Alcohol Abuse: Critical Pathophysiological Processes and Contribution to Disease Burden

Alcohol abuse; the most common and costly form of drug abuse, is a major contributing factor to many disease categories. The alcohol-attributable disease burden is closely related to the average volume of alcohol consumption, with dose-dependent relationships between amount and duration of alcohol consumption and the incidence of diabetes mellitus, hypertension, cardiovascular disease, stroke, and pneumonia. The frequent occurrence of alcohol use disorders in the adult population and the significant and widespread detrimental organ system effects highlight the importance of recognizing and further investigating the pathophysiological mechanisms underlying alcohol-induced tissue and organ injury.

Moderate alcohol (ethanol) consumption, defined as up to 1 drink/day for women and up to 2 drinks/day for men is a socially accepted behavior, endorsed by >50% of adults in the United States (25a). Harmful alcohol use, encompassing both alcohol binge drinking (consuming >4–5 drinks on a single occasion, generally under a 2-h period, and elevating blood alcohol concentration (BAC) levels to 0.08% (legal limits) or higher] and chronic heavy alcohol consumption (>7 drinks/wk for women and >14 drinks/wk for men), remains the most common and costly form of drug abuse. Approximately 7% of the adult U.S. population meets diagnostic criteria for alcohol abuse and/or alcoholism (52). Alcohol abuse is a major factor contributing to many disease categories, including cancer, cardiovascular disease, liver cirrhosis, and traumatic injury.

Alcohol can permeate to virtually all tissues in the body, resulting in alterations in significant multi-systemic pathophysiological consequences. Approximately 3.4% of global noncommunicable disease-related burden of deaths, 5% of net years of life lost, and 2.4% of net disability-adjusted life years can be attributed to alcohol abuse, with higher burden for cancer and liver cirrhosis (86). Thus alcohol abuse is the third leading lifestyle-related cause of death in the United States. Dose-dependent relationships between alcohol consumption and incidence of diabetes mellitus, hypertension, ischemic heart disease, dysrhythmias, stroke, pneumonia, and fetal alcohol syndrome have been reported (95). However, recognition of alcohol as an underlying causal factor in comorbid conditions remains a challenge in the clinical setting (103). This review provides a brief summary of salient alcohol effects on nonneural tissues. Because often this is based on evidence derived from preclinical studies, it is important to take into consideration the context of alcohol administration (acute vs. chronic), the route of administration (oral, intraperitoneal, vapor), and the specific outcome studied under each condition. Thus the authors caution against generalizations on the effects of alcohol described in some preclinical studies to those resulting from years of alcohol abuse in the clinical setting. Moreover, the existing comorbid conditions, dietary habits, and additional drugs consumed by most individuals who abuse alcohol are not directly replicated in animal studies. This too should be taken into consideration when the existing preclinical literature is interpreted. When appropriate, this is highlighted in the review.

The fact that chronic alcohol abuse is conducive to tissue injury is a well accepted, evidence-based fact as described in this review. Several pathophysiological mechanisms have been identified as causative factors in tissue and organ injury resulting from alcohol abuse, including oxidative stress, inflammation, acetaldehyde generation and adduct formation, decreased barrier function, impaired anabolic signaling, upregulation of catabolic processes, fibroblast activation, mitochondrial injury, and cell membrane perturbations (FIGURE 1) (77). Some of these mechanisms are the result of direct alcohol-induced cell perturbations; others are the consequence of tissue alcohol metabolism. Thus a brief overview of salient aspects of alcohol metabolism and pharmacokinetics (reviewed in detail by Cederbaum and Khanna; Refs. 24, 61) is relevant to appreciate its significant role in organ injury.
Neurological deficits and fetal alcohol syndrome resulting from alcohol abuse have been extensively reviewed by others. Here, we provide an overview of some of the critical, nonneuronal physiological systems impacted by alcohol abuse and their contribution to the pathophysiology underlying the most frequent comorbid conditions, and highlight critical areas in need of further research.

Alcohol Metabolism

The average rate at which alcohol is eliminated from the body is \( \sim 7 \text{ g/h} \), which translates to \( \sim 1 \text{ drink/hour} \) (24, 61). Alcohol undergoes first-pass gastric metabolism by the enzyme alcohol dehydrogenase (ADH). Most tissues express ADH and are capable of alcohol metabolism, as reflected in Table 1. However, most alcohol oxidation occurs in the liver. Alcohol is metabolized to acetaldehyde primarily by ADH and the cytochrome P450 2E1 (CYP2E1). This latter pathway is particularly relevant following chronic alcohol abuse. Acetaldehyde is converted to acetate in the mitochondria by the enzyme acetaldehyde dehydrogenase type 2. Most of the acetate produced enters the systemic circulation and is activated to acetyl coenzyme A (CoA), a key intermediate metabolite in peripheral tissues. Acetaldehyde can form adducts that can produce injury through activation of immune responses (108). This is particularly relevant in alcoholic liver disease. During the oxidative process, both ADH and ALDH1 reactions reduce NAD\(^+\) to NADH, shifting the cellular redox ratio, thereby affecting several NAD\(^+\)-requiring enzymes like lactate and pyruvate dehydrogenase and affecting pathways including glycolysis, citric acid cycle, fatty acid oxidation, and gluconeogenesis (39). In addition, the cytochrome P450 enzymes, particularly CYP2E1, contribute to the oxidation of alcohol to acetaldehyde, mainly at increasing alcohol concentrations as well as following their induction by chronic alcohol abuse. Because CYP2E1 is involved in oxidation of several drugs to their reactive intermediates (e.g., nitrosamines, acetaminophen, and halothane), their toxicity is enhanced in alcoholics. This pathway of alcohol oxidation results in the production of large amounts of reactive oxygen species (ROS) (25, 40) and is thought to be an important mechanism contributing to alcoholic liver injury (89). ROS are eliminated by antioxidants like glutathione (GSH) under normal conditions. Alcohol depletes cellular GSH stores, thereby further exacerbating ROS-mediated injury (50). ROS can interact with lipids, producing lipid peroxidation, leading to formation of reactive molecules such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), which can in turn form protein adducts (22). A minor fraction of alcohol metabolism occurs in peroxisomes through catalase-dependent oxidation. Alcohol can also react with glucuronic acid to form ethyl-glucuronide, a soluble, non-volatile conjugate that is readily excreted and detected in body fluids, tissue, sweat, and hair for an extended time following alcohol consumption. Clearly, alcohol metabolism and the generation of ROS, depletion of reducing equivalents, particularly GSH, and...
Alcohol metabolism reflected by dehydrogenase (ADH) activity in rat tissues was compiled from Riveros-Rosas et al. and Raskin and Sokoloff. Rates of metabolism are expressed as milli-enzymatic units (mU) per gram (g) of tissue (94, 98). For comparison purposes, values from Raskin and Sokoloff were normalized to the ADH enzymatic rate of liver (factor of 1.49). Absolute tissue-specific rates may vary between species.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>ADH Activity, mU/g of tissue</th>
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<tr>
<td>Liver</td>
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<tr>
<td>Stomach</td>
<td>11.80</td>
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<tr>
<td>Small intestine</td>
<td>7.50–19.30</td>
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<tr>
<td>Heart</td>
<td>0.80</td>
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<tr>
<td>Lungs</td>
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<td>Brain</td>
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<td>Testes</td>
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Alcohol intoxication, dependence, and withdrawal profoundly affect endocrine regulation and disrupt the body’s ability to maintain and restore homeostasis following a challenge (28). One of the most sensitive pathways to the acute and chronic effects of alcohol abuse is the hypothalamo-pituitary-adrenal (HPA) axis (FIGURE 3). Responsiveness of the HPA axis to psychological and physical stressors can be heightened or blunted depending on duration of alcohol abuse (97). Alcohol-mediated disruption in HPA function has been implicated in the pathophysiology of pseudo-Cushing’s syndrome (19), addiction (48), dependence (48), and relapse of recovering alcoholics (3). Alcohol produces dose-, frequency-, and duration-specific effects on arginine vasopressin (AVP), leading to alterations in water balance and mean arterial blood pressure homeostasis (115). Acute alcohol intoxication increases magnocellular and parvocellular neuronal activity; whereas chronic alcohol abuse significantly reduces the number of AVP-producing neurons in the supraoptic nuclei (SON) (29) and suppresses circulating AVP levels (29). Our studies have shown that acute alcohol intoxication augments paraventricular nucleus nitric oxide inhibitory tone and suppresses the hypovolemia- but not hyperosmolarity-induced AVP release (127). These acute effects of alcohol have the potential of affecting homeostatic mechanisms essential for restoring circulating blood volume following insults such as hemorrhagic shock. Although new set-points in osmolarity or hypovolemic responsiveness may be established following chronic alcohol abuse, persistent alterations in regulation of AVP release have been reported in abstinent alcoholics (35).

Acute and chronic alcohol abuse blunts responsiveness of the hypothalamic-pituitary-thyroid (HPT) axis to central stimulation (132), decreases circulating levels of triiodothyronine (T3) and thyroxine (T4) (54), deiodination of T4 to T3 (83), and thyroid gland volume (53), and increases hepatic thyroid hormone uptake (56). Thyroid axis function can be further compromised in alcoholics with comorbid conditions and can contribute to behavioral manifestaations of alcohol abuse-like depression (54). Chronic alcohol consumption disrupts the hypothalamic-pituitary-gonadal (HPG) axis, manifesting in decreased gonadotropin release, abnormal menstrual cycles, infertility, and impotence (33, 37). In addition, alcohol abuse markedly diminishes the growth hormone (GH) insulin-like growth factor (IGF-I) axis at multiple levels, including release, signaling, and cellular responses (109). This suppression in the GH/IGF-I axis is critical during adolescence, a period of widespread alcohol abuse, as well as during disease states (104). Thus the acute and chronic effects of alcohol abuse can lead to a multitude of endocrine-related disorders. Alcohol abuse contributes to an impaired ability of the host to respond to challenges and maintain homeostasis, affecting the ability to respond to stress. In addition, the cumulative impact of alcohol on disease burden results in detrimental effects on thyroid, gonadal, and somatotropic axis functions that can contribute to conditions including hypothyroidism, decreased reproductive function, and growth retardation.

Alcohol and the Gastrointestinal System

The gastrointestinal system participates in alcohol absorption and metabolism, and is an important target for alcohol-induced pathophysiology including esophageal and gastric dysmotility, altered acid secretion, impaired nutrient absorption, and disrupted intestinal barrier function. Esophageal dysmotility and delayed gastric emptying facilitating acid regurgitation increases the risk for postemetic lacerations of the distal esophagus induced by vomiting (Mallory-Weiss Syndrome) and for the development of esophageal varicosities resulting from increased intrahepatic pressure of liver fibrosis (73). Collectively, these factors promote acid injury and mucosal damage, increasing the risk of esophageal cancer. Gastric acid secretion and motility vary according to the
alcohol content and to the fed state of the individual at the time of ingestion. Beer and wine (low alcohol %) stimulate gastric acid secretion and gastrin release and increase gastric emptying (118). These effects may have little to no consequence following isolated episodes of alcohol ingestion. However, the direct effects of repeated high level alcohol exposure on the gastric mucosa promote chronic gastritis, characterized by inflammatory cell infiltration and mucosal hypertrophy during the acute phase followed by decreased mucosal thickness and atrophy during the chronic phase (99). Moreover, chronic alcohol abuse impairs intestinal essential amino acid and vitamin absorption, leading to increased frequency of nutritional deficiencies, including vitamins A, B1, B2, B6, C, and folic acid (70) (FIGURE 4).

Alcohol and its metabolites increase intestinal epithelial permeability (60) through disruption of

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**FIGURE 2.** Alcohol metabolism and its contribution to tissue injury

The average rate at which alcohol is eliminated from the body is ~7 g/h, which translates to ~1 drink/h. Alcohol undergoes first pass gastric metabolism by the enzyme alcohol dehydrogenase (ADH). However, most alcohol oxidation occurs in the liver. Alcohol is metabolized to acetaldehyde primarily by alcohol dehydrogenase (ALD) and the cytochrome P450 2E1 (CYP2E1). This later pathway is particularly relevant following chronic alcohol abuse. Acetaldehyde is converted to acetate in the mitochondria by the enzyme acetaldehyde dehydrogenase (ALDH) type 2. Most of the acetate produced enters the systemic circulation and is activated to acetyl coenzyme A (CoA), a key intermediate metabolite in peripheral tissues. Acetaldehyde can form adducts that can produce injury through activation of immune responses. During the oxidative process, both ADH and ALDH reactions reduce NAD⁺ to NADH, shifting the cellular redox ratio, thereby affecting several NAD⁺ requiring enzymes like lactate and pyruvate dehydrogenase and affecting pathways including glycolysis, citric acid cycle, fatty acid oxidation, and gluconeogenesis. In addition, the cytochrome P450 enzymes, particularly CYP2E1, contribute to the oxidation of alcohol to acetaldehyde, particularly at increasing alcohol concentrations as well as following their induction by chronic alcohol abuse. Because CYP2E1 is involved in oxidation of several drugs to their reactive intermediates (e.g., nitrosamines, acetaminophen, and halothane), their toxicity is enhanced in alcoholics. This pathway of alcohol oxidation results in the production of large amounts of reactive oxygen species (ROS) and is thought to be an important mechanism contributing to alcoholic liver injury. ROS are eliminated by antioxidants like glutathione (GSH) under normal conditions. Alcohol depletes cellular GSH stores, thereby further exacerbating ROS-mediated injury. ROS can interact with lipids, producing lipid peroxidation, leading to formation of reactive molecules such as malondialdehyde (MDA) and 4-hydroxy-2-nonenal (HNE), which can in turn form protein adducts. A minor fraction of alcohol metabolism occurs in peroxisomes through catalase-dependent oxidation. Alcohol can also react with glucuronic acid to form ethylglucuronide, a soluble, non-volatile conjugate that is readily excreted and detected in body fluids, tissue, sweat, and hair for an extended time following alcohol consumption.
the integrity of tight junctions formed by transmembrane proteins (i.e., claudin, occludin, etc.) cross-linked to the actin cytoskeleton and intercellular signaling components by adaptor proteins (e.g., ZO-1/2/3, PATJ, PAR-3, and PAR-6) (11, 113). Alcohol-mediated disruption of the intestinal barrier integrity leads to gut bacterial toxin (i.e., lipopolysaccharide (LPS)) translocation and dissemination to the systemic circulation (44). The majority of LPS from the GI tract is delivered to the liver through the portal circulation, where only a minor portion escapes detoxification. In contrast, LPS delivered by the collecting lymphatic vessels directly enters the systemic circulation by the thoracic duct (12). Studies from our group have shown that acute alcohol intoxication impairs mesenteric collecting lymphatic pump function, decreasing mesenteric lymphatic tone and increasing lymphatic ejection fraction (110). Overall, these modifications appear to enhance the ability of lymphatics to transport lymph during the alcohol intoxicated state, which we predict would favor LPS lymphatic dissemination. Whether this altered lymphatic pumping persists following chronic alcohol exposure is not known. However, because transport of LPS through the lymphatic route escapes hepatic detoxification, a considerable amount of bioactive LPS could be delivered into the systemic circulation through this system (126) and may potentially contribute to the alcohol-associated LPS-induced tissue and organ inflammatory injury. Bacterial toxin translocation has been proposed as an important mechanism contributing to generalized inflammation and alcohol-induced liver disease characterized by fat accumulation, inflammation, and fibrosis (1). Although the contribution of alcohol-induced gut leakiness to systemic inflammation and liver injury has been well recognized, the contribution of lymphatic vs. portal delivery of LPS to the liver and extra-hepatic organs remains to be elucidated.

The liver, the principal organ involved in alcohol metabolism, is considered one of the main targets of alcohol-induced pathology. Liver disease is one of the most salient pathophysiological conditions resulting from alcohol abuse and a major cause of alcohol-related morbidity and mortality. Alcohol abuse is the principal cause of chronic liver disease in Western countries and afflicts ~15% of alcoholics in the United States (71). Three mechanisms underlie the stages of alcoholic liver disease: hepatosteatosis, steatohepatitis, and cirrhosis. Although most heavy drinkers develop fatty liver, only 10–35% develop hepatitis and <20% progress to cirrhosis (49), suggesting the complexity of factors involved in alcoholic liver disease (ALD) progression.

Hepatosteatosis results from hepatocyte accumulation of cholesterol esters, phospholipids, and triglycerides (TG) due to alcohol-induced alterations in lipid metabolism. Among the mechanisms proposed are increased fatty acid mobilization from adipose tissues, increased hepatic lipid uptake, alteration of fat metabolism-associated transcription factors, and disruption of enzymes involved in fat metabolism. Chronic alcohol consumption results in progressive mitochondrial dysfunction characterized by decreased fatty acid oxidation leading to free fatty acid (FFA) accumulation (14). In the early stages of the disease, the liver adjusts to higher FFA levels to avoid TG accumulation but fails over time, leading to TG accumulation, steatosis, and lipotoxicity. The latter contribute to disruption of mitochondrial function and dysregulate numerous redox-sensitive signaling pathways, leading to apoptotic and necrotic cell death and additional TG accumulation (39). Steatosis is associated with an increased sensitivity to LPS, attributed to an imbalance of pro-inflammatory/oxidative and cytoprotective mechanisms (102). Steatosis is usually reversible.
with abstinence and sustained moderation of alcohol consumption, preventing the progression to chronic liver disease.

Steatohepatitis is characterized by hepatic infiltration of inflammatory cells, expression of pro-inflammatory cytokines, and oxidative injury resulting in hepatocellular impairment (46). Kupffer cells, liver-specific macrophages that play an important role in host defense mechanisms and have an essential role in maintaining liver homeostasis and preservation, have been implicated as being central players in liver damage induced by alcohol (31). Increased LPS delivery, resulting from a leaky intestinal barrier described above, can directly affect hepatocyte function but most importantly leads to Kupffer and hepatic stellate cell (HSC) activation, also resulting in hepatocyte injury (106, 113). LPS activation of Toll-like receptor 4 (TLR-4) leads to transcriptional activation and generation of potent innate immune responses (116), generation of pro-inflammatory cytokines and ROS, induction of apoptosis, and hepatocellular damage (113). However, the complexity of the etiology of alcoholic hepatitis is reflected in the failure of TNF-α antibody to improve outcomes in alcoholic hepatitis (120). In addition to activation of innate immunity by gut-derived LPS, alcohol abuse also has been shown to stimulate complement C3 and C5, which can in turn activate Kupffer cells (93). This pathway has been explored as a possible target for inducing anti-inflammatory and hepatoprotective cytokines to reduce alcohol-induced hepatocellular damage and to treat ALD (46). Activation of adaptive immunity also contributes to the pathogenesis of ALD. Elevated levels of IgG, T-lymphocytes, and antibodies against lipid peroxidation

**FIGURE 4. Alcohol and the gut-liver axis**

Alcohol abuse produces marked alterations in the gastrointestinal tract. Esophageal and gastric dysmotility facilitate acid regurgitation and contribute to postemetic lacerations of the distal esophagus induced by vomiting (Mallory-Weiss Syndrome). Liver fibrosis and the resulting intrahepatic pressure increase leads to development of esophageal varicosities. Alcohol promotes chronic gastritis followed by decreased mucosal thickness and atrophy during the chronic phase. Chronic alcohol abuse impairs intestinal essential amino acid and vitamin absorption. In the liver, alcohol metabolism increases the production of ROS and lowers antioxidant levels, which contributes to liver injury. ROS generation leads to lipid peroxidation, alterations in plasma and intracellular membranes, and release of proinflammatory and profibrotic mediators. Alcohol and its metabolites disrupt intestinal barrier function by affecting the integrity of tight junctions, promoting the dissociation and redistributing proteins like ZO-1, claudin, and occludin. Increased paracellular permeability leads to increased bacterial toxin translocation from the gut lumen and disseminated to the systemic circulation via the portal vein and the lymphatic route. This later route of dissemination may be significant, since alcohol intoxication has been shown to promote lymphatic pumping. GSH, reduced glutathione; ROS, reactive oxygen species; HCV, hepatitis C virus; LES, lower esophageal sphincter. The potential clinical consequences of alcohol abuse and its impact on the endocrine system are shown in the box.
have been reported in patients with advanced ALD (5). Oxidative stress has also been implicated as a major factor in the development of ALD. Acetaldehyde impairs hepatocyte mitochondria functionality, and promotes lipid peroxidation and glutathione depletion (108), promoting oxidative stress and sensitizing the hepatocyte to oxidative injury (38). Nevertheless, clinical trials examining the benefit of antioxidant therapy for treatment of ALD have not shown improved outcomes targeting this system (43).

The progression of steatohepatitis to liver fibrosis involves excessive accumulation of extracellular matrix (ECM) proteins including collagen (84) and disruption of hepatic structure forming a fibrous scar with subsequent development of nodules of regenerating hepatocytes (15). Acetaldehyde forms adducts with proteins and DNA, impairing cellular function and gene expression (108). Proteins such as collagen are targeted by acetaldehyde, leading to adduct formation and induction of HSC collagen 1 synthesis, contributing to the onset and maintenance of fibrogenesis (23). Activation of HSCs, the main producers of ECM in the injured liver, is the result of gut-derived LPS (8), ROS, and cytokines released from neighboring Kupffer cells (39), and alcohol-mediated depletion of natural killer (NK) T-cells (58). NK cells induce HSCs apoptosis during liver fibrosis and thereby play an antifibrotic role. Once activated, HSCs not only increase ECM synthesis and deposition but also increase their own proliferation rates (45). In addition, ALD is associated with increased risk for hepatitis C virus infection, cirrhosis, and development of hepatocellular carcinoma (80).

Chronic heavy alcohol consumption is the most important risk factor for chronic pancreatitis (107, 130). The local metabolism of alcohol has been suggested to contribute to its toxic effects (9). The course of alcoholic pancreatitis is initiated as an acute process that with repeated episodes of acute injury promotes inflammation, acinar atrophy, and fibrosis, resulting in exocrine and endocrine dysfunction (10). Similar to the cellular mechanisms involved in alcoholic cirrhosis, pancreatic stellate cells become activated during alcoholic oxidative metabolism and contribute to fibrogenic changes (124). The alcohol-associated risk for development of chronic pancreatitis is further exacerbated in smokers, contributing further to the overall risk of pancreatic cancer (130).

**Alcohol and the Cardiopulmonary System**

In contrast to the overall detrimental effects of alcohol on other organ systems, evidence indicates that low to moderate alcohol consumption is associated with a lower risk of coronary heart disease (30). In contrast, chronic heavy alcohol use increases risk for cardiovascular and pulmonary disease (125), including hypertension and non-ischemic dilated alcoholic cardiomyopathy (ADC) characterized by reduced ejection fraction, left ventricular dilation, and extensive interstitial cardiac fibrosis (87). Moreover, chronic alcohol abuse can exacerbate cardiac injury resulting from myocardial infarction, diabetes, hypertension, or pressure overload (4, 112). Several mechanisms have been proposed to contribute to alcohol-induced myocardial dysfunction, including oxidative stress, cardiomyocyte mitochondrial and sarcoplasmic reticulum damage, altered calcium dynamics, and cardiac fibrosis.

Cardiomyocyte damage resulting from chronic alcohol abuse is mediated by multiple mechanisms, including oxidative stress, alterations in calcium handling, and mitochondrial dysfunction. Alcohol abuse induces myocardial oxidative stress (89, 123) and depletes mitochondrial GSH, decreasing antioxidant capacity and enhancing myocyte susceptibility to oxidant injury and apoptosis (123). Alcohol-induced GSH depletion is not cardiac specific and is seen in liver and lung (40). Alcohol abuse disrupts cardiomyocyte contraction by damaging contractile proteins and interfering with calcium signaling and homeostasis through upregulation of L-type calcium channel expression and function, which can promote calcium overloading (51) and result in cardiomyocyte apoptosis and necrosis. Moreover, chronic alcohol abuse reduces myofiber calcium sensitivity and alters cellular calcium transients, resulting in reduced contractile function (88). Alcohol-mediated alterations in calcium handling have been implicated in sudden cardiac death and cardiac arrhythmias caused by binge drinking (65). Acetaldehyde has also been implicated as a causal factor in ethanol-induced cardiomyocyte damage by inhibiting calcium ATPases, leading to impaired excitation-contraction coupling and mitochondrial and sarcoplasmic reticulum toxicity (96).

The development of cardiac fibrosis appears to be a key mechanism of ADC dysfunction and is manifested in the initial stages as cardiac diastolic dysfunction (87). The extensive cardiac fibrosis impairs ventricular filling by decreasing ventricular compliance. Oxidative stress is considered one of the principal mechanisms underlying alcohol-induced fibrosis. Oxidative stress stimulates the production of collagen by fibrogenic cells, including cardiac fibroblasts, leading to both interstitial and perivascular fibrosis (89). Studies from our group have
shown that alcohol-induced transformation of fibroblasts to myofibroblasts results in excess deposition of collagen (36). In addition to the activation of fibrogenic cells, alcohol may promote fibrosis indirectly through cardiomyocyte apoptosis or necrosis and their replacement by collagen.

Cessation or decreased alcohol consumption is associated with a reduction in blood pressure in hypertensive patients (129). The mechanisms of alcohol-mediated hypertension include potentiation of the renin-angiotensin-aldosterone system (RAAS) (27). This is reflected in significantly elevated circulating angiotensin II levels (27), elevated cardiac angiotensin converting enzyme expression (63), and increased cardiac expression of angiotensin type 1 (AT1) receptors (27). AT1 receptors have been implicated in ventricular dysfunction, elevations of end-diastolic pressure, and alcohol-induced vascular injury (13, 27). Signaling through the AT2 receptor antagonizes the effects of AT1 signaling. Its contribution to alcohol-induced modulation of blood pressure is debatable (27).

As in the heart and other organs, chronic alcohol abuse causes oxidative injury of the lungs. Alcohol decreases GSH, which leaves pulmonary cells susceptible to oxidative stress injury (50). As mentioned above, alcohol activates the RAAS, which promotes superoxide production by NADPH-oxidases in the lung (90). Chronic alcohol also interferes with the production of pulmonary surfactant by disrupting the composition of dipalmitoyl-lecithin (50). As a result, susceptible alveolar type II cells are lost to oxidative stress-induced apoptosis and necrosis, which reduces barrier function and increases alveolar-capillary permeability.

Alcohol abuse is a well established risk factor for acute respiratory distress syndrome (ARDS) and pneumonia (41, 79). Alcohol negatively affects the pulmonary response to injury, infection, and inflammation, and increases ARDS susceptibility and mortality almost twofold over that of non-alcoholic patients (79). This striking difference appears to be due to the adverse effects of ethanol on the lung’s ability to respond to bacterial and inflammatory insult (41). The mechanisms responsible for alcohol-mediated impaired immune response to infection include altered balance between proinflammatory and anti-inflammatory cytokines by alveolar macrophages (131), impaired neutrophil function including phagocytosis and chemotaxis (21), attenuation of granulocyte-macrophage colony-stimulating factor (GM-CSF) release (81), and impaired airway ciliary function (128). The net result of these effects is suppression of the pulmonary immune response (76) (FIGURE 5).

### Impact of Alcohol on Body Composition

In addition to the well recognized effects on nutritional state of the individual, chronic alcohol abuse disrupts multiple factors involved in the balance between anabolic and catabolic mechanisms. Alcohol abuse is associated with an ~50% incidence of skeletal muscle myopathy (92), which is greater than the incidence of alcoholic cirrhosis (10–15%) in chronic alcoholics (46). Alcoholic myopathy has been shown to be the result of decreased muscle protein synthesis (85) and accelerated muscle proteolysis (117). Alcohol can alter the nutritional state of the individual either by decreasing food consumption and/or by producing malabsorption, resulting in decreased micronutrient availability and consequently modulation of circulating and tissue growth factors (75). Chronic alcohol abuse has been shown to increase whole body proteolysis and rates of amino acid oxidation (17), and to decrease the rate of skeletal muscle protein synthesis (91). Both capacity of muscle protein synthesis and translational efficiency are impaired by alcohol. In addition to adversely affecting multiple sites involved in regulating translational efficiency (66), chronic alcohol results in decreased circulating and tissue levels of androgens and IGF-I (69), upregulation of myostatin, a negative regulator of skeletal muscle growth (119), and increased proteolysis through the ubiquitin proteasome pathway (122). The detrimental impact of chronic alcohol abuse on skeletal muscle mass balance is further accentuated in diseased states. Studies from our group have demonstrated that chronic alcohol consumption markedly exacerbates the end-stage muscle wasting in a simian immunodeficiency virus-infected rhesus macaques (78), and this is the result of an inflammatory, oxidative milieu that promotes dysregulation of the ubiquitin proteasome pathway (67).

### Alcohol and Bone

Alcohol abuse is associated with altered bone metabolism, decreased bone mineral density and mass (20, 105), and increased risk of fractures (16) despite lack of liver failure. Overall, the prevalence of osteoporosis in alcoholics has been estimated at >40% (111). Both direct and indirect mechanisms are likely factors in decreased bone health in chronic alcoholics (64). Among the most important factors regulating bone, adipose, and skeletal muscle mass are the anabolic hormones, particularly testosterone. Androgens play a critical role in the control of bone remodeling by suppressing osteoclastogenesis and promoting osteoblastogenesis (121), as well as by antagonizing the effect of
pro-inflammatory cytokines (101) and promoting osteoprotegerin synthesis, reducing the activation and maturation of osteoclasts (55). The attenuation of the HPG axis in chronic alcoholics and the associated decreased circulating levels of testosterone (37) likely aggravates the pro-inflammatory cytokine’s impact on bone loss (64). The detrimental impact of alcohol on bone health is not limited to an increased risk for osteoporotic fractures and delayed fracture repair. It is compounded by the greater risk for falls during acute alcohol intoxication (resulting from altered gait and balance), coupled with alcoholic myopathy and decreased bone mineral content and density, which can collectively significantly aggravate the burden of bone disease in this population (59).

**Alcohol and Adipose Tissue**

The impact of chronic alcohol abuse on adipose tissue mass and phenotype has not been investigated in a systematic way. Studies have reported that chronic alcohol consumption is associated with decreased fat mass (2), and this has been attributed to altered neuroendocrine function resulting in increased cortisol release (68). In contrast, others have reported a high incidence of dyslipidemia and increased fat mass in alcoholics, with >20% of patients meeting criteria for metabolic syndrome (57) (FIGURE 6). However, some recent studies suggest that alcohol may not only alter fat mass but, in addition, disrupt adipokine profiles such as that of leptin (82) and adiponectin (100). These alterations in adipose tissue pheno-
type are likely to result in marked metabolic dysregulation, favoring an insulin-resistant state. These findings raise the question of whether chronic alcohol abuse by obese individuals may further contribute to risk of metabolic syndrome. Based on the known effects of chronic alcohol abuse, we predict that a significantly greater metabolic disregulation would prevail, further disrupting glycemic control and possibly enhancing the risk of liver disease.

**Perspectives and Translational Implications**

The systemic impact of alcohol abuse is reflected in the greater incidence of significant comorbid conditions, with a significant disease-related burden that spans all ages in alcohol-abusing individuals. The increasingly recognized relationships between chronic alcohol abuse and incidence of diabetes mellitus, hypertension, ischemic heart disease, dysrhythmias, stroke, and pneumonia, adds to the previously recognized risk for liver disease and fetal alcohol syndrome. The contribution of alcohol metabolism to organ injury is not trivial, as seen by the marked disruption in cellular processes resulting from ROS generation and altered cellular redox state. Among the critical pathophysiological mechanisms underlying the most frequent comorbid conditions are inflammation and oxidative stress. Oxidative stress resulting from either an excess production of ROS or a reduction in reducing antioxidant equivalents has been consistently demonstrated to be an overall mechanism of tissue injury resulting from chronic alcohol abuse (25, 40). Although acute alcohol intoxication has been consistently seen to reduce inflammation in response to infectious challenges, chronic alcohol consumption favors a pro-inflammatory milieu that plays an important role in tissue injury (114).

Overall, much remains to be learned regarding the mechanisms of alcohol-induced tissue injury, the possibility of reversibility, and ultimately the effectiveness of behavioral and pharmacological interventions to ameliorate alcohol abuse and its untoward consequences. Abstinence and nutritional therapy are still the first choice of intervention for ALD. Anti-inflammatory drugs, including cortico-

**FIGURE 6. Alcohol and the musculoskeletal and adipose tissues**

Chronic alcohol abuse disrupts multiple factors involved the balance between anabolic and catabolic mechanisms in bone and muscle. The underlying mechanisms include nutritional deficiencies, decreased growth factor availability and responsiveness, increased ubiquitin proteasome pathway activation, upregulation of negative regulators of skeletal muscle growth, and disruption of bone remodeling. Chronic alcohol abuse produces marked alterations in adipocyte function, resulting in fat mass redistribution, dyslipidemia, and altered pattern of adipokine release. The potential clinical implications of alcohol’s effects on skeletal muscle, bone, and adipose tissue are summarized in the box.

<table>
<thead>
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<td>• Alcoholic myopathy</td>
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<tr>
<td>• Osteoporosis</td>
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<td>• Metabolic syndrome</td>
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<tr>
<td>• Insulin resistance</td>
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<td>• ↑ Fracture risk</td>
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- ↑ Anabolic signaling
- ↓ Proteosomal degradation
- ↓ Protein synthesis
- ↑ Oxidative stress
- ↑ Inflammation
- ↑ Myostatin

- Δ Fat mass
- Dyslipidemia
- Δ Leptin and adiponectin

- Δ Bone metabolism
- ↓ Mineral density and mass
- ↑ Inflammation
- ↓ Osteogenesis

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steroids, pentoxifylline (32), TLR-4 antagonists (72), and interleukin-22 (IL-22; an anti-inflammatory cytokine) (62), have failed to result in consistent improvement for ALD but may still confer protection from injury of other organs. Novel approaches in the treatment of ALD that remain to be explored include modulation of gut microbiota (42). In addition to measures aimed at reducing cardiac workload, ALDH type 2 has recently been proposed as a viable therapeutic target for alcoholic cardiomyopathy. Novel studies suggest that overexpression or activation of ALDH type 2 prevents alcohol-mediated cardiac dilation, dysfunction, and fibrosis (34, 47), and reduces ischemia-reperfusion injury (26). N-acetyl cysteine and GM-CSF administration and inhibition of the RAAS are identified as potential therapies for reducing alcohol-induced pulmonary injury and associated ARDS (18). However, these approaches remain to be proven effective in large clinical trials. The annual costs ($235 billion) to our nation related to crime, lost work productivity, and healthcare of alcohol abuse is greater than that of tobacco ($193 billion) or illicit drugs ($193 billion) (80a). The alcohol-attributable disease burden is closely related to the average volume of alcohol consumption and particularly affects disadvantaged subgroups of the population. Prevention of alcohol use disorders can effectively curtail this healthcare burden. Other than cessation or significant decrease in alcohol consumption, there is no specific treatment for alcohol-related comorbid conditions.

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