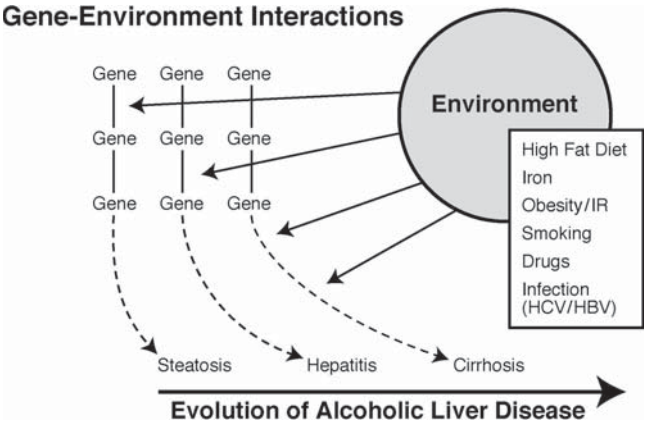

Fig. 2. A schematic diagram depicting proposed gene–environment interactions in the evolution of alcoholic liver disease. HCV, hepatitis C virus; HBV, hepatitis B virus

date, the only genes that have been shown to have definitive roles in determining the risk for alcoholism in humans are *Adh2* and *Aldh2*. Genetic analysis of ALD, as with that of any other chronic disease, usually leads to initial excitement over the disclosure of a novel genetic association in one population and a subsequent setback when the association cannot be confirmed in a different population. This result can mean one of two things: one of the two studies may be correct and the other study wrong; or both may be right. It is important to recognize that the latter is the most likely possibility, considering the complex gene–environment interactions that underlie ALD, as depicted in Fig. 2. In one population, one gene may be associated with the pathogenesis of ALD, but in a different population that lacks one or more critical environmental factors affecting the first population, this association may not be expressed. Only in a large cohort study involving comprehensive genetic and environmental data acquisition that allows stratification with environmental factors, can a more accurate analysis of gene–environment interactions be performed.

Synergy between alcohol, viral hepatitis, and diabetes

As described earlier, comorbidities are important determinants of the severity of ALD. In particular, a synergistic effect of alcohol and viral hepatitis or diabetes on the risk of developing hepatocellular carcinoma (HCC) has been reproduced by many studies[23,24,30] and represents one of the most significant medical problems that plague contemporary society. Most notably, the implications of the synergistic interactions between alcohol and obesity/diabetes may be substantial, considering the global prevalence of obesity. To highlight this

Table 1. Synergism between alcohol, diabetes, viral hepatitis and smoking for HCC risk

				HCC[a] OR(95% CI)	
Alcohol	Diabetes	HBV/HC V	Smoking	Hassan et al.[23]	Yuan et al.[30]
x				4.5	2.1
	x			4.3	3.0
x	x			9.9	17.8
		x		12.6/15.3	8.6
x		x		53.9	48.3
			x	n.d.	2.0
x			x	n.d.	5.9

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; OR, odds ratio; 95% CI, confidence interval; n.d., no data
[a]These data are from two recently published case–control studies

synergism, the results of two recently published studies[23,30] are extracted and summarized in Table 1. According to these population-based, case–control studies, which analyzed 115 and 285 patients with HCC and 230 and 435 control subjects, respectively, heavy alcohol drinking is an independent HCC risk factor, increasing the risk 4.5- or 2.1-fold, respectively. Diabetes is also shown to be an independent risk factor [odds ratio (OR), 4.3 and 3.0]. More importantly, if alcohol abuse and diabetes coexist, the risk is synergistically increased to 9.9- or 17.3-fold, respectively, according to these two studies. As predicted from the previous work, hepatitis C virus (HCV) and hepatitis B virus (HBV) are strong independent risk factors (OR, 12.6/15.3 and 8.6). When alcohol abuse is superimposed, the OR jumps to 48.3 and 53.9. Smoking also has an effect that is more than additive, with an OR of 5.9 when combined with alcohol, whereas smoking by itself results in an OR of 2.0.[30] These results again underscore the fact that the top ten risk factors listed by WHO (Figs. 1A and B), or pathological conditions resulting from them, represent key risk factors that synergistically interact with alcohol to produce high-risk conditions for liver damage. They also emphasize the need to shift the research focus onto molecular mechanisms that underlie the interfaces of these specific interactions.

Interfaces of alcohol and risk factor interactions

In 2006, leading investigators in the field of alcoholic liver and pancreatic diseases (ALPD) assembled in Southern California at the First International Symposium on ALPD and Cirrhosis. Major discussions focused on molecular mechanisms that underlie alcohol's actions to sensitize hepatocytes and to prime pathologic effects, as well as on how these mechanisms interface with the effects of secondary risk factors. The published symposium proceedings (*Journal of Gastroenterology and Hepatology* 2006;21 Suppl 3) includes excellent review articles and is an outstanding compendium of discussions on ALPD pathogenesis.

Alcohol abuse perturbs the biology of the host to generate signature biochemical characteristics that are interactive in the pathogenesis of ALD (summarized in Fig. 3). An adaptive increase in the activity of alcohol dehydrogenase (ADH) and Cyp2e1 leads to increased acetaldehyde exposure, increased generation of reactive oxygen species (ROS), and enhanced oxygen consumption and subsequent centrilobular hypoxia.[31] Chronic alcohol intake also reduces the hepatic level of *S*-adenosylmethionine (SAMe) by suppression of methionine adenosyltransferase activity, while homocysteine is accumulated owing to the inhibition of methionine synthesis from homocysteine.[32,33] A high homocysteine level, acetaldehyde, and oxidant stress all can cause an unfolded protein response in the endoplasmic reticulum (ER), called ER stress. ER stress can activate sterol regulatory element-binding proteins (SREBP)-1c and -2, which contribute to the accumulation of triglycerides and cholesterol, respectively.[34] The former leads to fatty liver and the latter may lead to enrichment of free cholesterol in the mitochondria, resulting in reduced uptake of glutathione (GSH) by mitochondria and subsequent depletion of this critical antioxidant in this organelle (mGSH). This defect represents the most crucial mechanism of hepatocyte sensitization to cell death mediated by oxidant stress, inducing molecules such as tumor necrosis factor (TNF) α.[35] ER stress also induces CHOP, a protein implicated in apoptosis of hepatocytes in an ALD model.[34] Reduced SAMe sensitizes the liver to further damage and causes spontaneous steatohepatitis and HCC, by mechanisms not fully defined.[32] SAMe supplementation has been shown to ameliorate mGSH depletion, suggesting a link between the two.[35] SAMe also appears to regulate cytokine expression by lymphocytes[33] and Kupffer cells,[32] suggesting its role in nonparenchymal liver cells besides

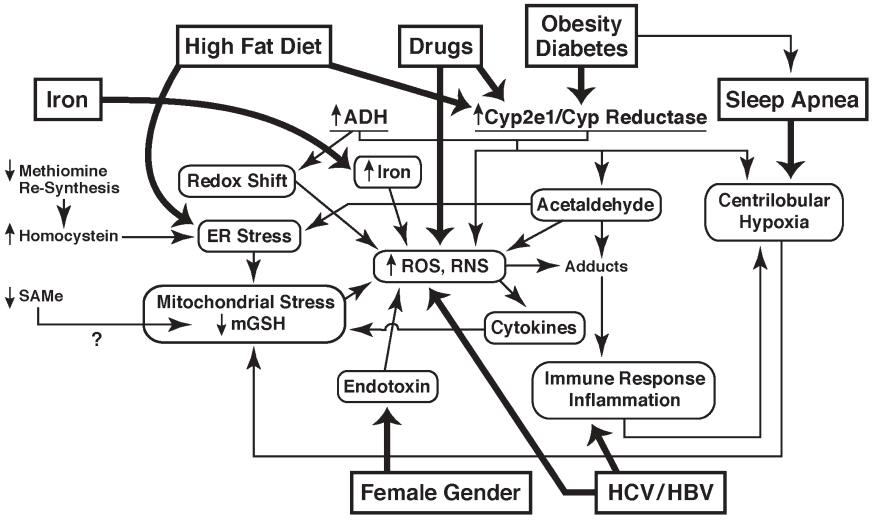

Fig. 3. Cross-interactions among alcohol-induced biochemical perturbations and their interactions with risk factors in the pathogenesis of alcoholic liver disease. Risk factors are enclosed in *rectangles*, and their interactions with alcohol-induced primary mechanistic events are shown by *bold arrows*. ROS, reactive oxygen species; RNS, reactive nitrogen-species; ER, endoplasmic reticulum; SAMe, *S*-adenosylmethionine; ADH, alcohol dehydrogenase; mGSH, mitochondrial glutathione

hepatocytes. With respect to Kupffer cell regulation in ALD, two new and intriguing hypotheses have emerged. One suggests an inhibitory effect of adiponectin on TNFα expression and a potential role of a reduced adiponectin level in upregulating TNFα in ALD.[36] The other proposes the importance of the signaling role of iron in IκB kinase (IKK) activation and TNFα expression by Kupffer cells in ALD.[37–39] Although endotoxin has been emphasized as a priming mechanism of hepatic macrophages for ROS generation and cytokine expression in ALD, it is difficult to explain chronic inflammation by this hypothesis alone, since we know Kupffer cells show endotoxin tolerance in ALD. In this respect, iron, which is known to accumulate in Kupffer cells in chronic liver disease such as ALD and nonalcoholic steatohepatitis (NASH), may be a critical regulator of inflammation, since this transition metal not only promotes endotoxin-mediated NFκB activation but also serves as endotoxin-independent agonist for NFκB-responsive genes via direct activation of IKK.[37–39] Adiponectin, a fat-derived cytokine, also serves as an upstream regulator for hepatocyte lipid metabolism. Adiponectin activates AMP-activated protein kinase (AMPK), which suppresses lipogenesis and promotes lipolysis via the following three mechanisms: (1) inhibition of SREBP-1c, a protein that induces lipogenic genes; (2) activation of peroxisome proliferator-activated receptor α, which induces fatty acid oxidation genes; and (3) inhibition of acetyl Co-A carboxylase and reduced production of malonyl-CoA, in turn activating carnitine palmitoyl-transferase-I, the rate-limiting enzyme for fatty acid transport into mitochondria. Thus, when adiponectin levels falls under chronic alcohol intake, AMPK activity is reduced, lipogenesis is induced, and fatty acid oxidation is suppressed, leading to the genesis of fatty liver. Indeed, a therapeutic effect of adiponectin on steatosis has been demonstrated in

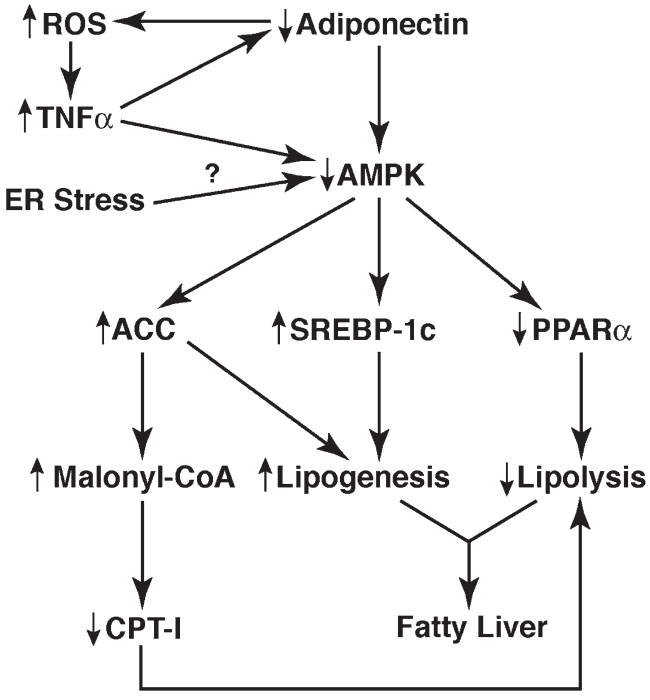

Fig. 4. Role of reduced adiponectin level in the genesis of alcoholic fatty liver. TNFα, tumor necrosis factor α; AMPK, AMP-activated protein kinase; ACC, acetyl Co-A carboxylase; SREBP-1c, sterol regulatory element-binding protein 1c; PPARα, peroxisome proliferator-activated receptor α; CPT-1, carnitine palmitoyl-transferase-I

animal models of both alcoholic and nonalcoholic fatty liver disease.[40] Of note is that inhibition of AMPK is also achieved by TNFα and ER stress, and reduced adiponectin levels favor ROS generation by NADPH oxidase in Kupffer cells and consequent TNFα expression, establishing circular and interactive inhibitory effects on AMPK (Fig. 4). Acetaldehyde, a major toxic

metabolite of alcohol, must be important in the pathogenesis of ALD. The question then is why do not all alcoholics, who presumably generate similar amounts of acetaldehyde owing to their similar high intake of alcohol and similar induction of ADH and Cyp2e1, develop progressive ALD. A difference in clearance of acetaldehyde is a possible explanation. But a more intriguing possibility was put forth by Dean Tuma and his colleagues more than 10 years ago.[41] Their study demonstrated the existence of a hybrid adduct, called MMA-protein adduct, composed of acetaldehyde and malondialdehyde, one of the major aldehyde products of lipid peroxidation. The important characteristics of the MMA adduct is that it forms in a synergistic manner in the presence of these two different aldehydes,[42] suggesting that the extent of oxidant damage (lipid peroxidation) determines the extent of MMA adduct formation in the presence of similar acetaldehyde concentrations. This adduct is very immunogenic, exhibits proinflammatory and profibrogenic properties, and its level correlates with ALD.[42]

Then, how do known risk factors of ALD such as high-fat diet, iron, drugs, female gender, viral hepatitis, and obesity/diabetes interact with the aforementioned mechanisms rendered by alcohol to promote ALD? Suspected interfaces are shown by the bold arrows in Fig. 3. For instance, a high-fat diet is known to induce Cyp2e1 and ER stress. Habitual drug intake similarly induces Cyp2e1 and other cytochrome isoforms, and their radical metabolites may directly promote oxidant stress. A diet high in iron or the co-existence of an iron metabolic disease exacerbates alcohol-induced iron accumulation in both hepatocytes and Kupffer cells, promoting oxidative damage via the Fenton pathway and accentuating IKK activation via iron signaling, inducing NFκB-responsive proinflammatory genes as described above. Type II diabetes is known to be associated with Cyp2e1 induction, which is implicated in the genesis of NASH. Obesity, which is a major predisposing condition for diabetes, may also increase sleep apnea, which in turn aggravates centrilobular liver hypoxia caused by a alcohol-induced hypermetabolic state. Hepatitis viral proteins have been shown to directly modulate innate and adaptive immunity[43,44] and induce oxidant stress in mitochondria.[45,46] HCV core protein also induces insulin resistance,[47,48] hepatic steatosis, and HCC via a mechanism involving the proteasome activator PA28γ.[49,50] HCV core transgenic mice fed ethanol show activation of extracellular signal-regulated kinase and p38 mitogen-activated protein kinase, which may be of relevance to the synergism for liver pathology.[51] Why female gender causes greater susceptibility to ALD is an important question. A difference in volume distribution or first-pass metabolism, increased endotoxin entrance into the portal system, and higher responsiveness to endotoxins have been proposed,[52] but the contribution of these mechanisms to the overall sensitization seen in female alcoholics is unclear. A global search for gender-specific targets that are affected by chronic alcohol abuse may be necessary to advance this specific field. More population-based studies are also essential to improve our knowledge of the effects of different risk factors on ALD. Precise molecular characterization of the interfaces of the interactions between alcohol and the various risk factors is of obvious importance and should be a focus of future research.

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References

1. Division of Epidemiological Surveillance and Health Situation and Trend Assessment Global Estimates for Health Situation. Assessment and Project. Geneva: World Health Organization; 1990.
2. Bellentani S, Saccoccio G, Costa G, Tiribelli C, Manenti F, Sodde M, et al. Drinking habits as cofactors of risk for alcohol induced liver damage. The Dionysos Study Group. Gut 1997;41:845–50.
3. Stinson FS, Grant BF, Dufour MC. The critical dimension of ethnicity in liver cirrhosis mortality statistics. Alcohol Clin Exp Res 2001;25:1181–7.
4. Harwood H. Updating estimates of the economic costs of alcohol abuse in the United States: estimates, update methods and data. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism; 2000.
5. Tao N, Sussman S, Nieto J, Tsukamoto H, Yuan JM. Demographic characteristics of hospitalized patients with alcoholic liver disease and pancreatitis in Los Angeles County. Alcohol Clin Exp Res 2003;27:1798–804.
6. Lieber CS, DeCarli LM. Hepatotoxicity of ethanol. J Hepatol 1991;12:394–401.
7. Lieber CS. Metabolism of ethanol and associated hepatotoxicity. Drug Alcohol Rev 1991;10:175–202.
8. Lelbach W. Quantitative aspects of drinking in alcoholic liver cirrhosis. In: Khanna H, Israel Y, Kalant H, editors. Alcoholic liver pathology. Toronto: Addiction Research Foundation of Ontario; 1975. p. 1–18.
9. Ramstedt M. Per capita alcohol consumption and liver cirrhosis mortality in 14 European countries. Addiction 2001;96 Suppl 1: S19–33.
10. Sorensen T, Orholm M, Bensen K, Hoybye G, Eghoje K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. Lancet 1984;2:241–4.
11. Sorensen TI. Alcohol and liver injury: dose-related or permissive effect? Liver 1989;9:189–97.
12. Kamper-Jorgensen M, Gronbaek M, Tolstrup J, Becker U. Alcohol and cirrhosis: dose-response or threshold effect? J Hepatol 2004;41:25–30.
13. Bellentani S, Tiribelli C, Saccoccio G, Sodde M, Fratti N, Demartin Ceal. Prevalence of chronic liver disease in the general population of northern Italy: the Dionysos Study. Hepatology 1994;20: 1442–9.

14. Klatsky AL, Armstrong MA. Alcohol, smoking, coffee, and cirrhosis. Am J Epidemiol 1992;136:1248–57.
15. Mukaiya M, Nishi M, Miyake H, Hirata K. Chronic liver diseases for the risk of hepatocellular carcinoma: a case–control study in Japan. Etiologic association of alcohol consumption, cigarette smoking and the development of chronic liver diseases. Hepatogastroenterology 1998;45:2328–32.
16. Kuper H, Tzonou A, Kaklamani E, Hsieh CC, Lagiou P, Adami HO, et al. Tobacco smoking, alcohol consumption and their interaction in the causation of hepatocellular carcinoma. Int J Cancer 2000;85:498–502.
17. Rotily M, Durbec JP, Berthezene P, Sarles H. Diet and alcohol in liver cirrhosis: a case–control study. Eur J Clin Nutr 1990;44: 595–603.
18. Mendenhall C, Anderson S, Weesner R, Goldberg S, Crolic K. Protein-calorie malnutrition associated with alcoholic hepatitis. Veterans Administration Cooperative Study Group on Alcoholic Hepatitis. Am J Med 1984;76:211–22.
19. Seeff L, Cuccherini B, Zimmerman H, Adler E, Benjamin S. Acetaminophen hepatotoxicity in alcoholics. A therapeutic misadventure. Ann Intern Med 1986;104:339–404.
20. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. Hepatology 1997;25:108–11.
21. Raynard B, Balian A, Fallik D, Capron F, Bedossa P, Chaput JC, et al. Risk factors of fibrosis in alcohol-induced liver disease. Hepatology 2002;35:635–8.
22. Peters M, Terrault N. Alcohol use and hepatitis C. Hepatology 2002;36:S220–5.
23. Hassan MM, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002;36:1206–13.
24. N'Kontchou G, Paries J, Htar MT, Ganne-Carrie N, Costentin L, Grando-Lemaire V, et al. Risk factors for hepatocellular carcinoma in patients with alcoholic or viral C cirrhosis. Clin Gastroenterol Hepatol 2006;4:1062–8.
25. Vidali M, Stewart SF, Rolla R, Daly AK, Chen Y, Mottaran E, et al. Genetic and epigenetic factors in autoimmune reactions toward cytochrome P4502E1 in alcoholic liver disease. Hepatology 2003;37:410–9.
26. Tavill AS, Qadri AM. Alcohol and iron. Semin Liver Dis 2004;24:317–25.
27. Aldrich MS, Brower KJ, Hall JM. Sleep-disordered breathing in alcoholics. Alcohol Clin Exp Res 1999;23:134–40.
28. Becker U, Deis A, Sorensen TI, Gronbaek M, Borch-Johnsen K, Muller CF, et al. Prediction of risk of liver disease by alcohol intake, sex, and age: a prospective population study. Hepatology 1996;23:1025–9.
29. Wilfred de Alwis NM, Day C. Genetics of alcoholic liver disease and nonalcoholic fatty liver disease. Semin Liver Dis 2007;27: 44–54.
30. Yuan JM, Govindarajan S, Arakawa K, Yu MC. Synergism of alcohol, diabetes, and viral hepatitis on the risk of hepatocellular carcinoma in blacks and whites in the U.S. Cancer 2004;101: 1009–17.
31. Tsukamoto H, Lu SC. Current concepts in the pathogenesis of alcoholic liver injury. FASEB J 2001;15:1335–49.
32. Lu SC, Martinez-Chantar ML, Mato JM. Methionine adenosyltransferase and S-adenosylmethionine in alcoholic liver disease. J Gastroenterol Hepatol 2006;21 Suppl 3:S61–4.
33. Barve S, Joshi-Barve S, Song Z, Hill D, Hote P, Deaciuc I, et al. Interactions of cytokines, *S*-adenosylmethionine, and *S*-adenosylhomocysteine in alcohol-induced liver disease and immune suppression. J Gastroenterol Hepatol 2006;21 Suppl 3: S38–42.
34. Kaplowitz N, Ji C. Unfolding new mechanisms of alcoholic liver disease in the endoplasmic reticulum. J Gastroenterol Hepatol 2006;21 Suppl 3:S7–9.
35. Garcia-Ruiz C, Fernandez-Checa JC. Mitochondrial glutathione: hepatocellular survival-death switch. J Gastroenterol Hepatol 2006;21 Suppl 3:S3–6.
36. Park PH, Thakur V, Pritchard MT, McMullen MR, Nagy LE. Regulation of Kupffer cell activity during chronic ethanol exposure: role of adiponectin. J Gastroenterol Hepatol 2006;21 Suppl 3:S30–3.
37. Tsukamoto H, Lin M, Ohata M, Giulivi C, French SW, Brittenham G. Iron primes hepatic macrophages for NF-kappaB activation in alcoholic liver injury. Am J Physiol 1999;277(6 Pt 1): G1240–50.
38. Xiong S, She H, Takeuchi H, Han B, Engelhardt JF, Barton CH, et al. Signaling role of intracellular iron in NF-kappaB activation. J Biol Chem 2003;278:17646–54.
39. Chen L, Xiong S, She H, Lin SW, Wang J, Tsukamoto H. Iron causes interactions of TAK1, p21ras, and phosphatidylinositol 3-kinase in caveolae to activate IkappaB kinase in hepatic macrophages. J Biol Chem 2007;282:5582–8.
40. Crabb DW, Liangpunsakul S. Alcohol and lipid metabolism. J Gastroenterol Hepatol 2006;21 Suppl 3:S56–60.
41. Tuma D, Thiele G, Xu D, Klassen L, Sorrell M. Acetaldehyde and malondialdehyde react together to generate distinct protein adducts in the liver during long-term ethanol administration. Hepatology 1996;23:872–80.
42. Tuma DJ. Role of malondialdehyde–acetaldehyde adducts in liver injury. Free Radic Biol Med 2002;32:303–8.
43. Foy E, Li K, Wang C, Sumpter R Jr, Ikeda M, Lemon SM, et al. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science 2003;300:1145–8.
44. Machida K, Cheng KT, Sung VM, Levine AM, Foung S, Lai MM. Hepatitis C virus induces toll-like receptor 4 expression, leading to enhanced production of beta interferon and interleukin-6. J Virol 2006;80:866–74.
45. Wang T, Weinman SA. Causes and consequences of mitochondrial reactive oxygen species generation in hepatitis C. J Gastroenterol Hepatol 2006;21 Suppl 3:S34–7.
46. Machida K, Cheng KT, Lai CK, Jeng KS, Sung VM, Lai MM. Hepatitis C virus triggers mitochondrial permeability transition with production of reactive oxygen species, leading to DNA damage and STAT3 activation. J Virol 2006;80:7199–207.
47. Shintani Y, Fujie H, Miyoshi H, Tsutsumi T, Tsukamoto K, Kimura S, et al. Hepatitis C virus infection and diabetes: direct involvement of the virus in the development of insulin resistance. Gastroenterology 2004;126:840–8.
48. Koike K. Hepatitis C virus infection can present with metabolic disease by inducing insulin resistance. Intervirology 2006;49: 51–7.
49. Miyamoto H, Moriishi K, Moriya K, Murata S, Tanaka K, Suzuki T, et al. Involvement of the PA28gamma-dependent pathway in insulin resistance induced by hepatitis C virus core protein. J Virol 2007;81:1727–35.
50. Moriishi K, Mochizuki R, Moriya K, Miyamoto H, Mori Y, Abe T, et al. Critical role of PA28gamma in hepatitis C virus-associated steatogenesis and hepatocarcinogenesis. Proc Natl Acad Sci USA 2007;104:1661–6.
51. Tsutsumi T, Suzuki T, Moriya K, Shintani Y, Fujie H, Miyoshi H, et al. Hepatitis C virus core protein activates ERK and p38 MAPK in cooperation with ethanol in transgenic mice. Hepatology 2003;38:820–8.
52. Thurman RG. II. Alcoholic liver injury involves activation of Kupffer cells by endotoxin. Am J Physiol 1998;275(4 Pt 1): G605–11.