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The Impact of Obesity and Metabolic Syndrome on Alcoholic Liver Disease

Dian J. Chiang, MD, MPH and

Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic, A51, 9500 Euclid Avenue, Cleveland OH, 44195, (216) 445-7841, (216) 445-5477 (fax), chiangd@ccf.org

Arthur J. McCullough, MD

Department of Gastroenterology and Hepatology, Digestive Disease Institute, Cleveland Clinic, A31, 9500 Euclid Avenue, Cleveland OH, 44195, (216) 444-2766, (216) 445-5477 (fax), mcculla@ccf.org

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Epidemiology of Alcoholic Liver Disease

Alcoholic liver disease (ALD) is a major health burden in the US. Approximately 18 million people abuse alcohol and 10 million people suffer from ALD[1–2]. ALD includes a spectrum of liver pathology from alcoholic fatty liver, alcoholic steatohepatitis (AH) to liver fibrosis and cirrhosis[3]. In the general population, the prevalence and mortality from alcoholic liver disease closely follows per capita ethanol consumption and increases as the per capita alcohol consumption increases[4]. ALD remains a major cause of liver failure and contributes to more than 20,000 deaths annually in the United States[2].

Spectrum of Alcoholic Liver Disease

Studies of the incidence and prevalence of different stages of ALD prior to the development of cirrhosis in the general population are difficult to conduct because patients with compensated liver disease usually do not seek medical attention[5]. Up to 90% of alcoholics have fatty liver, which usually resolves within 2 weeks if alcohol consumption is discontinued[6]. While patients with pure alcoholic fatty liver are mostly asymptomatic, they have a 10% risk of progressing to cirrhosis and an 18% risk of cirrhosis or fibrosis over a median time period of 10.5 years. Further, in those who drink more than 40 units of alcohol per week, the risk dramatically increases, with a 30% risk of cirrhosis and a 37% risk of

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cirrhosis or fibrosis[7–8]. Ten to thirty five percent of all alcoholics have changes on liver biopsy consistent with alcoholic hepatitis[8]. The amount of alcohol intake that puts an individual at risk for alcoholic hepatitis is unknown, but the majority of patients have a history of heavy alcohol use (more than 100 g/day) for two or more decades[9]. Once alcoholic hepatitis has developed, the risk of cirrhosis is increased compared with simple steatosis. In one study, over a five-year period, cirrhosis developed in 16 percent of patients with steatohepatitis and in 7 percent of patients with simple steatosis[10]. A subset of patients with ALD will develop severe AH, which often presents acutely against a background of chronic liver disease and has a substantially worse short-term prognosis[11]. The progression to cirrhosis is a leading cause of morbidity and mortality in ALD[2]. Hepatic decompensation is common among patients with alcoholic cirrhosis. The risk of complications including the development of ascites, variceal bleeding, or hepatic encephalopathy is about 25 percent after one year and 50 percent after five years[12]. Once hepatic decompensation develops, the expected five-year transplant-free survival rate is 60 percent for those who stop drinking alcohol and 30 percent for those who continue to drink alcohol[13]. However, only 10–15% of alcoholics develop cirrhosis. Although the amount and patterns of alcohol consumption are important, they do not fully account for the differences in cirrhosis incidence rates[3]. Several studies have been performed to investigate risk factors (gender, genetics, diet, type of alcohol, pattern of drinking, and HCV infection) in the progression of ALD[14]. Given the rising prevalence of obesity and metabolic syndrome, this review will focus on our current understanding of the potential impact of obesity and metabolic syndrome in the progression of ALD.

Obesity on the progression of ALD

The WHO and the National Center for Health Statistics define overweight as a body mass index (BMI) >25 and ≤ 29.9 and obesity as a BMI greater than 30 kg/m^2[15]. Alcohol and obesity synergistically increase the risk of liver injury as measured by elevated serum alanine aminotransferase and aspartate aminotransferase levels[16]. A study of 1604 alcoholic patients revealed that overweight (as determined by BMI ≥ 25 in women and ≥ 27 in men) is a risk factor for the progression of alcoholic liver disease[9]. Being overweight for at least 10 years is independently correlated with the presence of steatosis, acute alcoholic hepatitis, and cirrhosis. These results show that the presence of excess weight for at least 10 years is a risk factor for progression of ALD[9]. Another study of asymptomatic alcoholic patients revealed that higher body weight is a risk factor for more severe histological liver damage[17].

Whether the exacerbation of ALD in overweight patients is a result of additive injury from non-alcoholic steatohepatitis (NASH), which is a hepatic manifestation of metabolic syndrome; or the metabolic derangement in obesity exacerbates ethanol-induced liver injury remain a subject of further investigation. Ethanol feeding results in more pronounced hepatic steatosis and liver injury in genetically obese mice (*ob/ob*), compared with control lean wild type mice[18]. Further, ethanol feeding augments the impairment of hepatic sirtuin 1 (SIRT1)-AMP-activated kinase (AMPK) signaling in the *ob/ob* mice, which is associated with altered hepatic lipid metabolism pathways[18]. Emerging evidence also suggests that adipose tissue has a critical regulatory function in metabolism and immunity through adipose tissue-derived bioactive substances including TNFα, IL-6, monocyte/macrophage chemo-attractant

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protein 1 (MCP-1), and adipokines, which may regulate insulin resistance and tissue inflammation[19]. Further, chronic ethanol exposure results in inflammation in adipose tissue in mice[20] and alcohol intake can alter adipokines expression in adipose tissue and adipokines plasma levels[21]. The direct effects of alcohol on the metabolic and innate immune activity of adipose tissue likely contribute to ethanol-induced liver injury.

Obesity and metabolic syndrome on the mortality of ALD

Obesity, particularly abdominal obesity, is associated with insulin resistance on peripheral glucose and fatty acid utilization, which leads to type 2 diabetes mellitus[22]. Insulin resistance, the associated hyperinsulinemia and hyperglycemia, and adipokines may lead to increased risk for cardiovascular disease (CVD) due to vascular endothelial dysfunction, abnormal lipid profile, hypertension, and vascular inflammation[22]. The cooccurrence of metabolic risk factors for type 2 diabetes and CVD (abdominal obesity, hyperglycemia, dyslipidemia, and hypertension) suggest the existence of metabolic syndrome[23]. Obesity and metabolic syndrome are among the most important public health problems in the United States given the rising prevalence and comorbidities[24]. The prevalence of the metabolic syndrome, as defined by the 2001 ATP III criteria, was evaluated in the third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1994)[25]. The overall prevalence of metabolic syndrome is 22% in this population[25]. The prevalence of obesity and metabolic syndrome in ALD patients in the NHANES III cohort are 44.5% and 32.4% respectively (Table 1)[26]. Further, obesity and metabolic syndrome are associated with increased liver-related mortality in ALD patients (Table 1)[26]. Interestingly, there is no increased overall mortality risk with either obesity or metabolic syndrome in this cohort. However, type 2 diabetes and insulin resistance are both associated with increased overall mortality in ALD patients (Table 1)[26]. The findings from this large population-based study suggest a detrimental effect of concomitant obesity and components of metabolic syndrome in patients with ALD.

Data from two Scottish prospective cohorts also reveal that obesity and alcohol consumption are strongly associated with liver disease mortality in analyses adjusted for other confounders ($P=0.001$ and $P<0.0001$ respectively)[27]. Drinkers of 15 or more units per week have adjusted relative rates for liver disease mortality of 3.16 (95% confidence interval 1.28 to 7.8) for underweight/normal weight men, 7.01 (3.02 to 16.3) for overweight, and 18.9 (6.84 to 52.4) for obese men. The relative excess risk due to interaction between BMI and alcohol consumption is 5.58 (1.09 to 10.1) with a synergy index of 2.89 (1.29 to 6.47), suggesting obesity and alcohol consumption synergistically increase mortality in this population[27].

Obesity and alcohol on hepatic carcinogenesis

Hepatocellular carcinoma (HCC) is one of the complications of ALD and cirrhosis. Several epidemiologic studies have suggested that both alcoholic and nonalcoholic fatty liver disease are associated with increased risk of HCC[28–30]. Given the enhanced liver injury and fibrosis from concomitant alcohol consumption and obesity[16], it is plausible that alcohol and obesity may enhance hepatic carcinogenesis. In a population-based study of 23,712 Taiwanese

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residents from January 1, 1991 to December 31, 2004, there was an association betweem alcohol use (defined as those who consume alcohol at least 4 days per week for at least a year) and obesity (BMI ≥ 30) with the risk of HCC incidence in an unadjusted analysis (hazard ratio = 7.19, 95% confidence interval: 3.69, 14.00; $P < 0.01$) and a multivariable-adjusted analyses (hazard ratio = 3.82, 95% confidence interval: 1.94, 7.52; $P < 0.01$)[31]. Further, the data suggests a multiplicative interaction between alcohol use and obesity and that obesity and alcohol synergistically increase the risk of HCC incidence[31]. In addition, alcohol consumption is associated with increased risk of HCC in a cohort of patients with NASH cirrhosis from a tertiary referral center in the US[32].

Diabetes on the progression of ALD

Concomitant diabetes mellitus in alcoholics includes a wide spectrum of etiologies including insulin insufficiency due to alcoholic pancreatitis[33], hyperinsulinemia and insulin resistance associated with liver cirrhosis[34] and type 2 diabetes mellitus associated with the metabolic syndrome. The presence of diabetes is a significant risk factor for mortality in a Japanese cohort of alcoholic patients, in both cirrhosis and noncirrhosis groups[35]. Further, diabetes is an independent risk factor for hepatic carcinogenesis in patients with alcoholic cirrhosis[36]. Autonomic nerve dysfunction occurs in both alcoholics and diabetics. It is generally reversible in alcoholics if they abstain[37], but is irreversible in diabetics[38].

Clinical management and future direction

The corner stone of clinical management of ALD is alcohol cessation[14]. Since obesity and metabolic syndrome may exacerbate progression of ALD, it is critical for physicians to counsel patients with concomitant metabolic syndrome on their increased risk of ALD progression. Treatment options for patients with concomitant obesity, metabolic syndrome and advanced ALD remain limited. Therefore, detection of early stage disease and prevention of progression are critical in addressing this issue. Both obesity and alcohol use are modifiable risk factors, life style interventions should be undertaken to reduce the risks of disease progression. Early referral to alcohol rehabilitation program should be considered in these patients prior to the development of cirrhosis or severe AH to avoid disease progression. Further, treatment of components of metabolic syndrome may improve the outcomes in these patients. Prospective studies will be instrumental to demonstrate the clinical efficacy of such intervention. Further understanding of the mechanistic link of synergism among alcohol, obesity and metabolic syndrome in the progression of ALD may provide novel targets of intervention in this high risk population.

Conclusion

The intersection of the obesity epidemic and ALD poses a challenging health care issue with significant morbidity and mortality. Obesity and metabolic syndrome exacerbate progression of ALD, increase mortality and HCC incidence. Further, alcohol may modulate the metabolic and innate immune activity of adipose tissue and thus contribute to ethanol-induced liver injury. Recognition of these increased risks is crucial in patient counseling and disease management. Detection of early stage of liver injury in asymptomatic patients may

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offer the opportunity to prevent disease progression. Life style modifications including alcohol cessation and weight loss should be pursued along with the management of components of metabolic syndrome.

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Reference

1. Mandayam S, Jamal MM, Morgan TR. Epidemiology of alcoholic liver disease. Seminars in liver disease. 8 2004;24(3):217–232. [PubMed: 15349801]
2. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 11 2012;143(5):1179–1187 e1171–1173. [PubMed: 22885331]
3. Mann RE, Smart RG, Govoni R. The epidemiology of alcoholic liver disease. Alcohol research & health : the journal of the National Institute on Alcohol Abuse and Alcoholism. 2003;27(3):209–219. [PubMed: 15535449]
4. Corrao G, Ferrari P, Zambon A, Torchio P. Are the recent trends in liver cirrhosis mortality affected by the changes in alcohol consumption? Analysis of latency period in European countries. Journal of studies on alcohol. 9 1997;58(5):486–494. [PubMed: 9273913]
5. Kim WR, Brown RS, Jr., Terrault NA, El-Serag H. Burden of liver disease in the United States: summary of a workshop. Hepatology (Baltimore, Md. 7 2002;36(1):227–242.
6. Diehl AM. Alcoholic liver disease: natural history. Liver transplantation and surgery : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 5 1997;3(3):206–211.
7. Sorensen TI, Orholm M, Bentsen KD, Hoybye G, Eghoje K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. Lancet. 8 4 1984;2(8397):241–244. [PubMed: 6146805]
8. Teli MR, Day CP, Burt AD, Bennett MK, James OF. Determinants of progression to cirrhosis or fibrosis in pure alcoholic fatty liver. Lancet. 10 14 1995;346(8981):987–990. [PubMed: 7475591]
9. Naveau S, Giraud V, Borotto E, Aubert A, Capron F, Chaput JC. Excess weight risk factor for alcoholic liver disease. Hepatology (Baltimore, Md. 1 1997;25(1):108–111.
10. Deleuran T, Gronbaek H, Vilstrup H, Jepsen P. Cirrhosis and mortality risks of biopsy-verified alcoholic pure steatosis and steatohepatitis: a nationwide registry based study. Alimentary pharmacology & therapeutics. 6 2012;35(11):1336–1342. [PubMed: 22490057]
11. Orrego H, Blake JE, Blendis LM, Medline A. Prognosis of alcoholic cirrhosis in the presence and absence of alcoholic hepatitis. Gastroenterology. 1 1987;92(1):208–214. [PubMed: 3781189]
12. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology (Baltimore, Md. 5 2010;51(5):1675–1682.
13. Morgan MY. The prognosis and outcome of alcoholic liver disease. Alcohol Alcohol Suppl. 1994;2:335–343. [PubMed: 8974353]
14. O'Shea RS, Dasarathy S, McCullough AJ, Practice Guideline Committee of the American Association for the Study of Liver D, Practice Parameters Committee of the American College of G. Alcoholic liver disease. Hepatology (Baltimore, Md. 1 2010;51(1):307–328.
15. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obesity research. 9 1998;6 Suppl 2:51S–209S. [PubMed: 9813653]
16. Loomba R, Bettencourt R, Barrett-Connor E. Synergistic association between alcohol intake and body mass index with serum alanine and aspartate aminotransferase levels in older adults: the Rancho Bernardo Study. Alimentary pharmacology & therapeutics. 12 1 2009;30(11–12):1137–1149. [PubMed: 19737152]

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17. Iturriaga H, Bunout D, Hirsch S, Ugarte G. Overweight as a risk factor or a predictive sign of histological liver damage in alcoholics. The American journal of clinical nutrition. 2 1988;47(2): 235–238. [PubMed: 3341254]
18. Everitt H, Hu M, Ajmo JM, et al. Ethanol administration exacerbates the abnormalities in hepatic lipid oxidation in genetically obese mice. American journal of physiology. 1 1 2013;304(1):G38–47. [PubMed: 23139221]
19. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nature reviews. Immunology. 10 2006;6(10):772–783.
20. Sebastian BM, Roychowdhury S, Tang H, et al. Identification of a cytochrome P4502E1/Bid/C1q-dependent axis mediating inflammation in adipose tissue after chronic ethanol feeding to mice. The Journal of biological chemistry. 10 14 2011;286(41):35989–35997. [PubMed: 21856753]
21. Pravdova E, Fickova M. Alcohol intake modulates hormonal activity of adipose tissue. Endocrine regulations. 9 2006;40(3):91–104. [PubMed: 17100551]
22. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 12 1988;37(12):1595–1607. [PubMed: 3056758]
23. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 4 16–22 2005;365(9468): 1415–1428. [PubMed: 15836891]
24. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA : the journal of the American Medical Association. 10 9 2002;288(14):1728–1732. [PubMed: 12365956]
25. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA : the journal of the American Medical Association. 1 16 2002;287(3):356–359. [PubMed: 11790215]
26. Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut. 10 2010;59(10):1410–1415. [PubMed: 20660697]
27. Hart CL, Morrison DS, Batty GD, Mitchell RJ, Davey Smith G. Effect of body mass index and alcohol consumption on liver disease: analysis of data from two prospective cohort studies. Bmj. 2010;340:c1240. [PubMed: 20223873]
28. Franceschi S, Montella M, Polesel J, et al. Hepatitis viruses, alcohol, and tobacco in the etiology of hepatocellular carcinoma in Italy. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 4 2006;15(4):683–689.
29. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology (Baltimore, Md. 11 2002;36(5): 1206–1213.
30. Marrero JA, Fontana RJ, Su GL, Conjeevaram HS, Emick DM, Lok AS. NAFLD may be a common underlying liver disease in patients with hepatocellular carcinoma in the United States. Hepatology (Baltimore, Md. 12 2002;36(6):1349–1354.
31. Loomba R, Yang HI, Su J, et al. Synergism between obesity and alcohol in increasing the risk of hepatocellular carcinoma: a prospective cohort study. American journal of epidemiology. 2 15 2013;177(4):333–342. [PubMed: 23355498]
32. Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. Hepatology (Baltimore, Md. 6 2010;51(6):1972–1978.
33. Bank S Chronic pancreatitis: clinical features and medical management. The American journal of gastroenterology. 3 1986;81(3):153–167. [PubMed: 3513542]
34. Iversen J, Vilstrup H, Tygstrup N. Kinetics of glucose metabolism in relation to insulin concentrations in patients with alcoholic cirrhosis and in healthy persons. Gastroenterology. 11 1984;87(5):1138–1143. [PubMed: 6383936]
35. Yokoyama A, Matsushita S, Ishii H, Takagi T, Maruyama K, Tsuchiya M. The impact of diabetes mellitus on the prognosis of alcoholics. Alcohol and alcoholism. 3 1994;29(2):181–186. [PubMed: 8080599]

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36. Torisu Y, Ikeda K, Kobayashi M, et al. Diabetes mellitus increases the risk of hepatocarcinogenesis in patients with alcoholic cirrhosis: A preliminary report. Hepatology research : the official journal of the Japan Society of Hepatology. 7 2007;37(7):517–523. [PubMed: 17539994]

37. Yokoyama A, Takagi T, Ishii H, et al. Impaired autonomic nervous system in alcoholics assessed by heart rate variation. Alcoholism, clinical and experimental research. 10 1991;15(5):761–765.

38. Ewing DJ, Campbell IW, Clarke BF. The natural history of diabetic autonomic neuropathy. The Quarterly journal of medicine. Winter 1980;49(193):95–108. [PubMed: 7433630]

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Synopsis

Alcoholic liver disease (ALD) remains a major cause of chronic liver diseases and liver failure. Population-based prospective studies and patient cohort studies have demonstrated that obesity and the metabolic syndrome exacerbate progression of ALD, increase HCC incidence and mortality. Emerging evidence also suggests a synergism between alcohol and obesity in mortality and HCC incidence. Recognition of these increased risks and detection of early-stage liver disease may offer the opportunity to address these modifiable risk factors and prevent disease progression in these patients.

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Key points

- Obesity and metabolic syndrome are common in ALD patients and increase the risk of liver-related mortality.
- Obesity is an independent risk factor for steatosis, acute alcoholic hepatitis and cirrhosis in ALD.
- Obesity and alcohol synergistically enhance hepatic carcinogenesis.
- Diabetes is an independent risk factor for hepatic carcinogenesis in alcoholics and increases mortality in both cirrhosis and pre-cirrhosis patients.

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Table 1.

Prevalence and adjusted hazard ratio for overall and liver-related mortality of obesity and metabolic syndrome in ALD patients in NHANES III

	Prevalence (%)	Overall mortality (aHRs and 95% CIs)	Liver-related mortality (aHRs and 95% CIs)
Obesity	44.56±5.9	1.58 (0.57 to 4.40)	16.22 * (1.91 to 137.68)
Metabolic syndrome	32.46±5.2	2.37 (0.50 to 11.18)	2.06 * (1.21 to 3.31)
Type 2 diabetes	7.46±2.4	3.00 * (1.06 to 8.54)	3.60 (0.96 to 13.52)
Insulin resistance	33.76±5.1	3.21 * (1.56 to 6.58)	2.43 (0.28 to 21.38)
Hypercholesterolemia	64.56±6.0	0.79 (0.25 to 2.53)	0.04 (0.01 to 0.24)
Hypertension	36.56±5.7	1.76 (0.46 to 6.70)	1.77 (0.40 to 7.72)

* p value for the adjusted hazard ratio (aHR) is ≤0.05.

Data from Stepanova M, Rafiq N, Younossi ZM. Components of metabolic syndrome are independent predictors of mortality in patients with chronic liver disease: a population-based study. Gut. Oct 2010;59(10):1410–1415.