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Alcoholic Cardiomyopathy: a summary of current knowledge and possible future directions

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Abstract

Introduction and purpose:

Ethanol is still one of the most frequently consumed drugs worldwide and is a strong risk factor for more than 60 illnesses including alcoholic cardiomyopathy which is a specific

heart muscle disease caused by long-term excessive alcohol consumption. The review aims to gather available data and summarize it to give better understanding of the disease, to help select patients with the condition to implement proper treatment, and to present possible future directions as the incidence of the disease is projected to persist in the future.

Brief description of the state of knowledge:

Alcoholic cardiomyopathy (ACM) is characterized by dilation, increased mass of the left ventricle, and reduced ejection fraction leading to end-stage heart failure. It is caused by ethanol's direct toxicity on myocytes disturbing many different metabolic pathways. The result is a decrease in both systolic and diastolic function of the heart. The ACM development depends on factors such as genetics, gender, dietary factors and the dosage of ethanol consumption. The goal of the treatment is total alcohol abstinence, but the reduction of ethanol intake may also be beneficial. Patients should obtain a complete pharmacological treatment for heart failure.

Summary:

Ethanol overconsumption remains an unresolved problem, with the incidence of ACM projected to persist in the future, especially among patients with alcohol use disorder (AUD). Efforts for prevention, early detection, and effective treatment of ACM need to be established. A primary focus should be on treating AUD because it is the most effective way to halt the progression of the disease. Further research should focus on both asymptomatic and symptomatic patients with AUD to better define clinical manifestations, diagnostic approaches, and the most effective treatments for ACM.

Key words: alcoholic cardiomyopathy; ethanol; alcohol; heart; heart failure

Introduction

'Ethanol', commonly referred to as 'alcohol' is one of the most frequently consumed drugs worldwide [1]. There are many different factors that have a significant impact on alcohol use among society including age, gender, nationality, health status, economic issues, lifestyle, culture and religion. According to the World Health Organization Global Status Record on Alcohol and Health 2018, approximately 57% (3.1 billion people) of the global population had been abstinent in 2017, whereas 2.3 billion people are current alcohol drinkers [2]. The prevalence of alcohol consumption is still rising due to increasingly easier access, ineffective consumption policies, and wider distribution, especially of unrecorded alcohol, which is sold outside government control and not counted in official statistics [2,3].

The 2020 U.S. Dietary Guidelines Advice on Alcohol provide a definition of a standard drink-equivalents with their standard alcohol by volume (ABV) percentage: 1.5 ounces of 80-proof distilled spirits (40% ABV), 5 ounces of wine (12% ABV), and 12 ounces of regular beer (5% ABV) [4]. The National Institute on Alcohol Abuse and Alcoholism distinguishes three

drinking levels depending on the number of drinks consumed per specific time period. Moderate drinking is limited by intake to 2 drinks or less for men and 1 drink or less for women daily. Binge drinking is defined as the consumption of alcohol that elevates blood alcohol concentration (BAC) up to 0.08%, corresponding to 5 or more drinks for men and 4 or more drinks for women in about 2 hours. Consuming 5 or more drinks for men and 4 or more for women on any day is called heavy drinking. The same applies for 15 drinks or more for men and 8 drinks or more for women per week [4].

Alcohol consumption is a strong risk factor for more than 60 acute and chronic illnesses [5]. The total number of deaths worldwide caused by alcohol use was estimated at 3 million (5.3% of all deaths) in 2016 and also resulted in 132.6 million disability-adjusted life years (DALYs) that year. Injuries corresponded to 28.7% of deaths, 23.3% were due to digestive diseases and 19% due to cardiovascular diseases, including alcoholic cardiomyopathy (ACM), which this review focuses on [2].

Alcohol use disorder (AUD), commonly known as alcohol addiction, is a chronic illness defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as "a problematic pattern of alcohol use leading to clinically significant impairment or distress," and is diagnosed as mild, moderate, or severe based on the number of symptoms [6]. Approximately 4% of the adult population was affected by AUD in 2020 [7]. The presence of AUD significantly worsens the long-term effects caused by alcohol use due to larger amounts of alcohol intake as a result of developing tolerance and lack of control over the amount of alcohol consumed. People with AUD are more likely to develop critical and irreversible conditions such as liver cirrhosis, which in turn, causes homeostasis breakdown and further damage to organs, including the heart muscle, giving rise to cirrhotic cardiomyopathy, which is a separate condition from ACM with different pathophysiology [8].

Aim

The review aims to gather available data and summarize it to give better understanding of the disease, to help select patients with the condition to implement proper treatment as fast as possible, and to present possible future directions as the incidence of the disease is projected to persist in the future.

Methods

The research involved freely accessible databases such as PubMed, the National Library of Medicine, Google Scholar or Coachrane using keywords such as ‘alcoholic cardiomyopathy’, ‘alcohol and heart’, ‘idiopathic cardiomyopathy’ , ‘heart failure’. Articles were primarily selected based on their title, and subsequently their abstract. The study required exploring ethanol’s effects not only on the heart muscle but on the whole cardiovascular system.

Review

Metabolism

Ethyl alcohol is a highly reactive agent that has specific effects on various organs depending on the biochemical and physical characteristics of both the target tissue and ethanol itself. The low molecular mass, high bioavailability, and distribution capacity of ethanol facilitate its interaction with target cells. Different tissues are more or less susceptible to the influence of the substance. The toxicity is most pronounced in organs that are the site of its metabolism, such as the liver, pancreas and digestive tract, but also in organs that are extremely excitable, including the brain and the heart [9,10,11].

In order to fully understand the pathological mechanisms taking place in the heart muscle leading to ACM, comprehension of the underlying ethanol metabolism pathways is crucial. The first phase of metabolism includes oxidation of ethanol molecule producing acetaldehyde, which, as an active metabolite, also has a toxic effect on organs. The reaction is catalyzed by cytosolic alcohol dehydrogenase (ADH), an enzyme that is mainly expressed in hepatocytes but also in the gastrointestinal tract, lungs and kidneys. The microsomal pathway, which corresponds to 10% of ethanol metabolism in the oxidative phase, includes the contribution of the cytochrome P450 enzyme complex, with CYP2E1 being predominant [12]. This pathway takes place in the endoplasmic reticulum of hepatocytes, but CYP2E1 has also been found in neurons and glial cells in some parts of the brain [13]. This phase of metabolism produces reactive oxygen species (ROS) which exert toxic effects, burdening the functioning of the organs due to the oxidative stress as well. The acetaldehyde produced in these two pathways is subsequently processed to acetate by aldehyde dehydrogenase (ALDH). High consumption of oxygen molecules needed for the reactions to continuously occur leads to local hypoxia in the liver. Anaerobic conditions of the liver activate the hypoxia-inducible factor 1α (HIF1α) ,which increases fibrosis by multiple mechanisms including transcription of pro-inflammatory and pro-apoptotic genes [14,15].

Effects and Toxicity

Ethanol's toxicity is clearly visible in almost all organs in the human body. It is not only alcohol that has its direct damaging effect but also the metabolites created in the metabolic pathways, especially acetaldehyde and ROS. Ethanol's toxicity can be divided into acute and chronic toxicity.

The acute effects depend on the amount of alcohol ingested, the time, and the speed of absorption and detoxification. Acute toxicity is mainly associated with drinking an excessive amount in a short period of time, resulting in a rapid increase of BAC. The initial symptoms commence at a BAC of approximately 0.2g/L and these include decreased motor coordination, delayed reaction time, impaired judgment along with euphoria. As the BAC increases, dysphoria, coma, and respiratory depression may occur, leading to death in extreme cases. While acute toxicity is not the main focus of this review, chronic toxicity and its consequences will be taken more profoundly into consideration, especially paying attention to cardio and hepatotoxicity, which have a negative impact on each other, creating a vicious cycle.

Cardiovascular Disorders

According to most recent literature, alcohol consumption is associated with a higher incidence of many cardiovascular diseases such as ischemic heart disease (IHD), hypertension (HT), atrial fibrillation (AF), atherosclerosis, and cardiomyopathies [2,16]. There are various mechanisms involved in heart damage. Both ethanol's direct toxicity and acetaldehyde accumulation engage the recruitment of pro-inflammatory cytokines and ROS, resulting in mitochondrial dysfunction and structural damage of numerous proteins of the heart muscle. Such reaction is responsible for myocyte decreased performance, resulting in contractility dysfunction which can lead to cardiomyopathy and cardiac failure [17]. Induction of arrhythmias, especially AF, heart muscle motion dysfunction, induction of hypertension, enhancement of platelet aggregation, and activation of the clotting cascade are effects of ethanol that create conditions favorable for blood clot formation and occurrence of cerebral stroke [18,19]. Acute consumption of large amounts of ethanol has been proven to induce myocardial inflammation detectable by the rise in serum troponin concentration, supraventricular, and ventricular tachyarrhythmias [20,21].

Alcoholic Cardiomyopathy - Definition and Natural Course

Alcoholic cardiomyopathy was first described under various names such as “Tubingen Wine Heart" in 1877 or “Munich Beer Heart" in 1884 [22]. ACM is described as a specific heart muscle disease prevalent in individuals with long-term heavy alcohol consumption - "heavy drinkers". It is characterized by dilation of LV, increased LV mass, normal or reduced LV wall thickness, and reduced ejection fraction (EF). It may involve one or both chambers; however, the LV is much more often and more severely involved [23]. ACM is a subtype of dilated cardiomyopathy (DCM), which is principally caused by heart ischemia; however, excessive ethanol consumption is one of the main causes of non-ischemic DCM corresponding to one-third of cases, especially in Western countries [24,25]. The absence of specific biomarkers or other criteria for ACM makes it a diagnosis of exclusion by ruling out heart diseases having similar clinical manifestation [23].

The natural course of ACM is similar to that of idiopathic DCM. The end-stage is characterized by ventricle dilation and its dysfunction, but the progression of the disease is gradual, mostly asymptomatic at the beginning, and the clinical manifestations appear when the damage is significant and irreversible. The gradual course of the disease is caused by the fact that there must be a history of excessive ethanol consumption for more than 10 years after which subclinical HF follows [22].

When ventricle hypertrophy, dilation, and finally dysfunction appear, the clinical symptoms occur, the same as those in HF. It is unknown what appears to be the earliest manifestation of ACM. According to Kupari et al., diastolic dysfunction is the earliest manifestation of ACM. Due to some research, approximately 30% of patients with AUD developed diastolic dysfunction with no evident systolic dysfunction nor LV hypertrophy [26,27]. On the other hand, Lazarević et al. found ventricular dilation as a first manifestation with diastolic dysfunction and hypertrophy arising later in patients with AUD in echocardiography [28]. It is still unanswered what is the first clinical manifestation of ACM due to insufficient data and research. It could be the area of further investigation as the knowledge of that could fasten the diagnosis, earlier select patients at risk of irreversible damage and, thus, implement alcohol abstinence as fast as possible as the most effective way to stop further damage to heart muscle.

When myocyte destruction continues, the symptoms related to reduction of cardiac output follow, and these include exertional dyspnea and orthopnea, episodes of fainting, fatigue,

mental fusion and chest pain as in LV HF. In the advanced stage of the ACM, the congestive symptoms develop due to right ventricle (RV) failure such as jugular veins distention, third and/or fourth tone, and a systolic murmur along with peripheral edema [22,29].

In any stage of ACM, arrhythmias may occur most often in the form of AF but others may appear as well, such as ventricular tachycardia which is associated with worse complications and prognosis. In one study, the independent predictors of death or heart transplantation in ACM have been atrial fibrillation (OR: 9.7; 95% CI: 2.56 to 36.79; p ¼ 0.001); QRS duration >120 s (OR: 7.2; 95% CI: 2.02 to 26; p ¼ 0.002), and lack of beta-blocker therapy (OR: 4.4; 95% CI: 1.35 to 14.49; p ¼ 0.014), and these have been related to worse outcome. The arrhythmias are more frequent during binge drinking or alcohol withdrawal syndrome, probably due to electrolyte imbalance, vitamins deficiency, and increased levels of catecholamines - factors triggering arrhythmias [30].

Along with HF, other organs such as liver, central and peripheral nervous system, skeletal muscles, and pancreas are also affected by ethanol's toxicity not only by impairing their vital functions in the body but also by promoting carcinogenesis leading to increased risk of many cancers. Particular attention should be paid to alcoholic liver disease. Due to the similarity and overlapping of heart and liver failure symptoms, liver cirrhosis may mask ACM symptoms, thus, delaying its diagnosis.

Genetics

Genetic variation may play an important role in determining the susceptibility of an individual to ethanol-related myocardial toxicity. Genetic polymorphism primarily concerns certain myocardial proteins or enzymes participating in alcohol metabolism. So far, there has been only little scientific research concerning the genetic origin of ACM. Kajander et al. researched genes coding components for the renin-angiotensin-aldosterone system (RAAS) in relation to myocardial dimensions and weight. Myocardial biopsies from male victims of sudden cardiac death were evaluated for RAAS gene variants (e.g., insertion or deletion polymorphisms of angiotensin-converting enzyme and the cytosine allele of -344 cytosine/thymidine polymorphism of aldosterone synthase). Daily lifetime alcohol dose was linked with increased myocardial weight and right ventricular size, but there were no significant associations with the above RAAS genetic polymorphism [23,31]. In another study, Teragaki et al. investigated the occurrence of mitochondrial deoxyribonucleic acid (mtDNA) mutations in myocardial biopsies from the men diagnosed with DCM and AUD. Even though some mutations were

found, it is not certain if these were originally the cause of AUD or arose as a result of mtDNA repair in response to oxidative stress caused by heavy drinking [32].

The most promising research involves the study of Ware et al. where 9 genes associated with DCM development were examined in a cohort study of ACM (n=141), DCM (n=716), and control (n-445). Several of these genes encode sarcomeric proteins with truncated variants in the titin (TTNtv) gene being associated with 20% to 25% of familial DCM cases. The variants were more frequently detected in ACM subjects than in healthy controls (13.5% vs. 2.9%, respectively) but similar to that in the DCM cohort (19.4%). The TTNtv genes constituted the majority of variants in ACM patients (9.9%) [33,34]. This study shows that the presence of the TTNtv gene may predispose and increase vulnerability to ACM. Future studies should further explore the role of TTNtv and other genes in determining the influence of genetic predisposition on ACM prevalence.

Gender Differences in ACM

There is an evident gender difference regarding ethanol's toxicity on the heart muscle. In general, women are more susceptible to the toxic effects of ethanol than men with the same level of lifetime ethanol consumption [35]. In one study, alcoholic women diagnosed with ACM reported a significantly lower daily dose of ethanol ($p = 0.002$), a shorter duration of alcoholism ($p = 0.017$), and a lower total lifetime dose of ethanol consumption ($p = 0.001$), and had a lower New York Heart Association functional class than men diagnosed with ACM. Women showed almost the same prevalence of cardiomyopathy as men, despite having consumed far less ethanol. This supports a greater female susceptibility to alcohol-induced cardiac damage [36,37].

Even though such correlation is clearly visible in human studies, experimental data on rats show quite different outcomes. Piano et al. examined the effects of long-term ethanol consumption in adult males and females sham-operated and ovariectomized rats. All groups treated with ethanol demonstrated echocardiographic evidence of ACM with more significant ethanol-induced differences found in the male group in comparison to both female groups. Such differences included decreased muscle contractility and decreased posterior and septal wall thickness [38]. Fogle et al. examined structural changes and protein expression in the myocardium in male and female rats after 18 weeks of alcohol consumption. Apart from a decrease in end-diastolic dimension, no other changes were found in echocardiography

between control and alcohol-treated female groups. On the contrary, in the male ethanol group, decreases were found in LV mass, stroke volume, cardiac output, and end-diastolic dimension as well compared to the control group [39].

Nutrition and Dietary Factors

Nutritional deficiency was originally thought to be the main cause of ACM development, especially thiamine (vitamin B1) deficiency, as it is a common situation present in patients with AUD [40]. In addition, electrolyte imbalance (Na, K, Mg, Ca, P) caused by excessive drinking may play an important role in dysfunction of the ion channels, thus disturbing both the systolic and diastolic function of the myocytes. However, when AUD patients received thiamine or other nutritional supplements, structural and functional changes did not disappear [23].

Another hypothesis was put forward that malnutrition, including protein and caloric deficit, frequently related to chronic alcohol overconsumption, was the origin of ACM [41]. In experimental studies, Reinke et al. used electron paramagnetic resonance spectroscopy to detect increased free radical generation in the hearts of female rats (140-150g) fed a high fat ethanol-containing diet compared to those fed a control or low fat ethanol-containing diet. This study suggested that the presence of a moderate-to-high amount of dietary fat increased the creation of free radicals over a low-fat ethanol-containing diet, thus denying the caloric deficit as the origin of ACM [42]. Even though ACM may develop in absence of protein or caloric malnutrition, these can worsen the natural course of the ACM and should be avoided.

The Dose-Related Effect of Ethanol

ACM is considered to be the result of alcohol dosage and individual predisposition [43]. It is an accumulated effect that develops when a person consumes more than 7 kg of ethanol per kg of body weight in men (approximately 60 drinks per month), and 5 kg of ethanol per kg of body in women (approximately 43 drinks per month) in their lifetimes [44]. This, of course, depends on a person's susceptibility, making a wide range of doses that can contribute to myocyte damage. In this review moderate consumption, binge-drinking, and low-dose ethanol consumption will be taken into consideration.

<u>Low-Dose Ethanol Consumption</u>

There is still an ongoing discussion over harmful and beneficial effects of alcohol consumption. Low-dose ethanol consumption which, is a daily consumption of up to one standard drink for women and two for men, is proved to prevent coronary heart disease (CHD), HF, and global mortality as illustrated by a "J-shape" or "U-shape" curve of effect. The J-shaped curve describes a relationship where the relative risk (RR) decreases at low-to-moderate alcohol intake, but eventually rises above the level of the reference population of abstainers at higher doses. Meanwhile, the U-shaped curve describes a relationship where the RR decreases at low-to-moderate alcohol intake but does not rise above the level of the reference population of abstainers. (Figure 1.) [30].

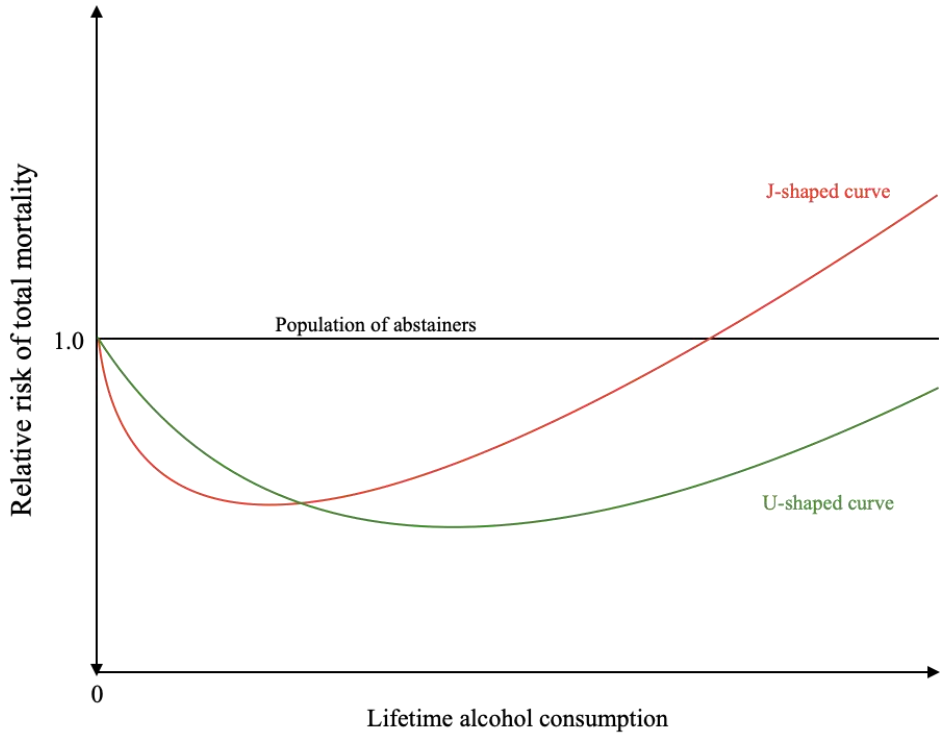

Figure 1. A sketch presenting the relationship between total lifetime alcohol consumption and relative risk of total mortality, coronary heart disease, and heart failure in the form of J-shaped curve and U-shaped curve.

Many studies have reported these curves for the relationship between alcohol intake and total mortality, with reduced mortality associated with low-to-moderate intake, relative to abstention [45,46]. However, it is not recommended to consume alcohol as a cardiovascular prophylactic, especially in non-drinkers, as even low-to-moderate alcohol dosage can induce myocardial damage after reaching the threshold level of accumulated lifetime dose of ethanol required to develop ACM. Moreover, even low-to-moderate doses of alcohol are not

beneficial for the general population because it increases mortality resulting from other causes such as hepatic cirrhosis, injuries and some cancers [30].

Moderate Consumption of Ethanol

Moderate alcohol consumption, which is 20-60 g per day in men (equivalent to 1.5-4 standard drinks) and 10-40 g per day in women (equivalent to 1-3 standard drinks), is not associated with high cardiotoxicity, but it does not mean that it exerts zero damage, especially to other organs [30]. According to Fernández-Solà et al., moderate alcohol consumption is a risk factor for ACM development only if this pattern continues for more than 10 years. Although high doses of ethanol obviously increase the risk of HF, low-to-moderate doses are associated with lower risk of HF development relative to abstinence [47]. In one study where abstainers and moderate drinkers (1-60 drinks per month) were compared, no differences were observed in health-status measures, HF hospitalizations, or mortality at a baseline and at a 1 year [48]. In addition, moderate alcohol consumption increases high-density lipoprotein (HDL) cholesterol serum levels, which are speculated to have a protective effect against congestive HF development [49].

Binge Drinking

Binge drinking constitutes one of the most dangerous drinking patterns as it can induce acute myocardial stress resulting in temporary LV EF depression. In one study, acute alcohol administration in a rat model significantly raised plasma cardiac troponin T level after 2.5 h, which is suggestive of acute myocardial damage [50]. In another study, a high prevalence of left ventricular dysfunction was found among asymptomatic persons who binge drink, in opposition to modest associations between alcohol consumption and subclinical abnormalities of LV structure and function in persons who consume significantly less alcohol [49]. Moreover, binge drinking is a potential inducer of some arrhythmias, especially AF, which may initiate due to the direct toxicity of ethanol or due to coexisting effects of alcohol abuse such as hypertension, which itself damages the myocardium [21]. Even if a person has already developed ACM, binge drinking may worsen the natural course of the disease by implementing an additional negative inotropic effect on the already reduced LV EF; thus, binge drinking should be strictly prohibited in ACM patients.

Cellular Pathophysiology

Ethanol has a vast array of disastrous effects on the myocardium because it exerts its effect at multiple sites including receptors, membranes, myocardial proteins, deoxyribonucleic acid (DNA) and mitochondria. This is due to its high reactivity and a relatively small molecular size. Its easy permeability through biological membranes allows ethanol not only to achieve membrane proteins and receptors but also endocellular structures and proteins [25,51]. Ethanol disturbs the functioning of many ion channels such as L-type Ca^{2+} channel, Na^{+}/K^{+} ATPase channel, Na^{+}/Ca^{2+} exchanger, and Na^{+} and K^{+} channel currents [36,57,58]. Regarding decreased heart contractile function in ACM, ethanol disturbs the ryanodine Ca^{2+} release, the sarcomere Ca^{2+} sensitivity, the excitation-contraction coupling, myofibrillar structure, and protein expression [52,53]. The mitochondrion is another important target for ethanol where it alters its function and structure, including respiratory complex activities, and also induces mitochondrial-dependent oxidative damage and apoptosis [12,23]. The structure of myocyte cytoskeleton and intercellular connections such as connexin channels and desmosomal contacts are also affected by ethanol's toxicity, resulting in structural cell instability and worsened intercellular signaling [54,55]. Irreversible tissue damage of the heart muscle promotes ineffective repair mechanisms, leading to progressive fibrosis, which further disturbs both the systolic and diastolic function of the myocardium [56,57]. The effects of these multiple site disturbances are additive, resulting in much greater overall damage.

Ethanol and Calcium Homeostasis

Calcium is essential for generating appropriate contraction of myocytes by initiating cross-bridge cycling and regulating myocardial force. Ca^{2+} regulation depends on multiple factors such as the abundance and functioning of sarcolemmal L-type Ca^{2+} channels, sarcolemmal Na^{+}/Ca^{2+} exchanger, and the sarcoplasmic reticulum Ca^{2+} storage and release. Myocytes are highly excitable cells, making them very susceptible to alcohol's toxicity. Ethanol can easily disrupt the excitation-contraction mechanism by modifying sarcolemmal membrane L-type Ca^{2+} channels leading to a decrease in electrically induced Ca^{2+} transients and generating insufficient contractile force [58]. Another hypothesis relates to decreased myofilament sensitivity to Ca^{2+} despite the normal level of calcium present in the cytosol. This can be supported by a study where Piano et al. compared the effect of inotropic interventions (isoproterenol and pimobendan) and the relation between Ca2+ and isometric twitch force in

atrial muscle from control rats and rats that had consumed alcohol for 2 months. As a result, it was indicated that 2 months of alcohol consumption is associated with decreases in myofilament Ca2+ sensitivity and altered responsiveness to different inotropic agents [59]. As an adaptive process, in order to maintain appropriate heart muscle contraction, chronic alcohol misuse induces up-regulation of L-type Ca^{2+} channels, whose activity decreases when ACM is present [60].

Oxidative Stress and Mitochondrial Disturbances

Long-term alcohol consumption is associated with the development of oxidative stress due to increased generation of free radicals. The production of ethanol-induced ROS has multiple sources, with a significant portion stemming from ethanol metabolism that occurs in mitochondria. Ethanol causes an increase in the flux of reducing equivalents into the electron transport chain due to an increase in nicotinamide adenine dinucleotide (NAD^{+}) production. Another source may be an increase in cytochrome P450 2E1 and alcohol dehydrogenase metabolism of ethanol, leading to the accumulation of acetaldehyde [23]. Apart from mitochondria, alcohol also affects antioxidant proteins, enzymes, and their transport in cytosol, such as the inhibition of transport proteins responsible for transporting glutathione from the cytosol into the mitochondria [61]. Accumulation of ROS induces changes in intracellular organelles or processes through lipid peroxidation or other chemical modifications of many complex proteins [62].

Mitochondrial dysfunction can be directly observed in postmortem myocardial biopsies from human AUD patients. Investigators have found microscopic evidence of myocardial mitochondrial enlargement, disorganization, and degeneration of the cristae. Hibbs et al. reported that mitochondria were swollen and had few to no cristae, while others had deformed cristae [63]. As the mitochondria constitute the main site of ROS generation, mitochondrial damage is primarily due to free radical injury. MtDNA is highly susceptible to oxidative damage due to its proximity to ROS generation and the lack of protective histones and DNA repair mechanisms compared to nuclear DNA [64]. Because cardiac myocytes require a significant amount of energy to induce adequate muscle contraction, they contain the highest volume of mitochondria relative to other cell types. Such a large number of damaged and dysfunctional mitochondria leads to ACM development.

Apoptosis

Myocyte apoptosis has been identified as the cause of myocyte loss in many cardiomyopathies, including ACM [65]. Apoptosis may be induced in two different ways. The first involves mitochondria through membrane permeabilization and the release of pro-apoptotic factors (cytochrome c) from inter-membrane space to the cytosol. Chronic ethanol overconsumption, along with oxidative stress and calcium imbalance, mainly triggers apoptosis through mitochondrial mechanism [66]. The alternative, extrinsic pathway, is independent of mitochondria and involves cell surface death receptors. Additionally, ethanol inhibits the generation of anti-apoptotic molecules such as BCL-2 [67,68]. In a recent study, Wang et al. investigated how microRNAs may participate in the induction of cardiomyocyte apoptosis associated with ethanol exposure in vitro. It was observed that increasing the concentrations of ethanol to primary rat cardiomyocytes resulted in elevated apoptosis, assessed by annexin V and propidium iodide staining, and reduced expression of an enzyme for alcohol detoxification, aldehyde dehydrogenase 2 (ALDH2). This suggests a likely involvement of microRNA-378a-5p in the stimulation of cardiomyocyte apoptosis through ALDH2 gene suppression, which might play a potential role in the pathogenesis of ACM. However, more research is required to determine its significance and potential benefits for humans in clinical studies [69].

Autophagy

Histopathological observation of hearts from ACM patients revealed contractile protein loss, fragmentation, and disarray [70]. In one study, Fogle et al. investigated the effect of 16 weeks of ethanol consumption in rats on protein expression. Findings included a decrease in myofibrillar, mitochondrial, and fatty acid metabolism proteins, as well as glycolytic enzymes. Ethanol-induced accelerated protein catabolism may be mediated by decreases in mammalian target of rapamycin (mTOR) activity [71]. The mTOR signaling pathway is a nutrient-, growth factor-, and mechanically sensitive anabolic pathway that plays a key role in load-induced muscle hypertrophy, including cardiac muscle [72]. Ethanol-induced dysregulation of mTOR activity may be involved in the decrease in myocardial protein synthesis, ventricular wall thinning, and dilation. In one study, after 20 weeks of alcohol consumption in female rats, myocardial proteins were investigated. Investigators found increased markers of autophagy, such as LC3B, autophagy-related gene 7 proteins, tumor necrosis factor α (TNF-α), along with a reduction in mTOR activity [73]. Autophagy is a catabolic process in which lysosomes remove defective organelles and cell debris. There is

evidence of enhanced autophagy in certain pathological conditions such as cardiomyopathies [74]. The autophagy pathway is significantly up-regulated during adenosine triphosphate (ATP) depletion, mitochondrial dysfunction, and oxidative stress, all of which are the effects of ethanol misuse. Considering these facts, ethanol-induced increase in autophagy may be an underlying cause of the adverse effects of ethanol on the myocardium. Autophagy and its relation to the mTOR pathway in the myocardium need to be further investigated regarding probable molecular target points for the prevention or treatment of ACM.

Sarcomere Damage

Chronic ethanol consumption causes changes in the structure and function of contractile proteins, leading to disturbances in cross-bridge cycling and force production within sarcomeres [58]. Myocytolysis occurs due to the distortion and disruption of the Z-line pattern in sarcomeres, leading to processes such as myofiber dissolution, cell vacuolization, and fiber disarray [30]. Ethanol also decreases the levels of titin protein in the sarcomere complex, which is essential for sarcomere relaxation and LV distensibility [75]. Other contractile proteins affected by ethanol include actin, myosin, and troponin [23]. Diastolic dysfunction is affected earliest but may initially be subclinical before becoming clinically apparent later on. The ongoing damage to sarcomeres further decreases systolic function of the myocytes, ultimately leading to HF [76].

Cardiac Hypertrophy and Remodeling

Cardiac remodeling is a process that occurs in response to damage to the myocardium, serving as an adaptive mechanism. Although myocytes are relatively resistant to ethanol's toxicity, they undergo cardiac remodeling as a compensatory mechanism to repair ethanol-induced damage [77]. Hypertrophy is mainly observed in the early stages of ACM to prevent a decrease in systolic function, with diastolic dysfunction being the first clinical manifestation. As sarcomeres are damaged, the ventricles undergo wall hypertrophy and compensatory dilation. Cardiac output progressively decreases in a dose-dependent relationship with the lifetime accumulated total dose of alcohol consumed [78]. This compensatory mechanism aims to prevent myocyte necrosis and heart fibrosis, but the final outcome depends on the equilibrium between the degree of damage and the capacity of heart repair mechanisms [77].

Heart Fibrosis

Ethanol-induced damage to the heart leads to low regenerative capacity, resulting in an ineffective repair mechanism characterized by progressive fibrosis. Subendocardial and interstitial fibrosis gradually develop during the course of ACM, typically in advanced stages when myocardial damage surpasses its regenerative capacity [56,79,80]. Some studies suggest that more than 30% of the ventricular myocyte fraction can be replaced by fibrotic tissue, reducing heart elasticity and contractile capacity [81]. Cardiomyokines, such as FGF21, may regulate the fibrotic process, warranting further research to explore their role in ACM and their potential as therapeutic targets [82].

Diagnosis of ACM

The diagnosis of ACM involves excluding other causes of DCM in patients with a history of chronic alcohol overconsumption, as there are no specific clinical, biochemical, or histological features of this condition [23]. Thorough assessment of excessive alcohol consumption is crucial, and criteria from the DSM-5 may aid in diagnosing AUD and evaluating its severity [6].

Regarding laboratory findings, BAC in an acute ethanol intoxication gives only basic information and does not allow assessment of chronic misuse. There are other markers that allow this such as gamma-glutamyl transferase (GGT), glutamic oxaloacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT). Elevations of the transaminases (GOT, GPT), especially a ratio of GOT/GPT above 2 may indicate alcoholic liver disease instead of liver disease from other etiologies. Mean corpuscular volume (MCV), carbohydrate deficient-transferrin (CDT), and ethyl glucuronide are also used to confirm alcohol abuse, alcoholic liver disease and to monitor abstinence [83,84].

Chest X-ray may reveal cardiomegaly, pleural effusion, and pulmonary congestion [85]. ECG findings are typically non-specific and include changes in ST segments, T-waves, and arrhythmias resulting from dilated heart chambers [86]. Echocardiography can visualize features of ACM that can be present many years before the onset of clinical manifestations such as hypertrophy, dilation, and systolic and diastolic dysfunction, aiding in the exclusion of other causes of congestive HF[30].

The diagnosis of ACM may be supported by improvements in myocardial function following abstinence or a significant reduction in alcohol consumption [22].

Treatment of ACM

Treatment of ACM primarily focuses on achieving absolute alcohol abstinence. However, complete abstinence can be challenging for many patients, especially those with symptoms of AUD such as alcohol cravings and impaired impulse control. In such cases, even significant reduction of alcohol consumption to a low dose can help slow down or stop the progression of ACM and prevent further organ damage. Therefore, it is essential to promptly identify and treat AUD to effectively manage ACM. Over the past few decades, several pharmacotherapies have been proposed to treat AUD, most of which focus on reducing alcohol cravings. The three medications approved in the United States to treat AUD are disulfiram, naltrexone, and acamprosate. Additionally, although not officially approved for treating AUD, topiramate and gabapentin have demonstrated efficacy and are used off-label. Recently, many studies have been conducted to search for new drug candidates, including psychedelics and phosphodiesterase-4 inhibitors. They may be helpful for the treatment of AUD, although they require further evaluation before being used clinically [87]. Even though pharmacotherapy may partly relieve the symptoms of AUD, optimal medical management should be performed by an alcohol addiction specialist in the AUD treatment unit.

Apart from AUD, patients should receive comprehensive pharmacological treatment for HF. The treatment of ACM does not differ from the treatment of idiopathic-dilated cardiomyopathy [88]. Patients should receive mineralocorticoid receptor antagonists (MRA) to decrease preload, angiotensin-converting-enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) /angiotensin receptor-neprilysin inhibitor (ARNI), and beta-blockers to decrease afterload and relieve the signs of acute HF. The sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin are recommended for all patients with heart failure with reduced ejection fraction (HFrEF) as per the newest 2021 European Society of Cardiology (ESC) guidelines. In patients with persistent ventricular dysfunction and ineffective pharmacotherapy, an implantable cardioverter-defibrillator (ICD) implantation or heart transplantation should be considered. (Table 1.) [89].

Total alcohol abstinence	
Management in all patients with HFrEF:	
Drug/strategy	**Comment**
ACE-I	• to reduce the risk of HF hospitalization and death
Beta-blocker	• to reduce the risk of HF hospitalization and death
MRA	• to reduce the risk of HF hospitalization and death
SGLT2 Inhibitor	• dapagliflozin/empagliflozin • to reduce the risk of HF hospitalization and death
Sacubitril/valsartan (ARNI)	• as a replacement for an ACE-I • to reduce the risk of HF hospitalization and death
Exercise rehabilitation	• to reduce HF hospitalization and improve QOL
Multidisciplinary disease management	• to reduce HF hospitalization and improve QOL
Management in selected patients with HFrEF:	
Loop diuretics	• in patients with symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalization
ARB	• in patients with ACE-I/ARNI intolerance
CRT-P/D	• in patients with sinus rhythm and LBBB with QRS > 150 ms
ICD	• in patients with ischaemic aetiology
Heart transplantation	• in advanced HF

Table 1. Overview of the management of heart failure with reduced ejection fraction (HFrEF) with division of drugs/strategies recommended in all patients with HFrEF and in selected patients with HFrEF. Only Class I Therapy Indications are presented. Based on 2021 European Society of Cardiology (ESC) guidelines. ACE-I = angiotensin-converting enzyme

inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor-neprilysin inhibitor; CRT-D = cardiac resynchronization therapy with defibrillator; CRT-P = cardiac resynchronization therapy pacemaker; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; MRA= mineralocorticoid receptor antagonist; QOL = quality of life; SGLT2 = sodium-glucose cotransporter 2.

New therapies are being investigated for the treatment of ACM. The targets for these new therapies include inhibition of pathways responsible for myocardium hypertrophy and cell destruction (e.g., sirtuins, caspases, myostatin), cardiac fibrosis (e.g., miRNAs, TGF-β, relaxin), oxidative stress damage (e.g., cardiomyokines, leptin, ghrelin), and the improvement of myocardium regeneration (e.g. telocytes,, stem cells) [90].

Prognosis

The extent and duration of ethanol consumption directly influence the long-term survival rate and are the most significant prognostic factors for ACM. In general, ACM shows a better prognosis than idiopathic dilated cardiomyopathies. Worse outcomes are associated with AF, QRS width > 120 ms, and the absence of beta-blockers, which are independent predictions of poor outcome. Some authors also mention a shorter distance in the 6-minute walking test and the use of digoxin as bad prognostic indicators [91]. Patients who continue consuming ethanol at moderate to high doses show progressive functional and structural cardiac impairment, with episodes of cardiac left or congestive failure, arrhythmias, and progression to death, with a mortality rate of 10% per year [92]. Episodes of binge drinking are especially dangerous and may lead to acute alcohol intoxication and its complications.

Alcohol abstinence, as the most effective treatment, significantly improves cardiac function. However, as most patients have AUD, effective abstinence is only achieved by 50% to 60% of patients submitted to specific programs [93]. In patients who cannot maintain total abstinence, even the reduction of ethanol consumption to 60 g per day is highly beneficial to cardiac function, but to a lesser extent compared to total abstainers [94].

Discussion and Conclusions

Ethanol overconsumption remains a significant and unresolved problem today, with the incidence of ACM projected to persist in the future, especially among patients with AUD and initial high cardiovascular risk. The easy access to alcohol, the constantly growing alcohol industry, and ineffective drinking policies are expected to increase the prevalence of alcohol

consumption [2]. Therefore, efforts for prevention, early detection, and effective treatment of ACM need to be established. A primary focus should be on treating AUD because it is the most effective way to halt the progression of the disease.

Genetic factors play a crucial role in determining a person's susceptibility to ethanol, particularly genetic polymorphisms in certain myocardial proteins or enzymes involved in alcohol metabolism. The study is limited by little existing research over genetic variants that may predispose to ACM occurrence and that constitutes the area for further investigation. Women tend to be more prone to ethanol's toxicity, as a smaller amount of alcohol can cause the same incidence of disease as in men [36]. Electrolyte imbalance and malnutrition may exacerbate the course of ACM, emphasizing the importance of maintaining a healthy and balanced diet to avoid serious complications of ethanol consumption. There is a significant association between the daily amount of alcohol consumed and the development of ACM. While moderate alcohol consumption is not associated with high cardiotoxicity, low-dose ethanol consumption may even be beneficial in preventing CHD, HF, and global mortality, as illustrated by a "J-shape" or "U-shape" curve of effect. However, no amount of alcohol is recommended due to the parallel risk of developing cancer, liver cirrhosis, and other chronic diseases [30].

The multiple sites of myocyte damage caused by alcohol create a significant individual clinical variability and make it challenging to establish a simple, effective treatment for ACM. As the disease progresses with heart hypertrophy, remodeling, and progressive fibrosis, HF becomes an end-stage complication [23]. Optimal pharmacotherapy, along with proper support from an alcohol addiction specialist in the AUD treatment unit, can improve the prognosis. The primary goal of treatment is to maintain total abstinence from alcohol. Ongoing research into new pharmacotherapies offers hope for improving treatment and reducing complications of ACM [90].

Further research should focus on both asymptomatic and symptomatic patients with AUD to better define clinical manifestations, diagnostic approaches, and finally the most effective treatments for ACM.

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