Determinants of Alcohol Use and Abuse: Impact of Quantity and Frequency Patterns on Liver Disease

Samir Zakhari and Ting-Kai Li

More than 70% of alcohol is consumed by 10% of the population in the United States. Implicit in this statistic is that tremendous variation in the pattern of drinking (quantity, frequency, and duration) exists among alcohol consumers. Individuals who are binge or chronic drinkers will have different health outcomes than social drinkers. Therefore, knowing the pattern of drinking will shed light on how severely individuals are alcohol-dependent and on the extent of liver damage. Thus, these parameters assume particular relevance for the treatment-providing physician. Genetic factors contribute substantially to differences in alcohol metabolism. Variations in the activities of the alcohol-metabolizing enzymes, cytosolic alcohol dehydrogenase and mitochondrial aldehyde dehydrogenase, in part determine blood alcohol concentration, thereby contributing to the predisposition to becoming alcohol-dependent and to susceptibility to alcohol-induced liver damage. Chronic alcohol consumption induces cytochrome P450 2E1, a microsomal enzyme that metabolizes alcohol at high concentrations and also metabolizes medications such as acetaminophen and protease inhibitors. Alcohol metabolism changes the redox state of the liver, which leads to alterations in hepatic lipid, carbohydrate, protein, lactate, and uric acid metabolism. The quantity and frequency of alcohol consumption severely impact the liver in the presence of comorbid conditions such as infection with hepatitis B or C and/or human immunodeficiency virus, type 2 diabetes, hemochromatosis, or obesity and thus have implications with respect to the extent of injury and response to medications. *Conclusion:* Knowledge of the relationships between the quantity, frequency, and patterns of drinking and alcoholic liver disease is limited. A better understanding of these relationships will guide hepatologists in managing alcoholic liver disease. (HEPATOLOGY 2007;46:2032-2039.)

Alcohol-induced disorders, including alcoholism, are major health problems in the United States. According to the National Epidemiologic Survey on Alcohol and Related Conditions, more than 136 million Americans ages 18 and older drink alcohol. Of these, 5.8% meet the criteria for alcohol dependence (AD) or alcoholism, and 7.1% meet the criteria for alcohol abuse.[1] To date, only the genes encoding the principal alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH), have been linked to vulnerability to alcoholism and possible risk for alcoholic liver disease. Chronic alcohol consumption may lead to cirrhosis and is associated with an increased risk for hepatocellular carcinoma, and these are primary concerns for hepatologists. Cirrhosis is ranked the 12th leading cause of death in the United States, with a total of 28,085 deaths in 2003, of which 44% were alcohol-related.[2] However, only 10%-15% of alcoholics develop hepatitis and cirrhosis.[3] One obvious factor contributing to the variability in the occurrence of alcoholic liver disease (ALD) is the pattern of drinking (daily versus binge) and total alcohol intake (quantity and frequency).

The blood alcohol concentration (BAC) is a factor in the pathogenesis of liver disease. BAC is determined by environmental factors (for example, the quantity and frequency of alcohol drinking and the presence of food in the

Abbreviations: AD, alcohol dependence; ADH, alcohol dehydrogenase; AIDS, acquired immune deficiency syndrome; ALD, alcoholic liver disease; ALDH, aldehyde dehydrogenase; AUDIT, Alcohol Use Disorders Identification Test; βHB, β-hydroxybutyrate; BAC, blood alcohol concentration; CoA, coenzyme A; CYP2E1, cytochrome P450 2E1; ET, electron transport; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; $NADP^+$, oxidized nicotinamide adenine dinucleotide phosphate; NADPH, reduced nicotinamide adenine dinucleotide phosphate; NRTI, nucleoside reverse transcriptase inhibitor; PDH, pyruvate dehydrogenase; ROS, reactive oxygen species; T2D, type 2 diabetes; TCA, tricarboxylic acid; VLDL, very low density lipoprotein.

From the National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD.

Received June 18, 2007; accepted August 28, 2007.

Address reprint requests to: Samir Zakhari, Ph.D., National Institute on Alcohol Abuse and Alcoholism, 5635 Fishers Lane, Room 2031, Bethesda, MD 20892-9304. E-mail: szakhari@mail.nih.gov; fax: 301-594-0673.

Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.22010

Potential conflict of interest: Nothing to report.

stomach) and genetic factors [that is, variants of cytosolic ADH and mitochondrial ALDH as well as cytochrome P450, in particular the cytochrome P450 2E1 (CYP2E1) isoform]. There are large individual variations in alcohol elimination (3-fold) and the consequent deleterious effects of equivalent amounts of alcohol consumed.[4] An understanding of the role of the quantity and frequency of alcohol consumed and genetic variations in alcohol metabolism is essential for appreciating both the short-term and long-term effects of alcohol in liver pathogenesis and approaches to patient treatment.

Drinking Pattern and Alcohol Abuse/Dependence

Although most people drink responsibly, it has been reported that 10% of the population consumes over 70% of alcohol, with males drinking 76% of all alcohol consumed.[5] The US Department of Agriculture Dietary Guidelines define moderate drinking as up to 2 drinks/day for men and up to 1 drink/day for women. A drink is 12 oz (360 mL) of beer or wine cooler, 5 oz (150 mL) of wine, or 1.5 oz (45 mL) of 80-proof distilled spirits. Such standard drinks contain approximately 12.5 g of ethanol. As defined by the National Institute on Alcohol Abuse and Alcoholism,[6] binge drinking is the consumption of 5 or more drinks (male) or 4 or more drinks (female) in about 2 hours, resulting in a BAC of 0.08 g % or above. It is estimated that 28% of the adult population exhibits a high-risk drinking pattern, such as binge drinking, resulting in increased risk of developing AD. Binge drinking at least once a week is an early quantifiable marker for alcohol use disorders.[7]

While the value of quantity and frequency measures in the diagnosis, treatment, and prevention of alcohol use disorders is discussed elsewhere,[5] this article focuses on the impact of quantity and frequency patterns on liver disease. However, it is paramount for hepatologists to identify patients who are prone to AD because of the implications for treatment, especially in the presence of other alcohol-induced metabolic derangements. The Alcohol Use Disorders Identification Test (AUDIT) is a widely used screening instrument to detect hazardous and harmful alcohol consumption.[8] The AUDIT comprises 10 questions that can be answered by the patient before seeing a clinician. It takes only about 5 minutes to complete, and it has high levels of validity and reliability. This one-page questionnaire can be downloaded from www.niaaa.nih.gov/guide. The AUDIT is then scored by the hepatologist or assistants; a score of 8 or higher for men or 4 or higher for women is considered a positive screen.

Drinking too much too fast (binge drinking) can lead to glycogen depletion, which would be aggravated in the presence of liver disease, and may lead to acidosis and hypoglycemia. On the other hand, drinking too much (more than 5 drinks for men and 4 drinks for women/day) and too often over a long period of time results in ALD, which encompasses fatty liver, steatohepatitis, liver fibrosis, and cirrhosis and may proceed to hepatocellular carcinoma. In addition, people who drink heavily tend to have hyperuricemia after alcohol ingestion and exhibit hypertriglyceridemia, which may exacerbate diabetic hypertriglyceridemia.

Quantity and Frequency of Drinking and Liver Damage

Although there is a vast scientific literature pertaining to hepatotoxicity due to excessive drinking (for example, see Reuben[9]), the effects of drinking too much too fast (4-5 drinks in 2 hours) or too much too often (4-5 drinks/day) on the liver have been sparingly studied. Past studies focused on the incidence of cirrhosis among alcoholics[10] or sought the clinical manifestations of alcoholism among patients with cirrhosis.[11] In these two approaches, the classification of cirrhosis into alcoholic or nonalcoholic was subjective (what is the definition of alcoholic or heavy drinker or what other comorbidities contribute to the development of cirrhosis?), and the quantity of alcohol consumed and the drinking pattern were undetermined. A third indirect approach attempted to correlate average quantities of alcohol consumption (based on demographic and economic statistics) with cirrhosis mortality. This approach, however, did not measure the quantity and frequency of alcohol consumption and did not provide information on individual consumption and risk.

In 1963, Pequignot (cited in Pequignot et al.[12]) attempted to directly measure alcohol consumed by interviewing patients with liver problems, but that approach resulted only in determining that patients with cirrhosis drink much higher amounts of alcohol than others. In one of the earliest studies of drinking patterns, 184 ascitic patients with cirrhosis were administered a detailed questionnaire about their eating and drinking habits, including type of alcoholic beverage and amount consumed between meals.[12] Daily alcohol consumption was stratified in 20-g increments, and the relative risk was shown to be dose-related. To correlate drinking patterns and cirrhosis, Parrish and colleagues[13] examined 334 cases of cirrhosis deaths, of which 148 were alcohol-related. Patients with alcoholic cirrhosis tended to be heavy drinkers (5 or more drinks/day) who drank every day. This study was limited because it gathered drinking pattern information from the next of kin, and drinking information was

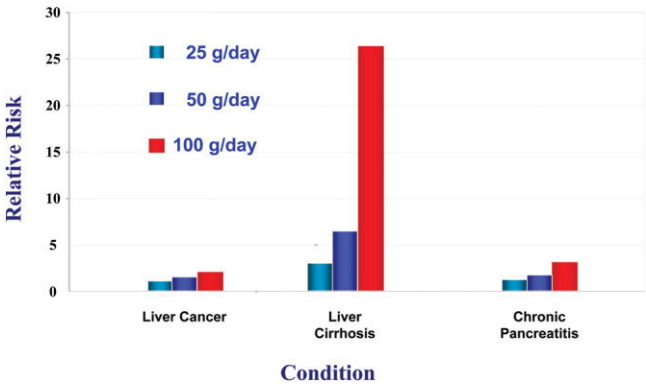

Fig. 1. The relative risk of alcohol-related conditions is increased with amounts of alcohol consumed per day. Adapted from *Preventive Medicine*.[17]

limited to quantity and frequency during an unspecified period of time.

In a prospective study, Kamper-Jørgensen and colleagues[14] interviewed a cohort of 6152 alcohol-abusing men and women about their drinking pattern, frequency of alcohol intake, duration of alcohol misuse, and beverage type. The rate of alcoholic cirrhosis mortality in men and women was 27 and 35 times the rate of the Danish general population, respectively. They also reported that "alcohol has a threshold effect rather than a dose-response effect on mortality from alcoholic cirrhosis." This is not surprising because their lowest tier of drinking comprised an average of 5-9 drinks/day, which is already in the heavy drinking category. They also found that men and women who drank periodically had a significantly lower relative risk for developing cirrhosis. Another Danish prospective study reported a significant increase in risk for ALD at 7-13 drinks/week for women and 14-27 drinks/week for men.[15] An analysis of the quantity consumed and drinking patterns of an Italian population showed that consuming 30 g/day is the minimum quantity to induce measurable risk of developing cirrhosis in men and women.[16] Also, the pattern of drinking was an important determinant of risk. Drinking without food, independent of the quantity, was associated with an increased prevalence of alcoholic liver disease. A meta-analysis of alcohol consumption and risk of various diseases, including cirrhosis and cancer, reported an increased risk as alcohol consumption increased from 25 (2 drinks) to 100 g/day (8 drinks)[17] (Fig. 1). More studies are needed to better dissect the relationship between the quantity and pattern of drinking and alcohol-induced liver damage.

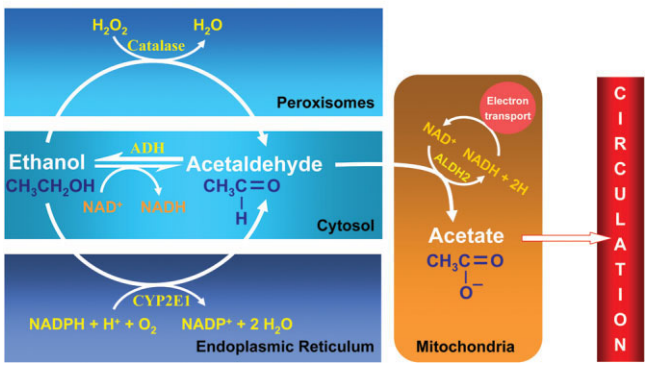

Fig. 2. Alcohol is oxidatively metabolized primarily in the liver. Cytosolic ADH and mitochondrial ALDH2 are the main enzymes involved in this metabolic pathway. ADH indicates alcohol dehydrogenase; ALDH2, aldehyde dehydrogenase 2; CYP2E1, cytochrome P450 2E1; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; $NADP^+$, oxidized nicotinamide adenine dinucleotide phosphate; and NADPH, reduced nicotinamide adenine dinucleotide phosphate.

Alcohol Metabolism and Liver Damage

Although alcohol metabolism is often considered the predominant factor in causing alcohol-associated liver damage, other factors such as inflammatory cytokines and immunologic and metabolic pathway derangements are beyond the scope of this article.

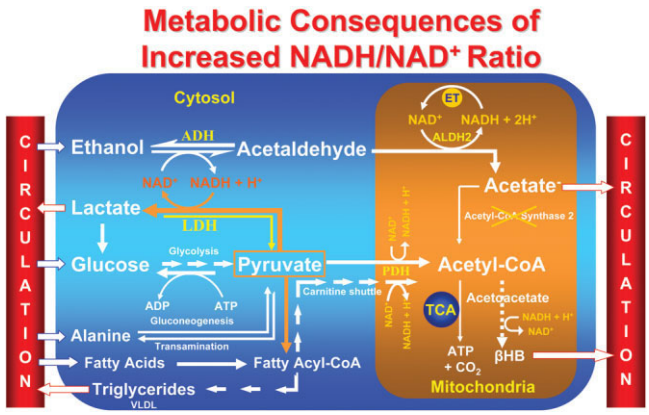

Fig. 3. Alcohol metabolism to acetaldehyde in the cytosol by ADH and then to acetate by mitochondrial ALDH2 increases the ratio of NADH to NAD^+. NADH in the mitochondria is oxidized via the ET chain. Pyruvate in the cytosol is formed from glucose via glycolysis and can undergo three pathways: (1) entering the mitochondria to form acetyl CoA by oxidative decarboxylation with PDH; (2) being reduced to lactate by LDH, a process that requires NADH; or (3) being converted to glucose (gluconeogenesis) via an ATP-requiring reaction. Almost all of the acetate formed from acetaldehyde metabolism cannot be converted to acetyl CoA and enters the circulation to be metabolized by extrahepatic tissues. The increase in cytosolic NADH favors the formation of lactate resulting in lactic acidosis, and in the mitochondria forms βHB from acetoacetate by BHB dehydrogenase. ADH indicates alcohol dehydrogenase; ADP, adenosine diphosphate; ALDH2, aldehyde dehydrogenase 2; ATP, adenosine triphosphate; βHB, β-hydroxybutyrate; CoA, coenzyme A; ET, electron transport; NAD^+, oxidized nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid; and VLDL, very low density lipoprotein.

Table 1. Polymorphisms of Alcohol Dehydrogenase (ADH) Genes

ADH Class	Gene	Enzyme Subunit	K_m for Ethanol (mM)	V_{max} (min^{-1})	Ethanol Catalytic Efficiency	Expression in Liver	Population
I	*ADH1A*	α	4.0	30	Low	✓	
	*ADH1B*1*	β_1	0.05	4	High	✓	
	*ADH1B*2*	β_2	0.9	350	High	✓	Asians
	*ADH1B*3*	β_3	40.0	300	Low	✓	African Americans
	*ADH1C*1*	γ_1	1.0	90	High	✓	All groups
	*ADH1C*2*	γ_2	0.6	40	High	✓	Caucasians
	*ADH1C*3*	γ_3	−*	−*			Native Americans
II	*ADH4*	π	30	20	Low	✓	
III	*ADH5*	χ	>1000	100	Very low	✓	
IV	*ADH7*	σ	30	1800	High	✓	
V	*ADH6*	?	?	?	Not identified		

Adapted from *Pharmacogenomics: The Search for Individualized Therapies*.[25]

*The value is unknown.

K_m, or Michaelis Constant, is a measure of relative affinity of an enzyme for its substrate. V_{max} describes the maximal rate at which an enzyme catalyzes a reaction.

Alcohol metabolism is achieved mainly by oxidative pathways involving ADH, CYP2E1, and catalase enzymes (Fig. 2), resulting in the formation of acetaldehyde, a highly reactive and toxic molecule that contributes to liver damage (for a review, see Zakhari[18]). The liver is the main organ for metabolizing ingested alcohol by oxidative pathways; this may explain its susceptibility to alcohol-induced injury. Multiple isoenzymes of ADH exist (Table 1) with variable affinities for ethanol. At high concentrations (such as following binge drinking), alcohol is eliminated at a high rate because of the presence of high-K_m enzyme systems such as the class II B ADH, the class I β_3-ADH, and CYP2E1. (K_m, or Michaelis Constant, is a measure of relative affinity of an enzyme for its substrate.) Alcohol oxidation by ADH is accompanied by the reduction of oxidized nicotinamide adenine dinucleotide (NAD^+) to reduced nicotinamide adenine dinucleotide (NADH), thereby generating a highly reduced cytosolic environment in hepatocytes. Because mitochondria are not permeable to NADH, the malate-aspartate shuttle transfers the reducing equivalents of cytosolic NADH into mitochondria. Acetaldehyde is rapidly metabolized, mainly by mitochondrial ALDH2, to form acetate and NADH. Mitochondrial NADH is oxidized by the electron transport chain. The cytochrome P450 isozymes CYP2E1, CYP1A2, and CYP3A4, which are present predominantly in the endoplasmic reticulum, also contribute to ethanol oxidation in the liver. CYP2E1 is induced by chronic ethanol consumption and assumes an important role in metabolizing ethanol to acetaldehyde at elevated alcohol concentrations (K_m = 8-10 mM). It also produces highly reactive oxygen species (ROS) and metabolizes medications such as acetaminophen. Thus, alcohol metabolism can cause ALD through the formation of acetaldehyde, through ROS production, and by changing the redox state of hepatocytes, thereby influencing the direction of several reversible reactions with metabolic consequences.

The increase in mitochondrial NADH in hepatocytes due to acetaldehyde metabolism contributes to the saturation of NADH dehydrogenase, thus hampering the function of the tricarboxylic acid (TCA) cycle. Liver mitochondria have a limited capacity to oxidize acetate to CO_2 in the TCA cycle because acetyl coenzyme A (CoA) synthase 2, a mitochondrial enzyme involved in the oxidation of acetate, is absent from the liver but abundant in heart and skeletal muscles.[19] Thus, most of the acetate resulting from ethanol metabolism escapes the liver into the blood circulation (Fig. 3) and is eventually metabolized to CO_2 by way of the TCA cycle in cells with mitochondria that contain enzymes to convert acetate to acetyl CoA, such as heart, skeletal muscle, and brain. During ethanol metabolism, when circulating ethanol is in the millimolar range, acetaldehyde is in the micromolar range, and acetate is in the millimolar range.

Consequences of Increased NADH/NAD^+ Ratio

Increased NADH/NAD^+ ratios in both the cytosol and mitochondria of hepatocytes influence the direction of several reversible reactions leading to alterations in hepatic lipid, carbohydrate, protein, lactate, and uric acid metabolism (Fig. 3). These changes happen after binge drinking and seem to be attenuated with chronic ethanol ingestion, although some changes, such as accumulation of fat in the liver, continue with chronic consumption.

Alcoholic Hypoglycemia. The increase in NADH due to alcohol metabolism prevents pyruvate conversion to glucose by lowering the concentration of pyruvate, which in turn decreases the pyruvate carboxylase reaction, one of

the rate limiting steps of gluconeogenesis.[20] Collectively, the result can be clinically significant hypoglycemia.

Alcoholic Acidosis. Ketoacidosis is common in chronically malnourished alcoholics and is due to the formation of ketone bodies, primarily β-hydroxybutyrate.[21] In addition, the increase in NADH favors the conversion of pyruvate to lactate, resulting in lactic acidosis. Binge drinkers may present with severe acidosis with relatively low ketone bodies and hypoglycemia. The increase in the $NADH/NAD^+$ ratio diminishes pyruvate dehydrogenase activity in the mitochondria, resulting in diminished conversion of pyruvate to acetyl CoA. Pyruvate dehydrogenase activity is further diminished in chronic alcoholics because of hypomagnesemia and thiamine deficiency, and this results in the inhibition of pyruvate utilization in the TCA cycle.

Hyperuricemia. Patients who drink too much frequently may develop hyperuricemia because lactate and ketone bodies formed after alcohol metabolism compete with urate for excretion in the distal tubules of the kidney.[22] Alcohol metabolism also releases the adenosine triphosphate degradation products, hypoxanthine and adenosine, which enter the purine nucleotide degradation pathway, resulting in increased formation of urate.

Hypertriglyceridemia. Heavy alcohol consumption increases the synthesis of triglycerides, resulting in fatty liver and hypertriglyceridemia, and may exacerbate diabetic hypertriglyceridemia. The increase in the $NADH/NAD^+$ ratio results in an increase in α-glycerophosphate, which favors hepatic triglyceride accumulation, and also inhibits mitochondrial β-oxidation of fatty acids.[23]

Hypoxia. Metabolism of ethanol by hepatocytes tends to increase oxygen uptake, resulting in significant hypoxia in the perivenous hepatocytes, the site of early liver damage due to chronic alcohol consumption. Ethanol indirectly increases oxygen use by hepatocytes through lipopolysaccharide-induced activation of Kupffer cells, resulting in the release of prostaglandin E2 and stimulation of hepatocyte metabolic activity, further contributing to the onset of hypoxia. Binge drinkers could have severe hypoxia and hepatic reperfusion injury.[24]

Genetic Aspects of Ethanol Metabolism

Genetic variations in ethanol metabolism are centered on class I ADH and ALDH2. Allelic variants of the genes encoding ADH and ALDH2 produce alcohol-metabolizing and acetaldehyde-metabolizing enzymes with variable activity. These genotypes influence AD and modify susceptibility to liver damage. As shown in Table 1, ADH genetic polymorphisms occur at the *ADH1B* and *ADH1C* loci; the enzyme encoded by *ADH1B*1* has high affinity and low capacity for ethanol oxidation, whereas those encoded by *ADH1B*2* and *ADH1B*3* have lower affinity and higher capacity for ethanol oxidation. As a result, individuals with *ADH1B*2* and *ADH1B*3* metabolize alcohol at a faster rate than those with *ADH1B*1*.[25] Although correlations between ADH polymorphisms and cirrhosis have been observed, the findings have been inconsistent.[26] For example, studies in Japanese[27] and Chinese[28] populations showed higher frequencies of the *ADH1B*1/*1* genotype in patients with alcoholic cirrhosis. However, the development of alcoholic cirrhosis in Korean patients was not associated with any polymorphisms in ADH.[29] ADH1B*1/*2 was associated with alcoholic cirrhosis in Caucasian Spanish women.[30]

The mitochondrial allelic variant *ALDH2*2*, a deficient phenotype, is present in about 50% of the Taiwanese, Han Chinese, and Japanese populations and shows virtually no acetaldehyde metabolizing activity. The deficient *ALDH2*2* allele is protective for AD because of the aversive effect of high circulating levels of acetaldehyde during alcohol consumption. Alcoholic cirrhosis is reduced over 70% in populations carrying the *ALDH2*2* allele.[31] Studies are needed to further identify the role of alcohol-metabolizing enzymes in ALD.

Quantity/Frequency, Comorbid Conditions, and Liver Disease

The definition of moderate or heavy drinking takes on a new perspective when one is dealing with patients who have liver disease and comorbid conditions, such as hepatitis C virus (HCV) or human immunodeficiency virus (HIV) infection, diabetes, hemochromatosis, or obesity. In such patients, drinking even moderate amounts of alcohol can exacerbate liver damage. Acute alcoholic hepatitis is observed in chronic alcoholics (with or without noticeable liver impairments) and in moderate drinkers after a binge.[32]

HCV. Despite different histological appearance in precirrhotic stages, alcohol drinking aggravates liver fibrosis due to chronic HCV infection. For example, drinking more than 50 g/day of alcohol increased the relative risk of liver fibrosis in HCV patients 1.3-fold compared to HCV-infected nondrinkers and was associated with higher viremia.[33] Other studies showed a dose-dependent increase in risk for cirrhosis, even at lower alcohol intake (for example, see Hezode et al.[34]). Although the role of light alcohol intake on disease progression remains to be elucidated, it is recommended that patients with chronic hepatitis C abstain from alcohol, especially because alcohol consumption has been associated with increased treatment discontinuation and lower sustained virologic response.[35]

HIV/Acquired Immune Deficiency Syndrome (AIDS). Approximately 50% of HIV-infected patients drink alcohol, sometimes heavily. Liver disease is now the second leading cause of death in AIDS patients. Alcohol consumption in HIV-infected persons is not routinely assessed, and its role as a cofactor in HIV progression is frequently disregarded, particularly in patients without evidence of liver disease. A better appreciation for alcohol's effects on HIV and liver disease may increase utilization of alcohol cessation interventions, thus improving treatment outcomes.

Coinfection with viral hepatitis is common in HIV+ individuals. Approximately 15%-30% of patients with HIV also have HCV, and hepatitis B virus occurs in 5%-10% of patients. Alcohol consumption by HCV-coinfected AIDS patients exacerbates steatosis, resulting in more rapid fibrosis progression. More importantly, mitochondrial toxicity is a serious side effect of nucleoside reverse transcriptase inhibitors (NRTIs), and lactic acidosis is a rare but clinically important manifestation of NRTI toxicity. The interactions between alcohol and NRTIs in HIV-infected patients and their impact on the course of liver disease need further investigation.

Most protease inhibitors are metabolized by the cytochrome P450 enzymes CYP3A4 and CYP3A5. Chronic ethanol use/abuse induces hepatic CYP3A4 activity and thus may interfere with highly active antiretroviral therapy in AIDS patients by accelerating the metabolism of protease inhibitors.[36]

Diabetes. Type 2 diabetes (T2D) is influenced by the quantity and frequency of alcohol consumed. Although moderate alcohol consumption seems to be beneficial in T2D, heavy drinking is detrimental. Consuming 1 drink per week or per day reduced the relative risk of developing T2D to 0.89 or 0.57, respectively, with respect to nondrinkers.[37] Moderate alcohol consumption (5-10 drinks/week) reduced the incidence of diabetes in men 2-fold, whereas increasing consumption to 10-22 drinks/week increased the incidence slightly above that of nondrinkers.[38] In women, 4-10 drinks/week was associated with a decreased risk of diabetes.[39] Heavy drinking led to the development of frank clinical diabetes with glucose intolerance and insulin deficiency, which were reversed following abstinence.[40] Thus, moderate drinking may not impact diabetic control (except for occasional hypoglycemia if taken without a meal), whereas heavy drinking induces glucose intolerance, increased insulin resistance, and hypertriglyceridemia.

Obesity. The relationship between quantity and frequency of drinking and body mass index is complex. People who consumed the smallest quantity frequently were leanest, whereas those who drank heavily but less frequently were heaviest.[41] Binge drinking or drinking 4 or more drinks/day was associated with greater odds for obesity. Freiberg et al.[42] found that the prevalence of metabolic syndrome in subjects who drank 1-19 drinks/month was 65% of that in nondrinkers. In alcoholics, risk factors for developing liver fibrosis and cirrhosis are obesity, hyperglycemia, and iron overload.[43]

Patients on Acetaminophen. Chronic alcohol consumption induces CYP2E1, the enzyme involved in the oxidative metabolism of acetaminophen to the reactive intermediate metabolite *N*-acetyl-*p*-benzoquinoneimine, which is thought to be the major cause of acetaminophen hepatotoxicity. Alcohol-acetaminophen interactions are complex and depend on the relative timing of alcohol and acetaminophen administration. Thus, acute alcohol consumption inhibits the microsomal oxidation of acetaminophen and decreases its hepatotoxicity. Alcohol is protective at concentrations as low as 2 mM, but once alcohol is metabolized, acetaminophen metabolism resumes. This protective effect is generally due to competitive inhibition. Chronic alcoholics are likely to be more vulnerable to acetaminophen hepatotoxicity during withdrawal, when ethanol has been completely metabolized. However, toxicity could be accentuated in chronic alcoholics by glutathione depletion and the induction of multiple isoforms of the cytochrome P450 family that are involved in acetaminophen metabolism.[44] It is important to ascertain the amount of alcohol consumed and the timing of consumption.

Quantity and Frequency of Drinking: Implications for Treatment

The quantity and frequency of drinking alcohol determine not only the extent of liver damage but also the risk for AD/alcohol abuse. Recognizing an alcohol-dependent person is important for the treatment approach. Treatment of alcohol withdrawal could further endanger the liver. For example:

1. Patients with acute alcoholic hepatitis undergoing alcohol withdrawal should be treated with benzodiazepines (ideally short-acting lorazepam).[32]
2. Tetrabamate, a drug used for the treatment of symptoms of alcohol withdrawal, may exacerbate alcoholic liver disease because of its hepatotoxic effects.[45]
3. Enhanced susceptibility to acetaminophen-induced hepatotoxicity was observed during alcohol withdrawal in humans with clinically compromised liver.[46]
4. Clomethiazole is an extremely useful drug for the management of acute alcohol withdrawal. It is considered beneficial because it inhibits CYP2E1 and, therefore, decreases ROS production. However, CYP2E1 expression during withdrawal is diminished and may not be an im-

portant factor. Reduced clomethiazole clearance in patients with moderate/severe liver impairment necessitates a reduction of clomethiazole dosage.[47]

5. Of the three medications approved for the treatment of AD, disulfiram is known to cause sometimes fatal hepatitis.[48] Therefore, for alcoholic patients with liver disease, the hepatologist should suggest the use of acamprosate[49] or naltrexone,[50] which are safer for the liver.

Future Research

Emerging evidence suggests that quantity and frequency of drinking are important in the pathogenesis of liver disease. New studies are needed to dissect the effects of quantity and frequency on alcohol hepatotoxicity. Epidemiological studies depend on questionnaires to ascertain quantity, frequency, and pattern of consumption, which inject patient bias and memory problems, especially in alcoholics. The development of sensitive and selective biomarkers using proteomics and metabolomics is needed not only for detecting the extent of drinking but also for identifying responders to treatment.

References

1. Alcohol use and alcohol use disorders in the United States: main findings from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). In: U.S. Alcohol Epidemiologic Data Reference Manual. Vol. 8. National Institute on Alcohol Abuse and Alcoholism Web site. Available at: http://niaaa.census.gov/pdfs/nesarc_drm.pdf. Accessed September 2007.
2. Yoon YH, Yi HY. Surveillance report #75: liver cirrhosis mortality in the United States, 1970-2003. National Institute on Alcohol Abuse and Alcoholism Web site. Available at: http://pubs.niaaa.nih.gov/publications/surveillance75/Cirr03.htm. Accessed September 2007.
3. Mann RE, Smart RG, Govoni R. The epidemiology of alcohol liver disease. J Natl Inst Alcohol Abuse Alcohol 2003;27:209-219.
4. Li TK, Yin SJ, Crabb DW, O'Connor S, Ramchandani VA. Genetic and environmental influences on alcohol metabolism in humans. Alcohol Clin Exp Res 2001;25:136-144.
5. Li TK, Hewitt BG, Grant BF. Is there a future for quantifying drinking in the diagnosis, treatment, and prevention of alcohol use disorders? Alcohol Alcohol 2007;42:57-63.
6. National Advisory Council on Alcohol Abuse and Alcoholism, summary of meeting, February 4-5, 2004. National Institute on Alcohol Abuse and Alcoholism Web site. Available at: http://www.niaaa.nih.gov/AboutNIAAA/AdvisoryCouncil/CouncilMinutes/min2–04.htm. Accessed September 2007.
7. Saha TD, Stinson FS, Grant BF. The role of alcohol consumption in future classifications of alcohol use disorders. Drug Alcohol Depend 2007;89:82-92.
8. Barbor TF, de la Fuente JR, Saunders J, Grant M. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Health Care. Geneva, Switzerland: World Health Organization; 1992.
9. Reuben A. Alcohol and the liver. Curr Opin Gastroenterol 2007;23:283-291.
10. Lelbach WK. Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. Ann N Y Acad Sci 1975;252:85-105.
11. Caroli J, Mainguet P, Ricordeau P, Foures A. L'importance de la laparoscopie dans la classification anatomo-clinique des cirrhoses du foie. Paper presented at: Cirrhose Alcoolique et Nutritionnelle XXXIIe Congres Français.
12. Pequignot G, Tuyns AJ, Berta JL. Ascitic cirrhosis in relation to alcohol consumption. Int J Epidemiol 1978;7:113-120.
13. Parrish KM, Dufour MC, Stinson FS, Harford TC. Average daily alcohol consumption during adult life among decedents with and without cirrhosis: the 1986 national mortality followback survey. J Stud Alcohol 1993;54:450-456.
14. Kamper-Jorgensen M, Gronbaek M, Tolstrup J, Becker U. Alcohol and cirrhosis: dose—response or threshold effect? J Hepatol 2004;41:25-30.
15. Becker U, Deis A, Sorensen TIA, 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;23:1025-1029.
16. 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. Gut 1997;41:845-850.
17. Corrao G, Bagnardi V, Zambon A, La Vecchia C. A meta-analysis of alcohol consumption and the risk of 15 diseases. Prev Med 2004;38:613-619.
18. Zakhari S. Overview: how is alcohol metabolized by the body? Alcohol Res Health 2006;29:245-257.
19. Fujino T, Kondo J, Ishikawa M, Morikawa K, Yamamoto TT. Acetyl-CoA synthase 2, a mitochondrial matrix enzyme involved in the oxidation of acetate. JBC 2001;276:11420-11426.
20. Krebs HA, Freedland RA, Hems R, Stubbs M. Inhibition of hepatic gluconeogenesis by ethanol. Biochem J 1969;112:117-124.
21. Gauthier PM, Szerlip HM. Metabolic acidosis in the intensive care unit. Crit Care Clin 2002;18:289-308.
22. Yamanaka H. Alcohol ingestion and hyperuricemia. Nippon Rinsho 1996;54:3369-73.
23. Lieber CS. Alcohol and the liver: 1984 update. HEPATOLOGY 1984;4:1243-1260.
24. French SW. The role of hypoxia in the pathogenesis of alcoholic liver disease. Hepatol Res 2004;29:69-74.
25. Hurly TD, Edenberg HJ, Li TK. The pharmacogenomics of alcoholism. In: Pharmacogenomics: The Search for Individualized Therapies; Weinheim, Germany: Wiley-VCH; 2002:417-441.
26. Zintzaras E, Stefanidis I, Santos M, Vidal F. Do alcohol metabolizing enzyme gene polymorphisms increase the risk of alcoholism and alcoholic liver disease? HEPATOLOGY 2006;43:352-361.
27. Tanaka F, Shiratori Y, Yokosuka O, Imazeki F, Tsukada Y, Omata M. High incidence of ADH2*1/ALDH2*1 genes among Japanese alcohol dependents and patients with alcoholic liver disease. HEPATOLOGY 1996;23:234-239.
28. Chao YC, Young TH, Tang HS, Hsu CT. Alcoholism and alcoholic organ damage and genetic polymorphisms of alcohol metabolizing enzymes in Chinese patients. HEPATOLOGY 1997;25:112-117.
29. Lee HC, Lee HS, Jung SH, Yi SY, Jung HK, Yoon JH, et al. Association between polymorphisms of ethanol-metabolizing enzymes and susceptibility to alcoholic cirrhosis in a Korean male population. J Korean Med Sci 2001;16:745-750.
30. Lorenzo A, Auguet T, Vidal F, Broch M, Olona M, Gutierrez C, et al. Polymorphisms of alcohol-metabolizing enzymes and the risk for alcoholism and alcoholic liver disease in Caucasian Spanish women. Drug Alcohol Depend 2006;84:195-200.
31. Nagata N, Hiyoshi M, Shiozawa H, Shiraishi K, Watanabe N, Tsuda M, et al. Assessment of a difference in ALDH2 heterozygotes and alcoholic liver injury. Alcohol Clin Exp Res 2002;26:11S–14S.
32. Ceccanti M, Attili A, Balducci G, Attilia F, Giacomelli S, Rotondo C, et al. Acute alcoholic hepatitis. J Clin Gastroenterol 2006;40:833-841.
33. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-832.
34. Hezode C, Lonjon I, Roudot-Thoraval F, Pawlotsky JM, Zafrani ES, Dhumeaux D. Impact of moderate alcohol consumption on histological activity and fibrosis in patients with chronic hepatitis C, and specific influence of steatosis: a prospective study. Aliment Pharmacol Ther 2003;17:1031-1037.

35. Anand BS, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, et al. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. Gastroenterology 2006;130:1607-1616.
36. Feierman ED, Melinkov Z, Nanji AA. Induction of CYP3A by ethanol in multiple in vitro and in vivo models. Alcohol Clin Exp Res 2003;27:981-988.
37. Ajani UA, Hennekens CH, Spelsberg A, Manson JE. Alcohol consumption and risk of type 2 diabetes mellitus among US male physicians. Arch Intern Med 2000;160:1025-1030.
38. Wei M, Kampert JB, Gibbons LW, Blair SN, Mitchell T. Alcohol intake and incidence of type 2 diabetes in men. Diabetes Care 2000;23:18-22.
39. Stampfer MJ, Colditz GA, Willett WC, Manson JE, Arky RA, Hennekens CH, et al. A prospective study of moderate alcohol drinking and risk of diabetes in women. Am J Epidemiol 1988;128:549-558.
40. Yoshitsugu M, Sekiya Y, Ihore M. A chronic alcoholic patient with the development of frank diabetes after heavy drinking and perfect improvement following abstinence from alcohol. Arukoru Kenkyuto Yakubutsu Ison 1992;27:276-283.
41. Breslow RA, Smothers BA. Drinking patterns and body mass index in never smokers: National Health Interview Survey, 1997-2001. Am J Epidemiol 2005;161:368-376.
42. Freiberg MS, Vasan RS, Cabral HJ, Ellison RC, Heeren TC. Alcohol consumption and the prevalence of the metabolic syndrome in the U.S.: a cross-sectional analysis of data from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2954-2959.
43. 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;35:635-638.
44. Prescott LF. Paracetamol, alcohol and the liver. Br J Clin Pharmacol 2000;49:291-301.
45. Dumortier J, Bellemin B, Jacob P, Berger F, Chevallier M, Scoazec JY, et al. Liver injury due to tetrabamate (Atrium): an analysis of 11 cases. Eur J Gastroenterol Hepatol 2000;12:1007-1012.
46. Campbell S, Timms PM, Maxwell PR, Doherty EM, Rahman MZ, Lean ME, et al. Effect of alcohol withdrawal on liver transaminase levels and markers of liver fibrosis. J Gastroenterol Hepatol 2001;16:1254-1259.
47. Centerholt C, Ekblom M, Odergren T, Borga O, Popescu G, Molz KH, et al. Pharmacokinetics and sedative effects in healthy subjects and subjects with impaired liver function after continuous infusion of clomethiazole. Eur J Clin Pharmacol 2003;59:117-122.
48. Bjornsson E, Nordlinder H, Olsson R. Clinical characteristics and prognostic markers in disulfiram-induced liver injury. J Hepatol 2006;44:791-797.
49. Scott LJ, Figgitt DP, Keam SJ, Waugh J. Acamprostate: a review of its use in the maintenance of abstinence in patients with alcohol dependence. CNS Drugs 2005;19:445-464.
50. Brewer C, Wong VS. Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of the literature. Addict Biol 2004;9:81-87.