Nonalcoholic fatty liver disease and alcoholic liver disease: metabolic diseases with systemic manifestations

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Abstract: The progression of liver disease is portrayed by several common, overarching signs and symptoms. Classically, these include findings such as spider angiomata, jaundice, palmar erythema, and as cirrhosis decompensates, ascites, variceal hemorrhage (VH), hepatic encephalopathy (HE), and hepatocellular carcinoma (HCC). Aside from these universal hallmarks among cirrhotics, patients with nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) harbor their own distinct systemic associations and manifestations. NAFLD is tightly linked to metabolic syndrome, which appears to be a driving force for a multitude of comorbidities, such as insulin resistance, cardiovascular disease, chronic kidney disease (CKD), obstructive sleep apnea (OSA), as well as increased malignancy risk. ALD also maintains a variety of comorbidities congruent with systemic effects of chronic alcohol use. These findings are highlighted by cardiovascular conditions, neuronal damage, myopathy, nutritional deficiencies, chronic pancreatitis, in addition to increased malignancy risk. While a general, guideline-driven management for all cirrhotic patients remains imperative for minimizing risk of complications, a tailored treatment strategy is useful for patients with NAFLD and ALD who entertain their own constellation of unique systemic manifestations.

Keywords: Nonalcoholic fatty liver disease (NAFLD); alcoholic liver disease (ALD); systemic

Introduction

The progression of liver disease and cirrhosis have a multitude of extrahepatic manifestations. These findings include spider angiomata, Terry's nails, palmar erythema, hepatosplenomegaly, jaundice, scleral icterus, and caput medusa (see *Table 1*) (1,2). As patients with this disease continue to deteriorate, signs of decompensation arise as defined by the presence of ascites, spontaneous bacterial peritonitis (SBP), variceal hemorrhage (VH), and hepatic encephalopathy (HE). These clinical clues materialize along a similar trajectory towards a common endpoint of end stage liver disease, which also harbors increased risk for hepatocellular carcinoma (HCC) (3).

Both nonalcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) represent two common etiologies of liver disease and cirrhosis. Although both conditions ultimately share common endpoints of decompensated and end stage liver disease as addressed

Table 1 Common systemic findings ubiquitously seen among progression of cirrhosis of all etiologies

Constitutional symptoms

  Fatigue/weakness

  Obesity

  Anorexia

  Weight loss

  Sarcopenia

Neurologic

  Asterixis

  HE

Cardiovascular

  Decreased effective intra-arterial pressure

  Cirrhotic cardiomyopathy

  Peripheral edema

  Clubbing and hypertrophic osteoarthropathy

Sequela of portal hypertension

  Hepatosplenomegaly

  Ascites

  Caput medusa

  Esophagogastric varices

  Internal hemorrhoids

  Mesenteric vein thrombosis

Head and neck

  Fetor hepaticus

Dermatologic

  Jaundice and/or scleral icterus

  Spider angiomata

  Telangiectasia

  Palmar erythema

  Terry's nails

  Muehrcke's nails

  Decreased body hair

Serologic testing

  Hyponatremia

  Hypoalbuminemia

  Elevation of liver chemistries (AST, ALT, alkaline phosphatase, bilirubin)

Table 1 (*continued*)

Table 1 (*continued*)

Hematologic

  Deficiency of procoagulant (protein C & S) and anticoagulant factors (factors II, V, VII, VIII, IX, X, XII)

  Thrombocytopenia

  Anemia

  Leukopenia

  Hyperglobulinemia

Reproductive/genitourinary

  Testicular atrophy

  Gynecomastia

Increased malignancy risk

  HCC

HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

above, NAFLD and ALD accommodate unique features both in their presenting diagnoses and as well as throughout the development of the disease course. While initially triggered by metabolic disturbances, several distinct systemic manifestations of both NAFLD and ALD have become hallmarks of the diagnosis and management of these conditions.

NAFLD

Pathogenesis and association with metabolic syndrome

The interwoven affinity of NAFLD with metabolic syndrome has firmly been established. Peripheral insulin resistance, obesity, dyslipidemia, and altered lipid metabolism synergistically catalyze the accumulation of hepatic triglycerides, which ultimately generates the lipotoxicity and insistent inflammation necessary for the progression towards nonalcoholic steatohepatitis (NASH) and cirrhosis.

One large meta-analysis determined among a pooled population of 81,411 patients across eight studies that patients diagnosed with NAFLD harbored a significantly elevated risk for development of metabolic syndrome within a median 4.5 year follow up (4). This relative risk was calculated to be 1.80 (95% CI: 1.89–2.07) based upon alanine aminotransferase levels, 1.98 (95% CI: 1.89–2.07) based upon GGT, and 3.22 (95% CI: 3.05–3.41) when diagnosed via ultrasonography. Another recent systematic

review and meta-analysis established that obesity portends worse prognosis among NAFLD patients, however no direct correlation was observed among degree of obesity with severity of NAFLD (4).

Perhaps the most potent association, however, is that of type 2 diabetes mellitus (T2DM) with NAFLD. By itself, T2DM carries its own slew of comorbidities and elevated cardiovascular risk. One recent meta-analysis calculated a HR 2.22 (95% CI: 1.84–2.60) with respect to NALFD patients' risk of developing T2DM (5). Hepatic steatosis and ensuing lipotoxicity produce a state of hyperglycemia, dyslipidemia, and a proinflammatory environment that catalyzes the development of insulin resistance, atherosclerosis, and pancreatic beta-cell dysfunction and apoptosis (6). One recent meta-analysis from China, revealed an accelerated increase in NAFLD over a 10-year period, possibly attributing this rise to increased prevalence of metabolic syndrome and T2DM (7).

Overall, there is an intimate connection of NAFLD and metabolic syndrome, with particular respect to T2DM, which catalyzes the continuous insult of hepatic steatosis, lipotoxicity, fibrosis, and progression towards NASH.

Adipokines

In addition to the presence of metabolic syndrome and obesity, the increasing role of adipokines has specifically been shown to fuel this pathogenesis and other findings seen in NAFLD (8). The mere presence of triglycerides and release of free fatty acids contributes to dyslipidemia. However, the endocrine-mediated release of other hormones from adipose tissue have been shown to be increased, such as resistin, RBP4 (retinol-binding protein 4), leptin, and 11HSD-1, in addition to a decrease in adiponectin, which all perpetuate the function of insulin resistance (9).

Furthermore, elevated release of the adipokines PAI-1 (10) and angiotensinogen (11) place NAFLD patients at an increased propensity for thrombosis and atherosclerosis, respectively. Adipokines also fuel a proinflammatory state via the secretion of IL-6, TNF-α, and CCL2, which not only stimulates a local injury and fibrotic response, but also a number of systemic conditions (12,13).

The multi-faceted inputs from adipokines clearly augments NAFLD pathogenesis in addition to the development of common systemic manifestations seen in this disease.

Cardiovascular disease

A bevy of preliminary data had originally suggested this association, however more robust evidence has firmly planted the rooting of atherosclerosis with NAFLD. Two original systematic reviews were able to confirm these findings based upon increased carotid intima media thickness, endothelial dysfunction, arterial stiffness, and coronary calcification among NAFLD subjects (14,15). Similar findings among subsequent systematic reviews/ meta-analyses were replicated across a wide range of patient populations (16-22).

There has been an overall trend towards increased risk of CV events among NAFLD patients, such as acute coronary syndrome (ACS), cerebrovascular accident (CVA), or peripheral artery disease (PAD), however there were a minor discordance of the statistical significance of these findings among individual observational studies (23-27). Notwithstanding these differences, more robust evidence has been performed across three systematic review/meta-analyses that have settled this discussion. One Chinese meta-analysis reported an increased risk of prevalent (OR 1.81, 95% CI: 1.23–2.66) and incident (HR 1.37, 95% CI: 1.10–1.72) CV events, however no overall difference in mortality (19). Another Italian meta-analysis revealed an increased risk of CV events with OR 1.64 (95% CI: 1.26–2.13) (28). The risk of CV events appeared to increase with the severity of NAFLD with OR 2.58 (95% CI: 1.78–3.75) based upon imaging and histologic parameters. A third systematic review and meta-analysis found an elevated risk of CV events (RR 1.77, 95% CI: 1.26–2.48) and CV mortality (RR 1.46, 95% CI: 1.31–1.64) among NAFLD patients as compared to controls. While most of this data was performed across observational studies where causality cannot be surmised, the risk of CV events among NAFLD patients seems to be verified across multiple, large-scale systematic reviews and meta-analyses.

Meanwhile, further data illuminate the role of T2DM in this process by analyzing the synergistic increase in CV risk in the presence of both NAFLD and T2DM (29). This concept introduces a limitation we called attention to in a prior review (30). That is, it is difficult to delineate the CV risk specifically from NAFLD apart from its comorbidities based upon current studies, in particular, metabolic syndrome, obesity, insulin resistance, and T2DM. There appears to be a large discrepancy on the prevalence of T2DM between NAFLD and control subjects in a number of these studies. And even among studies exclusively

performed in nondiabetic patients, there is a great disparity of insulin resistance observed between NAFLD and control patients. Overall, there is an increase in CV diseases among NAFLD patients, however the pathogenesis and causality of these disease processes remain in question given the substantial confounding influence of metabolic syndrome and T2DM observed in these studies.

Venous thromboembolism

Cirrhotic coagulopathy is a complex topic which actually portends increased overall risk towards both bleeding and thrombosis owning to the loss of procoagulants and anticoagulants, respectively. However, NAFLD provides a unique perspective further complicating this coagulopathic snafu. Multiple studies have identified the presence of NAFLD as a risk factor for thrombosis and unprovoked veno-thromboembolism (VTE) (31-33). While there are currently no prospective or randomized trials to date, one Italian, cross sectional study was able to establish interesting findings towards coagulopathy and propensity towards procoagulation (34). A total of 113 patients, who had previously had liver biopsy, underwent further testing of thrombin, coagulation factors, and protein C activity. One of the markers for procoagulation and thrombosis formation was defined by the endogenous-thrombin-potential (ETP), which was statistically increased along the NAFLD spectrum among control subjects, hepatic steatosis, and cirrhosis with values of 0.57, 0.72, and 0.80, respectively (P<0.001). Among this cohort, there was no significant difference in ETP of patients with NASH cirrhosis as compared to other etiologies of cirrhosis, such as alcoholic or viral. Perhaps the presence of cirrhosis or obesity represent confounding factors in this study, however it appears that there is increased predilection for VTE as the severity of NALFD progresses.

Chronic kidney disease (CKD)

Many cohort studies have shown an association between CKD and NAFLD. This may serve as an unsurprising finding given the large amount of concomitant metabolic syndrome, obesity, diabetes mellitus, and atherosclerosis in this patient population. Perhaps the most robust data with respect to this topic lies within two systematic reviews/meta-analyses.

In the first by Musso et al. 2014, it was demonstrated that patients with NAFLD had both an elevated prevalent

(OR 2.12, 95% CI: 1.69–2.66) and incident (HR 1.79, 95% CI: 1.65–1.95) CKD risk (35). The presence of NASH was found to additionally increase the prevalence of CKD (OR 2.53, 95% CI: 1.58–4.05). No statistically significant heterogeneity was present in this analysis. However, major differences in the number of biopsy-proven NAFLD patients, possibility of selection bias, and utilization of ultrasound and/or liver chemistries for the selection of controls among some studies may have inappropriately misclassified patients and limited the external validity of this meta-analysis.

In the only other meta-analysis to date, Mantovani et al. 2018 also illustrated the close link of NAFLD and CKD (36). Patients with NAFLD were found to have HR 1.37 (95% CI: 1.20–1.53) for CKD development as compared to controls. This risk appears to increase with worsening NAFLD steatosis and fibrosis. However, it is important to note that most of the studies in both of these meta-analyses were observational, and thus, the strong association of NAFLD and CKD development should not be mistaken for causality of these two disease processes.

Polycystic ovarian syndrome (PCOS)

There has been mounting evidence in the recent literature anchoring the association of PCOS with NAFLD. A multitude of studies among recent years have characterized this association, which has been further validated through three major systematic reviews and/or meta-analyses. The first study was a systematic review in 2011 that reported the current literature on the topic (37). The interplay among PCOS, NAFLD, insulin resistance, hyperandrogenism, and obesity was clearly present. However, it was noted that most studies observed a proportionate rise in prevalence of PCOS and NAFLD with the degree of insulin resistance and adipose tissue. A second systematic review and meta-analysis performed across 17 studies and included 2,700 PCOS patients with matched controls (38). PCOS patients were found to have higher prevalence of NAFLD as compared to controls with OR 2.54 (95% CI: 2.19–2.95). These studies revealed an overall association with elevated serum androgen levels, obesity, and insulin resistance among patients with both PCOS and NAFLD. Finally, another meta-analysis solidified this association, citing an OR 2.25 (95% CI: 1.95–2.60) among patients with PCOS and the risk of NAFLD (39). This meta-analysis also found an increased association of PCOS patients with hyperandrogenism with development of NAFLD.

Interestingly, PCOS patients without hyperandrogenism were not found to have increased risk of NAFLD (OR 1.46, 95% CI: 0.55–3.87), suggesting elevated serum androgen levels are integral in this pathogenesis. Overall, current literature demonstrates a robust relationship between the presence of NAFLD and PCOS, and this link appears to be heightened in the setting of hyperandrogenism, obesity, and insulin resistance.

Obstructive sleep apnea (OSA)

Undoubtedly intertwined to its close connection to metabolic syndrome, NAFLD patients have been demonstrated to have increased frequency of OSA. This association has been validated through its first systematic review and meta-analysis including 2,183 patients, which revealed increased risk of OSA not only among the presence, but also the severity of NAFLD (40). These included increased OSA risk among NAFLD patients with OR 2.01 (95% CI: 1.36–2.97), 2.99 (95% CI: 1.79–4.99), 2.36 (95% CI: 1.46–3.82), and 2.60 (95% CI: 1.88–3.61) when diagnosed by histology, imaging, AST, and ALT elevation, respectively. Another recent systematic review and meta-analysis illustrated that OSA was tightly linked to degree of hepatic steatosis, lobular inflammation, ballooning degeneration, and fibrosis among biopsy-proven NAFLD patients (41). This evidence not only suggests that OSA is a common manifestation seen among NAFLD patients, but also that this association proportionately strengthens along the continuum of NAFLD severity.

Osteopenia

Sedentary lifestyle more commonly observed among NAFLD patients (42) may lead to increased osteoporosis (43). However, several other aberrancies in bone metabolism among NAFLD subjects have been noted.

Osteocalcin is a protein produced by osteoblasts in order to promote bone matrix formation (44). Osteocalcin has been shown to be decreased in a severity-dependent relationship with NAFLD (45,46). Osteoprotegerin is a glycoprotein that inhibits osteoclast activity and promotes osteoclast apoptosis via a RANKL (receptor activator of nuclear factor kappa-B ligand) mediated process (47). It has been established that osteoprotegerin is decreased in NAFLD (48). Osteopontin modulates osteoblast and osteoclast activity in order to inhibit mineral crystal growth, enhance bone resorption, and decreased bone deposition (49). Osteopontin has been found to be increased among NAFLD subjects (50).

Overall, the presence of sedentary lifestyle and aberrancies in multiple bone hormones construct an ideal foundation for osteoporosis among NAFLD patients.

However, these findings have not been corroborated in future studies on this topic. In a study performed by Upala et al. (51), there was no significant difference calculated between NAFLD and bone mineral density as compared to controls. Body mass index (BMI) was found to be the variable that most strongly correlated with variations in bone mineral density.

Another large systematic review and meta-analysis revealed an increase in osteoporotic fractures among NAFLD patients, however this was not associated with low bone mineral density itself (52).

While several confounding factors exist among this population with a high prevalence of obesity and sedentary lifestyle, more studies isolating the differences between bone mineral density, osteoporosis, and NAFLD are required to further delineate this relationship.

Nutritional considerations

NAFLD has not had a classical association with nutritional deficiencies per se, however have been more linked with obesity, diabetes, and excessive caloric intake.

One large systematic review and meta-analysis revealed that hypercaloric fructose and glucose diets were found to increase hepatic triglyceride content and raise liver chemistries (53). However, these diets appear to be confounded by overall excessive caloric intake, more so than by the intake of sugars themselves, which potentially skews the external validity of this study. Another large systematic review and meta-analysis conducted in 1,361 NAFLD cases with matched controls unveiled a strong link of NAFLD with sugar sweetened beverage consumption (54). Finally, another systematic review and meta-analysis illustrated that while no reduction in liver chemistries were observed among patients with NAFLD, a low carbohydrate diet decreased intrahepatic lipid content by 11.53% (95% CI: −18.10, −4.96) (55). Furthermore, a decrease in copper bioavailability has been demonstrated to contribute to atherosclerosis among NAFLD patients (56).

Overall, there is fairly robust evidence to validate the association of excess dietary sugar and carbohydrate intake on NAFLD development, which is particularly compounded in the presence of metabolic syndrome, obesity, and T2DM.

Increased malignancy risk

Aside from the overall increased incidence of HCC observed with progression of cirrhosis, two major systematic reviews and meta-analyses have shed light upon increased malignancy risk observed among NAFLD patients. One study analyzed seven case-control studies comparing a total of 9,102 patients with cholangiocarcinoma against 129,111 controls (57). NAFLD was identified as a risk factor for the development of both intrahepatic (OR 2.22, 95% CI: 1.52–3.24) and extrahepatic cholangiocarcinoma (OR 1.55, 95% CI: 1.03–2.33), respectively. However, the slightly increased predilection towards intrahepatic cholangiocarcinoma may suggests a similar pathogenic mechanism with HCC. Another major analysis performed across 11 observational studies concluded that NAFLD was associated with a significantly increased risk of prevalent and incident colorectal adenomas and colorectal cancer (58). This increased risk was found to be independent of age, gender, smoking history, BMI, diabetes, or metabolic syndrome. These two major systematic reviews and meta-analyses illuminate the association of NAFLD and increased malignancy risk, however, these analyses were performed primarily across observational studies from which causality cannot be inferred. Additionally, there has also been a documented association of NAFLD with HCC, however this risk is particularly more prevalent among patients with cirrhosis (59). There appears to be an overall link between obesity and cancer, perhaps through the underlying proinflammatory presence (60,61). However while revisiting the mounting evidence of adipokines, a recent study has demonstrated a strong link between adiponectin and leptin and the development of obesity-related cancers (62). Although this remains a topic still in the dawn of formation, there persists a strong impetus for malignancy among NAFLD patients from a variety of perspectives.

Other

NAFLD patients have also been found to have an increased predilection for the development of other medical conditions, including psoriasis, irritable bowel syndrome (IBS), asthma, and depression. Interestingly, one study published increased hepatic fibrosis among patients with psoriasis versus NAFLD patients who did not have psoriasis (63). This mechanism still remains relatively unknown. However, this association was also validated in a meta-analysis where patients with psoriasis had an increased risk of developing NAFLD as compared to non-psoriatic controls (OR 2.15, 95% CI: 1.57–2.94) (64). The link between IBS (65) and asthma (66) among NAFLD patients has also been suggested, however there in an overall lack of large, well-powered data to support this link across all patient populations. Alternative data also proposes an increased incidence of depression among NAFLD patients, particularly as compared to alternative forms of liver disease such as hepatitis B (67).

ALD

Pathogenesis

The effect of ethanol-medicated hepatocellular damage is relatively unambiguous. This direct cellular injury lays the foundation for interminable inflammation, cell death, and fibrosis that ultimately results in cirrhosis and decompensated ALD. However, these effects synergize with alcohol-induced gut barrier dysfunction and ensuing elevation in gut-derived bacterial translocation into the portal circulation (68). In particular, the bacterial endotoxin lipopolysaccharide (LPS) goes on to activate Toll-like receptors (TLR) on hepatocytes and Kupffer cells in order to generate a vigorous release of proinflammatory cytokines (69,70). In tandem with the direct toxicity of ethanol itself, it is this production of proinflammatory mediators, formation of reactive oxidative species (ROS), and subsequent cellular injury that not only progress ALD pathogenesis, but also incite many of the systemic manifestations so closely tied to this disease process (71).

Within the hepatocyte, ethanol is primarily metabolized to acetaldehyde via alcohol dehydrogenase (ADH). However, when this pathway is overwhelmed, increasingly more amounts of ethanol are digested by the microsomal ethanol oxidizing system (MEOS) in the endoplasmic reticulum (72). Utilization of the MEOS has an increased propensity for the formation of not only acetaldehyde, but also other toxic byproducts, such as ROS and protein adducts. Once ethanol is metabolized, acetaldehyde can then go on to be catalyzed by acetaldehyde dehydrogenase (ALDH), thus forming acetate. However, the amount and chronicity of ethanol ingested dictate the overall kinetics and enzymes employed, which directly correlate to the amount of ethanol, acetaldehyde, ROS, and protein adducts that mediate the primary toxicity emanating from this pathway.

Acid-base disorders

Ingestion of alcohol has the ability to create a state of alcoholic ketoacidosis (73). In addition to ketoacidosis, three other primary mechanisms seen in advancing ALD: hypoalbuminemia which precipitates a metabolic alkalosis, an aberrant Cori cycle which causes a buildup of lactic acid, and hyperventilation (74). Hyperventilation can be from a number of driving forces, such as central activation of estrogen receptors, HE, intrapulmonary pathology, or simply from diaphragm elevation in the setting of ascites. All of these factors influencing an alkalotic or acidotic milieu are generally kept in balance among stable cirrhotic patients. However, insults such as critical illness or decompensating liver failure can alter this balance creating unique acid-base disturbances depending on the inciting pathology.

Peripheral neuropathies and CNS pathology

Chronic effects of alcohol use can lead to a multitude of systemic effects. There is a direct effect of ethanol and its byproducts, which alters lipid function, generates ROS, increased mitochondrial damage, and ultimately leads to neuronal cell injury or death (75). Furthermore, ethanol is able to alter intracellular neuronal communications, which normally foster cell growth and differentiation. These direct effects of ethanol commonly manifest as cerebellar ataxia and alcoholic neuropathy, either in the central nervous system including brain atrophy (76), or peripheral neuropathy. Peripheral neuropathy typical presents in a classic "stocking-glove" pattern with early signs of paresthesias. As disease progresses under the influence of chronic alcohol use, proprioceptive impairments occur after deep tendon reflexes are lost, which ultimately may manifest as muscle weakness and atrophy once motor fibers are damaged (77). This axonal neuron damage oftentimes occurs in tandem with nutritional deficiencies, commonly folate and vitamin B12 (78). Similarly, nutritional deficiencies can also precipitate CNS findings, most notably from thiamine deficiency as seen in Wernicke-Korsakoff encephalopathy. This condition typically presents acutely with gait ataxia, cognitive changes, with or without nystagmus, and even coma in severe circumstances (75). These findings generally improve after administration of supplemental thiamine. Lastly, the progression of worsening liver disease due to chronic alcohol use often leads to a buildup of ammonia and manganese, which can promote neurotoxicity due to increased oxidative stress and changes in cerebral blood flow (79). Overall, the consequences of liver disease due to chronic alcohol abuse can lead to central and peripheral neuropathies secondary to both direct toxic effects and vitamin deficiencies.

Cardiovascular disease

Patients with ALD invariably develop concomitant cardiac conditions. The link between alcohol and hypertension has been well documented. A recent systematic review and meta-analysis has shown that there is a dose-dependent relationship with alcohol reduction on blood pressure improvement (80).

Alcohol also has a profound association with the development of cardiac arrhythmias, most notably atrial fibrillation. Four major systematic reviews and meta-analyses have been performed highlighting this link. In the first study, it was shown that alcohol exerted a dose-dependent relationship that elevated risk of atrial fibrillation with increasing doses of alcohol (81). A second meta-analysis corroborated these dose-dependent effects of alcohol on atrial fibrillation (82). A third study has reported a OR of 1.51 (95% CI: 1.31–1.74) among alcohol use and the association with atrial fibrillation (83). Lastly, a recent systematic review and meta-analysis stratified alcohol use to low (up to one standard drink per day), moderate (1–2 standard drinks per day), and high. This analysis demonstrated no association with atrial fibrillation in the low alcohol intake group with HR 0.95 (95% CI: 0.85–1.06), elevated risk of atrial fibrillation in the male, moderate alcohol intake group with HR 1.26 (95% CI: 1.04–1.54) but not the females, and finally an overall association of high alcohol intake and incident atrial fibrillation with HR 1.34 (95% CI: 1.20–1.49) (84). Clearly, there appears to be a direct relationship to the amount of alcohol ingested and the link to atrial fibrillation.

While some conflicting data exist regarding potential beneficial effects of light-to-moderate alcohol consumption, another cardiac manifestation commonly seen among patients with ALD is dilated cardiomyopathy. These cardiac findings generally present as a dilated left ventricle, increased left ventricular mass, with normal or reduced systolic dysfunction (85). These cardiac manifestations are not to be confused with cirrhotic cardiomyopathy, as seen with advanced cirrhosis of any etiology, which is typically characterized by impaired relaxation, diastolic dysfunction,

and hyperdynamic cardiac changes resulting in increased cardiac output (86). Heavy chronic alcohol intake continues to have a strong association with cardiomyopathy and development of cardiac dysfunction (87,88).

Pulmonary abnormalities

Given the side effects of alcohol use and altered sensorium, it may be unsurprising that patients with ALD are at risk for aspiration of gastric contents (89). This can lead to a multitude of other complications including pneumonia, empyema, and lung abscesses, traditionally stemming from pathogens endogenous to gastric or oropharyngeal flora (90). Furthermore, chronic alcohol abuse is a risk factor for transfusion-related acute lung injury (TRALI) and acute respiratory distress syndrome (ARDS) (91).

Skeletal myopathies

Patients with ALD can harbor several forms of myopathy throughout their disease course. While sarcopenia is a common manifestation as ALD progresses to advanced stages, this will be discussed below with the nutritional deficiencies and malabsorption. Alcohol appears to be a risk factor for the development of acute rhabdomyolysis (92). And even though this patient population is at increased risk for falls, the development of rhabdomyolysis has been shown to occur in a non-traumatic setting (93). The management of rhabdomyolysis poses some challenges among patients with ALD, particularly with respect to intravenous fluid resuscitation, volume status, and renal function. More chronic manifestations among ALD patients can be seen with alcoholic myopathy. Chronic alcohol intake fuels stunting of skeletal muscle formation and the promotion of autophagy through the effects of alcohol and its acetaldehyde byproducts (94,95). Newer evidence also suggests a role of aberrant regenerative capacity of muscle progenitor cells contributing to alcohol-related skeletal muscle dysfunction (96).

Nutritional deficiencies, malabsorption, and sarcopenia

Patients with ALD oftentimes receive a majority of their caloric intake through the carbohydrates in alcohol, which is devoid of essential proteins, fats, and other micronutrients (97,98). Heavy chronic alcohol use intrinsically can cause diarrhea, malabsorption, and chronic pancreatitis, further hindering nutrient reabsorption through limited

initial intake (99). Certain vitamin deficiencies, as seen with vitamin A and zinc, can alter taste and smell (100), and aberrant levels of glucose, leptin, and ghrelin can affect overall satiety (101). Both alcohol and acetaldehyde also stunt skeletal muscle formation and promote autophagy (94,95). Not only does cirrhosis constitute a proinflammatory state, but it is also characterized by a hypermetabolic state (102). Furthermore, as liver disease advances, hyperammonemia also induces sarcopenia via a mTORC1-regulated pathway (103). Overall, there are several mechanisms that converge and contribute to decreased caloric intake, nutritional deficiencies, weight loss, and sarcopenia often seen among this patient population (104).

Specifically, there are a number of nutrient and vitamin deficiencies classically found among patients with ALD (100). Vitamin A deficiency has the ability to lead to night blindness and increased fibrosis. Thiamine deficiency contributes to the aforementioned Wernicke-Korsakoff syndrome, in addition to neuropathy and potentially heart failure. Diminishing levels of vitamin B3 give rise to pellagra, a syndrome commonly characterized by dermatitis, diarrhea, and dementia. Vitamin B6 deficiency fosters symptoms that include a rash, glossitis, neuropathy, and sideroblastic anemia. Vitamin B9 deficiency can lead to macrocytic anemia. Low levels of vitamin B12 similarly can present as macrocytic anemia, in addition to other findings, such as neuropathy and weakness. Loss of adequate vitamin C levels traditionally present with scurvy. Vitamin D deficiency manifests as decreased bone mineral density and osteoporosis. Vitamin E insufficiency typically engenders immune cell dysfunction, myopathy, and neurologic defects. Zinc deficiency harbors changes consistent with skin lesions, altered taste, change in smell, encephalopathy, hypogonadism, alterations in immune function, and impaired wound healing (105).

Chronic pancreatitis and pancreatic insufficiency

The impetus of chronic alcohol intake promotes the risk of acute pancreatitis, which overtime can manifest as chronic pancreatitis after repeated episodes. The continual exposure of alcohol and steady foundation of inflammation leads to "burn out" of these pancreatic cells that ultimately harbors both exocrine and endocrine pancreatic insufficiency. Exocrine pancreatic insufficiency is characterized by malabsorptive diarrhea that also contributes to decreased vitamin intake (106). The progression of exocrine

insufficiency is heightened with concomitant tobacco abuse, and thus, the first line in management is unsurprisingly cessation of alcohol and tobacco products (107). The potential simultaneous involvement and loss of pancreatic islet cells engenders endocrine insufficiency and progression towards diabetes mellitus. However, this modality of diabetes poses a unique quandary in the sense that there is a coexisting loss of glucagon secretion, which further portends episodes of hypoglycemia (108). In the setting of continued alcohol intake, this can be a difficult facet of ALD to manage given the elevated carbohydrate content among alcoholic beverages, particularly beer. Overall, the caveats of exocrine and endocrine pancreatic insufficiency portend a difficult situation in the management of ALD.

Osteopenia

Although it appears patients with cirrhosis are at increased risk for altered bone mineral density and microarchitecture, regardless of etiology (109), patients with ALD harbor a multitude of unique risk factors for the development of osteopenia. As previously mentioned, hypoalbuminemia and nutritional deficiencies construct an ideal milieu for altered bone health and turnover. In particular, vitamin D and zinc deficiencies appear to be integral to this process (110). Malabsorption in the setting of chronic pancreatitis further exacerbates this mechanism, with a recent study also highlighting a potential association of vitamin D and K deficiencies with osteoporosis (111). Alcohol-induced myopathy and neuropathy provide a lack of normal mechanical stressors on bone, leading to alterations in bone architecture and density (112). Lastly, alcohol abuse also portends increased risk of falls and trauma ultimately resulting in increased bone fractures among this patient population.

Ethanol also provides direct toxic effects to primary cellular pathways of bone formation and resorption. Both ethanol and acetaldehyde have been demonstrated to provide oxidative damage leading to reduced osteoblast function and bone formation (113). Simultaneously, through both an auspicious milieu of proinflammatory cytokines and also the stimulation of the RANK (receptor activator of NF-kB) pathway, there is an overall activation of osteoclast activity seen among patients with ALD (114). The synergistic effects upon osteoblasts and osteoclasts leading to decreased bone formation and increased bone resorption are responsible for the increased risk of osteopenia among this patient population. Yet, larger

clinical studies have not yet captured this overall risk. In the only meta-analysis to date regarding ALD and bone health, patients with ALD were found to have an elevated rate of bone fractures with RR 1.944 (95% CI: 1.354–2.791) as compared to controls (115). And while there was a trend towards lower bone mineral density among ALD patients, there was no statistical difference found in the development of osteoporosis or bone mineral density as compared to controls. Nevertheless, it appears that these changes of osteopenia are reversed with abstinence from alcohol, which remains the first line treatment in the management of alcohol-related bone disorders (116).

Increased malignancy risk

In addition to HCC risk associated with cirrhosis, patients with ALD have been linked to many other forms of malignancy based upon persistent alcohol use. One large systematic review and meta-analysis demonstrated patients with chronic alcohol intake for at a two-fold increase for the general development of "cancer", however the subtypes were not stratified (117). Further evidence has established a dose-dependent alcohol intake with oropharyngeal, laryngeal, esophageal, colorectal, pancreatic, and breast cancer (118-120). This elevated malignancy risk not only is imperative to screen and treat patients with ALD appropriately, but can also represent a challenging obstacle for patients ultimately requiring liver transplantation.

Parotid gland hypertrophy and Dupuytren's contractures

Two final systemic findings seen in a large proportion of patients with ALD include enlarged parotid glands and Dupuytren's contractures. Chronic alcohol appears to contribute to the hypertrophy of parotid glandular tissue. This hypertrophy is increased as compared to controls and diabetic subjects (121). Meanwhile, Dupuytren's contractures are areas of increased connective tissue and collagen deposition resulting in fibrosis typically characterized along the fourth and fifth digits of the palmar fascia (122). Dupuytren's contractures are tightly linked to chronic alcohol use and are not infrequently observed among patients with ALD (123).

Conclusions

In addition to common endpoints seen across all etiologies of cirrhosis, patients with NAFLD and ALD foster unique

Table 2 Systemic manifestations specifically linked to NAFLD and ALD

NAFLD
Metabolic syndrome
Obesity
Insulin resistance
T2DM
Dyslipidemia
Cardiovascular disease
Hypertension
Atherosclerosis
Increased ACS, CVA, PAD
Venous thromboembolism
DVT
PE
CKD
PCOS
Hyperandrogenism
OSA
Osteoporosis
Nutritional considerations
Excessive dietary sugar and carbohydrate intake
Overall increase daily caloric intake
Increased malignancy risk
Cholangiocarcinoma
Colorectal carcinoma
ALD
Acid-base disorders
Alcoholic ketoacidosis
Hypoalbuminemia-induced metabolic alkalosis
Increased lactic acid accumulation
Hyperventilation-mediated respiratory alkalosis

Table 2 (*continued*)

Table 2 (*continued*)

Peripheral neuropathy and central nervous system pathologies
Peripheral neuropathy
Cerebellar ataxia
Brain atrophy and dementia
Wernicke-Korsakoff encephalopathy
Cardiovascular disease
Hypertension
Atrial fibrillation
Dilated cardiomyopathy
Pulmonary abnormalities
Aspiration events, pneumonia, empyema
TRALI
ARDS
Skeletal myopathy
Acute rhabdomyolysis
Alcoholic myopathy
Nutritional deficiencies
Vitamin A, thiamine, vitamin B3, vitamin B6, vitamin B9, vitamin B12, vitamin C, vitamin D, vitamin E, zinc
Chronic pancreatitis
Exocrine pancreatic insufficiency
Endocrine pancreatic insufficiency
Osteoporosis
Increased malignancy risk
Oropharyngeal, laryngeal, esophageal, colorectal, pancreatic, breast cancer
Parotid gland hypertrophy
Dupuytren's contractures

ACS, acute coronary syndrome; ALD, alcoholic liver disease; ARDS, acute respiratory distress syndrome; CVA, cerebrovascular accident; DVT, deep vein thrombosis; NAFLD, nonalcoholic fatty liver disease; PAD, peripheral artery disease; PE, pulmonary embolism; TRALI, transfusion-related acute lung injury.

systemic manifestations associated with their individual disease processes (see *Table 2*). The major catalyzing factor appears to be a close partnership with metabolic syndrome and the systemic effects of alcohol use, respectively. There are a bevy of metabolic disturbances, comorbidities, concomitant nutritional aberrancies, and increased malignancy risks exclusively associated with both NAFLD and ALD. A broader understanding of these two disease processes, which constitute some of the most common etiologies of cirrhosis, will ideally guide clinicians to

focus on these unique systemic manifestations in order to promote a more comprehensive, and ultimately effective, treatment strategy for patients with NAFLD and ALD.

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Footnote

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