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TOPIC HIGHLIGHT

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Alcoholism: A systemic proinflammatory condition

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Abstract

Excessive ethanol consumption affects virtually any organ, both by indirect and direct mechanisms. Considerable research in the last two decades has widened the knowledge about the paramount importance of proinflammatory cytokines and oxidative damage in the pathogenesis of many of the systemic manifestations of alcoholism. These cytokines derive primarily from activated Kupffer cells exposed to Gram-negative intestinal bacteria, which reach the liver in supra-physiological amounts due to ethanol-mediated increased gut permeability. Reactive oxygen species (ROS) that enhance the inflammatory response are generated both by activation of Kupffer cells and by the direct metabolic effects of ethanol. The effects of this increased cytokine secretion and ROS generation lie far beyond liver damage. In addition to the classic consequences of endotoxemia associated with liver cirrhosis that were described several decades ago, important research in the last ten years has shown that cytokines may also induce damage in remote organs such as brain, bone, muscle, heart, lung, gonads, peripheral nerve, and pancreas. These effects are even seen in alcoholics without significant liver disease. Therefore, alcoholism can be viewed as an inflammatory condition, a concept which opens the possibility of using new therapeutic weapons to treat some of the complications of this devastating and frequent disease. In this review we examine some of the most outstanding consequences of the altered cytokine regulation that occurs in alcoholics in organs other than the liver.

Key words: Alcoholism; Cytokines; Brain; Bone; Muscle; Oxidative damage; Atherosclerosis; Sepsis; Lung; Chronic pancreatitis; Alcoholic liver disease

Core tip: Alcoholism is a multisystemic disease. In the last ten years it has been shown that an inflammatory response is triggered by ethanol itself, by reactive oxygen species derived from ethanol metabolism, and by increased amounts of mainly Gram-negative bacteria that reach liver and peripheral organs due to ethanol-induced increased intestinal permeability. In addition to direct organ injury caused by ethanol itself, these mechanisms especially affect end organs such as brain, lung, muscle, bone, heart, blood vessels, pancreas, and the immune system. The main features of these effects are highlighted in this review.

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INTRODUCTION

It has been well known for more than two decades that in alcoholic hepatitis, cytokine production (by Kupffer cells and other liver cells) and reactive oxygen species (ROS) production (by activated macrophages and through the effects of ethanol metabolism) play a major role in the development and progression of liver disease[1]. The role of ethanol and ethanol-mediated inflammation in the pathogenesis of alcoholic hepatitis, together with the importance of ethanol-mediated bacterial translocation (both Gram-negative and Gram-positive[2]) has been subjected to robust research in the last decade. Excellent reviews on this topic have been written recently[3-7]. However, the effects of ethanol metabolism and increased ROS and cytokine production are by no means restricted to the liver[8]. Along with the increased knowledge about the key metabolic pathways by which ethanol consumption leads to the development of alcoholic hepatitis, it has also been shown that cytokines and lipopolysaccharide (LPS) may induce damage in remote organs in alcoholics, even in those without significant liver disease. There is a clear-cut relation between oxidative damage and inflammation and alcoholism-associated diseases such as brain dysfunction, bone and muscle diseases, lung alterations, increased severity of infections, malnutrition, and an increased prevalence of cardiovascular disease or cancer. Lipid peroxidation may be also involved in ethanol-mediated testicular injury[9] and ovarian dysfunction[10]. Malnutrition, a frequent complication of alcoholism[11], is also associated with increased bacterial translocation and with spreading of bacteria due to altered immunity[12], therefore contributing to systemic alterations and increased mortality. Mortality of mice fed a protein-poor diet that were exposed to endotoxin was 70% *vs* 0% in normally fed animals[13].

This review is mainly devoted to analyzing the systemic effects provoked by ethanol on organs other than the liver. The development of cancer is an important consequence of heavy alcoholism. However, increased cytokine secretion and inflammation probably derive, in part, from the tumor itself. For this reason, cancer will not be discussed in this review.

Central nervous system alterations

Several different clinical scenarios derived from the effects of alcohol on the central nervous system (CNS) may be considered in the clinical evaluation of patients with impaired mood and/or judgement, obtundation or coma, with or without symptoms related to cerebellar dysfunction (Table 1).

Brain atrophy is the most common CNS complication of heavy alcoholics and it may lead to dementia, even in young drinkers[14]. Although some discrepancy exists regarding the prevalence of cognitive impairment, its mildest forms have been documented in 50%-80% of alcoholics[15].

Ethanol provokes generalized brain shrinkage and affects both cerebral white matter and cortical grey matter. This is especially evident using magnetic resonance imaging. Both increased neuronal death and decreased neurogenesis account for such an effect. In general, the intensity of brain atrophy has been associated with the intensity of ethanol consumption. Ding *et al*[16] observed a relation between the amount of ethanol ingested and the area of the fluid-filled spaces in the brain. Harper[17] showed an increase in the pericerebral space in men drinking more than 8 drinks per day.

Neuronal death in alcoholics is related to the inflammatory status of these patients. Two transcription factors are important for neuronal survival: cAMP responsive element binding protein (CREB), which promotes neuronal survival and protects neurons from excitotoxicity, and nuclear factor κB (NFκB), which is proinflammatory. Activation of NFκB transcription is associated with increases in tumor necrosis factor (TNF)-α. Ethanol treatment is associated with higher DNA binding to NFκB and a reduced binding to CREB[18]. CREB regulates brain derived neurotrophic factor. It is reduced in alcoholic models, especially in areas of neurodegeneration[19]. Therefore, ethanol causes a decrease in trophic signals together with an increase in proinflammatory ones.

Neurogenesis takes place in at least two regions of the normal adult brain: the subventricular zone of the anterior lateral ventricles and the subgranular zone of the dentate gyrus. Ethanol directly inhibits neurogenesis, mainly affecting neural stem cell proliferation[20]; ethanol-induced inflammation enhances this effect[21].

Peripheral endotoxemia results in brain inflammation, probably due to increased cytokine secretion. These cytokines may be locally produced or they may be transported from serum to brain - especially TNF-α, interleukin (IL)-1β, IL-6 and interferon γ (IFNG)[22]. Within the brain, several toll-like receptors (TLRs) are located on glial cells, especially microglia and astrocytes. Both cells produce cytokines when stimulated by their corresponding ligands[23]. In ethanol-treated mice, within an hour of LPS injection there is a several-fold increase in proinflammatory cytokines in serum, liver, and brain. Whereas liver and serum levels returned to normal values within a day, brain cytokines lasted for long periods[24]. On the other hand, there is also evidence that ethanol is able to directly activate the (TLR)-4/type I IL-1 receptor on astrocytes, leading to recruitment of downstream signaling molecules and promoting cytokine secretion[25]. Ethanol also up-regulates inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2, causing inflammation and cell death within 3 h[26]. In addition, ethanol increases the brain expression of NADPH oxidase (NOX) that persists at least 8 d after abstinence[25]. Increases in NOX induce production of ROS, which play an outstanding role in brain degeneration[27], since they enhance TNF-α production by microglial cells[28].

Oxidative stress may also depend on other mechanisms. Alcoholics are prone to falls and traumatic brain injury[29]. Increased iron has been related to early edema

Table 1 Central nervous system alterations in alcoholic patients

Anatomo-clinical forms of chronic central nervous system damage	Brain cortical and subcortical atrophy Cerebellar degeneration Decreased blood flow Pellagra Wernicke-Korsakoff encephalopathy Marchiafava-Bignami disease Central pontine myelinolysis Increased prevalence of stroke Cerebral trauma
Clinical features of brain atrophy	May vary from frank dementia to subtle alterations Reversible with prolonged ethanol withdrawal
Underlying anatomic lesions of brain atrophy	Neuronal death Apoptosis Decreased neuronogenesis White matter alterations
Main mechanisms of brain atrophy	Effects of ethanol and lipopolysaccharide Cytokine (especially TNF-α) mediated neuroinflammation. Oxidative damage (mainly ethanol-mediated), iron excess Vitamins (antioxidants?) deficiency Protein deficiency and malnutrition? Excitotoxicity? Co-existing liver disease?

TNF: Tumor necrosis factor.

and late brain atrophy after intracerebral bleeding, a process which may be reversed by deferoxamine[30]. After bleeding, once hemoglobin is degraded, iron concentration increases several fold[31], and causes edema and brain lesion by oxidative stress. A single study has failed to find any relation between vermal atrophy and dentate iron concentrations - assessed by magnetic resonance - in alcoholics[32]. Recent reports suggest that antioxidants - including red wine - may improve cognitive dysfunction, at least in Alzheimer disease[33], reinforcing the possibility that oxidative damage plays a major role in cognitive impairment.

By these mechanisms, ethanol leads to brain atrophy, which recovers slowly after months of abstinence[34,35]. As in other organs affected by ethanol, cytokines play a pivotal role.

Muscle

In alcoholics two forms of myopathy have been described: acute rhabdomyolysis and chronic alcoholic myopathy. The latter is defined by muscle atrophy and weakness that affects predominantly proximal muscles and that is sometimes incapacitating. It may affect 40%-60% alcoholics, constituting the most frequent form of myopathy, at least in Western countries[36].

The main histologic feature is type Ⅱ fiber atrophy[36]. Fiber atrophy ensues from an imbalance between protein synthesis and protein breakdown, although apoptosis of muscle fibers has been also described[37]. Ethanol exerts a direct effect on protein synthesis, reducing translational efficiency by dephosphorylation of mTOR, a protein-kinase system that controls mRNA translation, an effect which may be more intense in men[38]. In addition, ethanol may alter insulin and insulin-like growth factor (IGF)-1 signaling, which may contribute to muscle atrophy given their important roles in growth and muscle metabolism. The effect on these factors may also lead to oxidative damage and mitochondrial dysfunction. Oxidative stress may also inhibit acetylcholinesterase, which may be further involved in myofiber atrophy[39]. High TNF-α levels increase protein catabolism *via* the ubiquitin/proteasome system and impair protein synthesis in skeletal and cardiac muscle[38]. TNF-α exerts its action by activating the NFκB pathway in muscle, an effect strongly potentiated by IFNG. Indeed, several cytokines such as IL-6, IFNG, and IL-1β modulate the effects of TNF-α. Leptin, an adipokine which regulates fat mass by decreasing food intake and increasing resting energy, also exerts a proinflammatory effect in alcoholics[40]. Leptin promotes Th-1 immune response, increases macrophage production of IL-6 and TNF-α, and activates neutrophils[41]. The role of proinflammatory cytokines on muscle atrophy is supported by the finding of an inverse association between TNF-α and IL-6 and muscle mass in elderly individuals[42]. In a study on 55 alcoholics without cirrhosis, TNF-α was inversely related to lean mass, especially in the legs. Despite the theoretical protective effect of IL-15 on muscle, we failed to find an association between decreased lean mass in alcoholics and decreased levels of IL-15. Higher values were observed in alcoholics than in controls[43]. In these alcoholic patients, as was shown in the study mentioned previously, IL-6 was inversely related with muscle mass (measured on the left arm). Regarding oxidative damage, Fernández-Sola *et al*[44] did not find a clear relation between alcoholic myopathy and lipid peroxidation. They found a 16% reduction in gluthathione peroxidase activity but a 13% increase in superoxide dismutase activity. However, in an experimental study with rats using the Lieber-deCarli model, we found that both protein deficiency and ethanol contributed to type Ⅱ muscle fiber atrophy. This, in turn, was associated with increased muscle MDA levels and muscle iron overload[45].

Other factors may be also involved. Ethanol, and especially acetaldehyde, may alter muscle membranes by forming protein adducts which leads to disturbed function[46]. Ethanol was associated with increased myostatin expression in cardiac myocytes of alcoholic patients with dilated alcoholic cardiomyopathy[47]. Similar results were shown in an experimental study on skeletal muscle in ethanol-treated HIV-1 transgenic rats[48]. Decreased vitamin D levels, a common finding in alcoholics, may also contribute to the development of alcoholic myopathy. Serum 1,25 (OH)2D3 levels were lower in ethanol-fed rats following the Lieber-de Carli model and were directly related to type Ⅱ muscle fiber area[49]. However, the exact role and mechanism of action of vitamin D in alcoholic myopathy are still areas of uncertainty.

Alcoholics also develop peripheral polyneuropathy, which may lead to muscle atrophy. In addition to nutri-

tional deficiency, a direct toxic effect of acetaldehyde has been proposed as an etiologic factor. However, there is evidence that ethanol-induced lipid peroxidation and defective antioxidant mechanisms within the sciatic nerve may be involved in the genesis of polyneuropathy[50]. Therefore, the association between myopathy and neuropathy in alcoholics might be due to direct effects on ethanol/acetaldehyde and ethanol-mediated oxidative stress on both organs.

Lung damage

Ethanol intake is associated with an increased incidence of acute respiratory distress syndrome (ARDS), irrespective of the cause (septic, trauma, or ARDS in critically ill patients)[51]. Alcoholism carries a relative risk of 3.7 (1.83-7.71)[52] for ARDS, and alcoholics need mechanical ventilation more frequently than non-alcoholics[53]. There is also an increased prevalence of pneumonia, mainly due to *Streptococcus pneumoniae*[54], *Klebsiella*, *Haemophilus*, *Campylobacter*, or *Legionella*. Pneumonia is the main cause of sepsis, the course of pneumonia is protracted, and the severity of pneumonia and pneumonia-associated sepsis is greater[55,56]. Although many of these effects may depend upon altered oropharyngeal flora and esophageal motility, it is also important to be aware of local conditions in the lungs[57]. Alcohol alters the normal alveolar barrier function, induces oxidative stress and alters the channel function of alveolar type 2 epithelial cells[58]. This causes dehydration of the epithelial lining fluid, mucus stasis, and inflammation, a constellation which favors the growth of bacteria. As in other organs, there is also up-regulation of NADPH oxidase, with generation of increased amounts of H_2O_2. Additionally, a marked decrease - up to 80% - of glutathione in the epithelial lining fluid has been observed in the lungs[59], severely decreasing antioxidant capacity. This pro-oxidant milieu leads to activation of alveolar macrophages which secrete increased amounts of cytokines such as IL-13 and transforming growth factor β-1 (TGF β-1)[60]. After an endotoxemia challenge there was a five-fold increase of TGF-β into the alveolar space of alcoholized rats, inducing edema[61]. Pulmonary macrophages show decreased defensive capacity[62,63], and recover after restoration of glutathione[64]. Moreover, in the face of a decreased GSH pool, T-lymphocytes become activated with a shift to a Th-2 phenotype, which contributes to an increased secretion of the aforementioned immunosuppressive cytokines[65]. Depleted antioxidant mechanisms may also inactivate α-1 proteinase inhibitor[66], an event which would favor the development of emphysema. In addition, ethanol may also inhibit GM-CSF expression in the lung of experimental animals. This factor, the expression of which is reduced in oxidative stress, is essential for activating and priming alveolar macrophage function. Its decreased expression leads to a blunted defensive response[67]. In the lung, previous alcohol exposure favors burn injury by upregulation of IL-18[68].

In addition to the impairment of the defense system within the lung, ethanol also affects circulating cells such as neutrophils, macrophages, monocytes and lymphocytes. However, there are some conflicting results regarding total lymphocyte count, lymphocyte subsets, and monocyte function in alcoholic experimental models and human studies.

In the systemic circulation, uptake of endotoxin and cytokine production takes place primarily in splenic and alveolar macrophages. In peripheral monocytes, acute ethanol down-regulates TNF-α production whether induced by IFNG, LPS, or by a combination of both factors[69,70]. Simultaneously, it enhances production of IL-10[71], an inhibitory cytokine; the down-regulation of TNF-α production by monocytes depends not only on IL-10, but also on a direct effect of ethanol[72]. When IL-10 level was compared among 25 chronic alcoholics and 20 non-alcoholics immediately after surgery, the former showed a four-fold increase in IL-10 than the latter, and a three-fold increased rate of wound infection and pneumonia, as well as a prolonged stay in the intensive care unit[73]. Neutrophils from patients with alcoholic hepatitis show a lower baseline phagocytic capacity, possibly due in part to an inhibitory effect of LPS[74].

In contrast with acute ethanol exposure, which decreases monocyte activation, in chronic alcoholics there is an enhanced cytokine production by these cells[75]. In a murine model of septic peritonitis, splenic $CD4^+$ population was normal in ethanol-fed animals, but TNF-α and IFNG production was markedly increased compared with water-fed septic controls. In that study, the proportion of NK cells was decreased in alcoholic septic animals[76]. It is important to note that monocytes also become directly stimulated by Gram-positive bacteria through TLR-2[77]. Both signaling pathways contribute to increased TNF production.

Discrepancy also exists regarding lymphocyte count and function. Laso *et al*[78] studied peripheral blood in patients with a first episode of alcoholic hepatitis with no other lesions on liver biopsy and found an increased number of $CD4^+$ and $CD8^+$ lymphocytes, NK cells and NKT cells. They also found an increase in cytotoxic activity which persisted after a 3-mo withdrawal period. On the contrary, Matos *et al*[79] reported a decreased number of all the lymphocyte subpopulations in alcoholics without advanced liver disease, and also in cirrhotics. A decreased lymphocyte count was described in adolescent alcoholics[80]. Others have found an increase in cytotoxic lymphocytes[81]. Ethanol also affects late differentiation of progenitor B cells[82].

In any case, alcoholics are prone to more infections such as postoperative infections[83], pneumonia and sepsis, and also to an increased severity of these infections[84,85]. The role of altered immunity and cytokine response was studied in alcoholics with sepsis, non-alcoholics with sepsis, alcoholics admitted for programmed withdrawal, and controls. No differences were found in the inflammatory response in these groups besides low G-CSF and C-reactive protein (CRP) levels in alcoholics with sepsis[86].

Table 2 Main factors involved in ethanol-associated osteopenia

Factors	Main mechanism(s) involved
Direct effect of ethanol	Direct effect on osteoblast function (oxidative damage). Possible effect on bone resorption (cytokines)
Liver disease	Decreased absorption of proteins, calcium, vitamin D, nutrients in general Altered hormonal profile (altered IGF-1, vitamin D, gonadal hormones)
Chronic pancreatitis	Altered absorption. Malnutrition
Malnutrition	Decreased osteoid synthesis. Decreased IGF-1 levels. Altered nutrient intake. Altered absorption. Increased cytokine levels?
Alcoholic hypogonadism	Altered trophic effect on bone and muscle
Alcoholic myopathy/ neuropathy	Altered trophic effect on bone (probably via Wnt β catenin pathway)
Iron excess (increased absorption)	Interference with osteoblast function
Zinc deficiency (malnutrition; alcohol?)	Possibly, defective protein synthesis
Cytokines (IL-6; TNF-α)	Possibly, increased bone resorption
Lifestyle	Trauma. Bone fractures. Impaired nutrient intake

IGF: Insulin-like growth factor; TNF: Tumor necrosis factor; IL: Interleukin.

Siggins *et al*[87] showed that ethanol markedly impaired the granulopoietic response to pulmonary *Streptococcus pneumoniae* infection by interrupting normal signaling of G-CSF on granulopoiesis and enhancing the inhibitory signaling pathway which induces cell cycling arrest. Von Dossow *et al*[88] found a decreased inflammatory response in alcoholics in the early phase of septic shock, with lower TNF-α, IL-6, IL-8 and IL-1b than non alcoholics.

Therefore, alcoholics show impaired defense against infections. Both local and systemic alterations lead to an increased prevalence of severe lung disease.

Chronic pancreatitis

Acute pancreatitis is characterized by a "cytokine storm", which is not related to ethanol itself, but to the acute pancreatic inflammation. Chronic pancreatitis is common in alcoholics, is partly responsible for nutritional impairment among these patients, and poses a risk for the development of pancreatic cancer.

Ethanol leads to progressive fibrosis of the pancreas due to its direct and indirect effects on pancreatic stellate cells. Cytokines such as TGF β-1 activate pancreatic stellate cells, which leads to their transformation into myofibroblasts. These cytokines are produced by macrophages infiltrating the pancreas in early stages of the necrotic-fibrotic process[89]. Activated myofibroblasts, epithelial ductal cells, macrophages, granulocytes, and lymphocytes secrete TGF β-1, TGF β-1 precursor peptide, and platelet-derived growth factor B. These cytokines increase fibrous tissue deposition. Yasuda *et al*[90] studied 109 patients and reported significantly increased serum TGF β-1 and fractalkine - a soluble monocyte chemoattractant - in the 52 patients with chronic alcoholic pancreatitis compared with the 57 non-alcoholic patients. Fractalkine levels increased in all these patients compared to 116 controls, so they may constitute a valuable diagnostic tool for early stage of the disease. It is of interest that LPS may not only directly stimulate hepatic stellate cells, but also pancreatic ones, leading to pancreatic fibrosis[91]. The effect of angiotensin II on pancreatic fibrosis *via* induction of TGF-β is also remarkable[92]. TNF-α is a main factor involved in the activation of pancreatic stellate cells, whereas IL-6 seems to exert an anti-apoptotic effect on these cells[93].

Bone

Alcoholism is associated with several bone alterations, summarized in Table 2. Decreased bone synthesis is the common underlying mechanism. Aseptic necrosis is an uncommon complication of uncertain pathogenesis, perhaps related to liver steatosis[94].

Osteopenia depends on the disrupted homeostasis between bone synthesis and bone resorption. Ethanol directly inhibits osteoblast function. In 77 alcoholics and 28 controls, marked differences in osteocalcin levels - a biochemical marker of bone synthesis - and reduced bone mineral density (BMD) at different parts of the skeleton were observed[95]. In an experimental model, Giuliani *et al*[96] showed a direct toxic effect of ethanol, and especially acetaldehyde, on osteoblastogenesis. Ethanol-mediated oxidative stress may be involved in the reduced osteoblast activity[97]. In close association with the inhibition of bone synthesis, ethanol may exert an inhibitory effect on bone growth. In two different sets of patients[98], we have observed that those alcoholics who began to drink before 18 years of age (self reported data) were shorter than the controls. These patients also showed Harris lines in their right tibiae, a condition attributed to episodes of stunted growth and described in experimental malnutrition and in severe diseases and/or malnutrition during childhood. Delayed bone fracture repair may be also related to the inhibitory effect of ethanol on bone synthesis[99]. It was recently shown that TNF-α, acting through TNF receptor 1, may be responsible, at least in part, for this inhibitory action[100]. Zinc is involved in bone synthesis, probably due to its effects on enzymes involved in DNA and RNA synthesis. Zinc supplementation increases bone growth in zinc-deficient growing animals or in premature children. Zinc deficiency has been described in alcoholics. The addition of zinc increases reduced BMD in alcoholic rats, but the clinical significance of this finding is uncertain[101]. It has been also hypothesized that certain trace elements may be beneficial due to their antioxidant activity, but no consistent results are available. Inconclusive results were also observed for several substances with antioxidative properties, which theoretically could counteract the ROS-mediated inhibition of osteoblast function.

In addition to the inhibition of osteoblast function, increased bone breakdown has been reported in heavy alcoholics[95,102]. Ethanol effects on bone resorption may

be also mediated by oxidative damage[103]. Osteoclasts are the cells involved in bone resorption. Differentiation and activation of osteoclasts involves binding of receptor activator of NFκB (RANK) ligand (RANK-L) to RANK, expressed in pre-osteoclast cell membranes. Osteoprotegerin (OPG) is a soluble decoy receptor which ultimately inhibits binding of RANK-L to RANK, therefore preventing bone resorption. Cytokines such as TNF-α, IL-1 and IL-6 activate RANK-L[104]. However, hormones involved in bone homeostasis, such as estrogens, vitamin D, corticosteroids and parathyroid hormone modulate osteoprotegerin[105]. In the absence of OPG, RANKL becomes activated by TNF-α, and bone resorption ensues. On the other hand, activation of the Wnt-beta catenin system blocks osteoclastogenesis by increasing the OPG/RANKL ratio. Therefore, TNF-α, IL-1 and IL-6 are also involved in bone alterations observed in alcoholics. The effects of other cytokines, such as IL-4, IL-8, IL-13, IL-15, IL-17 and IL-10 on ethanol-mediated bone alterations are less consistent.

In any case, cytokines seem to play a role in ethanol-mediated bone changes. Similarly to what happens in other organs, abstinence ameliorates these changes[106].

Cardiovascular system

Alcohol may affect the cardiovascular system in four ways: (1) Heavy ethanol consumption is associated with cardiomyopathy, usually of the dilated phenotype. This process is reversible with ethanol withdrawal or even reduction in the amount consumed[107]; (2) It is associated with arrhythmias, usually atrial fibrillation, especially when binge drinking. The onset of arrhythmias can precipitate myocardial infarction and sudden death[108]; (3) It seems to be a risk factor for hypertension[109]. However, in 1995 Gillman *et al*[110] studied a cohort of 139 young men and found the lowest systolic blood pressure among those consuming 1-3 drinks a day (up to 60 g of ethanol); and (4) It is probably related to increased atheromatosis, although considerable controversy exists regarding this point. In this section we will discuss how alcohol, inflammation, and oxidative stress are intertwined to affect cardiovascular health. Finally, we will review the conflicting evidence of alcohol as a cardiovascular risk factor.

Alcoholic cardiomyopathy: The effects of alcohol on cardiac muscle are dose-dependent. In a study that compared alcoholic patients with healthy controls, the former had a lower ejection fraction, a greater end-diastolic diameter, and a greater left ventricular mass[107]. Ultrastructural changes in cardiomyocytes similar to those seen in humans have been shown in Wistar rats exposed to a diet where alcohol constituted 36% of total caloric intake. These changes include myofibrillar disarray, large intracellular vacuoles, mitochondrial swelling, lipofuscin granules, and lipid infiltration[111].

Metabolic changes have also been described, such as a decrease in respiratory enzyme and lactate dehydrogenase activity, a decrease in beta oxidation of fatty acids, and an increase in alcohol dehydrogenase activity, which may lead to acetaldehyde accumulation and impaired protein synthesis. However, some studies have shown that ventricular contractile and non-contractile protein synthesis inhibition may be directly mediated by alcohol. Additionally, the oxidation of acetaldehyde gives rise to ROS that are responsible for lipid peroxidation and organelle damage through the oxidation of amino acid residues. Possibly, autophagia is also induced by acetaldehyde. All these effects eventually lead to myocardial injury[112].

Atrial fibrillation: Heavy alcohol intake is a risk factor for the development of arrhythmias such as atrial fibrillation (AF). P wave signal averaging, which is a predictor of paroxysmal AF, has been found to be prolonged in healthy subjects exposed to alcohol and in sober patients who have been diagnosed with paroxysmal AF associated with previous alcohol intake[113]. Once again, ROS play a major role in the pathogenesis of AF in alcoholic patients. Reactive oxidative metabolites such as reduced glutathione and cysteine are associated with permanent AF. Interestingly, an association was not found between AF and elevated inflammatory markers such as C-reactive protein[114]. Lin *et al*[115] studied rabbit left atrium and pulmonary vein specimens exposed to hydrogen peroxide. They showed that oxidative stress induced an increase in contractile force and a decrease in action potential length which led to the onset of atrial fibrillation. These events are inhibited by free radical scavengers such as ascorbic acid or *N*-acetylcysteine, which has been used in clinical trials for the prevention of AF[116]. The information from these studies can be extrapolated to the oxidative stress that occurs in alcoholics.

Mechanical changes in myofibril activity have also been reported in association with oxidative stress. In particular, contractile dysfunction can be secondary to oxidative modifications of myofibrillar creatine kinase (MM-CK) by nitrate species formed by the reaction of NO with superoxide anions. Mihm *et al*[117] have shown that AF patients have decreased MM-CK maximum velocity and changes in myosin isoform gene expression. These patients tend to have a low velocity form of myosin (β-myosin). Additionally, the extent of nitration of MM-CK is inversely correlated with its maximum velocity and directly correlated with myosin isoform switching. These findings highlight the vulnerability of myofibrils to oxidative stress.

Hypertension: Epidemiological surveys show a J-shaped relationship between hypertension and alcohol consumption. The threshold for increased risk is variable: the intake of 3 to 5 drinks per day was associated with increased blood pressure in a study performed in 1977[118]. In an Australian study, hypertension was present in 10.4% of subjects who consumed 3 glasses of beer per day, whereas the prevalence of hypertension among teetotalers was 2.6%[119]. In an experimental study in alcoholized rats it was found that hypertension was related to an early

increase in catecholamine secretion, followed by a late increase in angiotensin Ⅱ[120].

Atherosclerosis: Angiotensin Ⅱ is an important mediator of atherosclerosis. Atherosclerosis is an inflammatory process of the vessel wall in which chemokines play a major role. These molecules recruit cells into the subendothelial space, leading to the formation of atherosclerotic plaques and vascular inflammation. Atherosclerotic plaques have an inflammatory infiltrate with cells that secrete TNF-α and IFNG. This infiltrate contains monocytes, macrophages, lipid-laden macrophages (foam cells) and T lymphocytes including T8 cytotoxic lymphocytes (containing proapoptotic perforin and Fas ligand), and T4 lymphocytes of the Th-1 phenotype[121]. There is also a high proportion (30%) of γδ lymphocytes and some Th-2 lymphocytes.

Vulnerable plaques have a large soft lipid core and a fibrous cap formed by collagen and vascular smooth muscle cells that are lined by endothelium. The proportion of macrophages is increased in vulnerable plaques. They are attracted to the plaques by an increased expression of endothelial cell adhesion molecules such as P-selectin, intercellular adhesion molecule 1 (ICAM-1), endothelial-leukocyte adhesion molecule-1, vascular cell adhesion molecule-1 (VCAM-1), and E- selectin[122]. These are upregulated by several risk factors (diabetes, oxidized low-density lipoproteins or LDL, smoking, and hypertension). Soluble mediators with a potent monocyte chemoattractant capacity, especially chemokines such as monocyte chemoattractant protein (MCP)-1, play a crucial role in the genesis and evolution of the plaque[123]. Macrophages infiltrating the plaque are of diverse phenotype and are able to promote vascular smooth muscle cell apoptosis. This process is mediated by NO and Fas/Fas ligand interaction and is facilitated by TNF-α[122]. Oxidized LDL, advanced glycosylation end products, angiotensin Ⅱ, and endothelin activate macrophages. In addition, T-helper ($CD4^+$) lymphocytes recognize oxidized LDL as an antigen. They are also able to activate macrophages by binding to CD40, a macrophage surface protein. Activated macrophages promote tissue damage, angiogenesis, inflammation, coagulation, and fibrinolysis, which may lead to plaque rupture and thrombus formation. Alternatively, activated macrophages may also play a role: IL-10 knockout mice are more susceptible to atherosclerosis. However, the role of other Th-2 cytokines, such as IL-4, is less known[124].

Impaired endothelial repair may also affect the development of atherosclerotic lesions. This reparative process is largely dependent upon the presence and activity of fibrocytes and endothelial progenitor cells which migrate to the injured sites and restore the integrity of the vascular endothelium. Stromal cell-derived factor 1 (SDF-1) and vascular endothelial growth factor promote differentiation and homing of these cells in injured sites.

Ethanol consumption can interfere with these mechanisms at different levels. In an experimental rat model, the intake of a high dose of ethanol was associated with considerable plaque formation. Low doses of ethanol were associated with increased secretion of SDF-1 by fibroblasts while high ethanol doses led to a reduced secretion. The number of circulating fibrocytes was significantly lower in the high ethanol dose group when compared with controls, although a reduction in their number was also observed in rats treated with low doses of ethanol[125]. Ethanol leads to increased iNOS expression, which may exert positive effects on myocardial blood flow. Ethanol also activates transient receptor potential vanilloid 1 channels on perivascular sensory nerve terminals, which release calcitonine gene-related peptide, a potent vasodilator[126]. Moreover, moderate alcohol use is associated with a favorable serum lipid profile (increased high density lipoprotein or HDL, cholesterol, and lipoprotein A1 levels), hemostatic factors (decreased fibrinogen), and adipokines (increased adiponectin)[127]. On the other hand, the effect of ethanol on several cytokines, chemokines, oxidative metabolism, and inflammatory cells makes it theoretically possible that alcohol or its metabolites play paramount roles in ongoing atherosclerosis and vascular inflammation. Ethanol metabolism is associated with oxidative damage, and oxidized LDL is a major factor contributing to atherosclerosis. In an experimental study on rats, ethanol promoted rat aortic vascular smooth muscle cell proliferation, accompanied by increased homocysteine levels and oxidized LDL. These findings support the pro-atherogenic effect of ethanol[128].

Alcoholic beverages usually contain several antioxidants which counteract the deleterious effect of excessive oxidation. In a study performed on 67 volunteers, individuals received 30 g of ethanol in the form of red wine, 30 g of de-alcoholized red wine, and 30 g of alcohol in the form of gin for 4 wk. The antioxidants contained in the alcoholic beverage reduced serum ICAM-1, E-selectin, and IL-6, and inhibited the expression of lymphocyte function-associated antigen and CCR2 receptor, which suggests a protective effect of antioxidants. However, in contrast with the deleterious effects of high doses of ethanol, data relative to the effect of lower doses are conflicting: ethanol added to polyphenols (in the form of red wine) reduced IL-16, MCP-1, CD40 and CD40 ligand, and VCAM-1[129].

Alcoholism as a cardiovascular risk factor: Many studies show that light to moderate drinking is associated with a lower rate of myocardial infarction[130] and stroke[131,132]. Although it has been argued that some bias could be present (self reported ethanol consumption, the inclusion of light to moderate drinkers with healthy lifestyle behaviors, among other factors), these studies include more than 107000 individuals and they provide quite robust evidence. Many other studies show a J-shaped curve that illustrates the association between cardiovascular disease or mortality and alcohol intake. However, there is controversy regarding the amount of ethanol that could

offer cardiovascular protection, since heavy drinkers are at increased cardiovascular risk.

The controversy surrounding alcohol as a cardiovascular risk factor extends to animal models. Several models of the cardioprotective effects of a moderate intake of alcohol have been published. In a study where rats were exposed to drinking water with 1% ethanol (equivalent to 18 g/d of alcohol in an adult male) harmful effects were not found[133], but instead beneficial effects such as an improved lipid profile and lower pulmonary arterial pressure were observed. In this study there were no changes in systemic arterial pressure. The beneficial effects of moderate alcohol intake were recently demonstrated by Lassaletta *et al*[134] in an experimental model of chronic myocardial ischemia in swine. In addition to improved vasorelaxation, animals supplemented with alcohol had increased arteriolar density and consequently improved myocardial perfusion. Notch 2 receptor and Notch ligands Jagged 1 and 2 (involved in vascular repair), were increased in the animals that received alcohol. Antiangiogenic proteins such as endostatin and IL-8 were decreased in this group, but no significant improvements were seen in hemodynamic variables.

CONCLUSION

This review illustrates the complexity of the interplay between ethanol, oxidative damage, cytokines and some organic complications seen in alcoholics. In addition to the direct effects of ethanol, cytokine production (which is ultimately dependent on ethanol) seems to be involved in many of the manifestations of these patients, including mortality at an early adult age. As briefly reviewed, there is a considerable body of knowledge about the systemic inflammatory reaction in alcoholics but there are many questions that remain unanswered. For instance, further studies are needed to elucidate the atherogenic effect of alcohol, the exact role of vitamin D on the development of alcoholic myopathy, the possible relationship between ethanol intake and emphysema, the therapeutic role of antioxidants, among others. In any case, the underlying proinflammatory status should be considered in the management of these patients, in addition to the effects of other unhealthy lifestyle behaviors that may be present in alcoholics such as protein-calorie malnutrition, viral infections and drug use. These factors complicate the correct diagnosis and management of the multiple organic complications presented by alcoholics who seek medical attention.

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