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Harmful Effects of Alcohol On Essential Physiological Organs

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ABSTRACT

Alcohol abuse is one of major and increasingly attributable risk factor for mortality and morbidity worldwide. The underlying purpose of this review is to promote awareness and significance in relation to the effects of alcohol on various body systems especially on cardiovascular system, liver, adipose tissue, skeletal muscle, brain, water and electrolyte metabolism and endocrine system. Alcohol when used above the normal range can results in harmful consequences on different biological organs. Average volumes consumed and patterns and frequency of drinking are three dimensions of alcohol consumption that need to be considered in efforts to reduce the burden of alcohol-related harmful effects. To reduce such harmful effects, national policies need to be developed to keep track of alcohol consumption and its consequences, and to raise awareness amongst the public. It is up to both public and concerned governments to encourage debate and formulate effective public health oriented policies and measures in order to minimize the harm caused by alcohol.

Keywords: Alcohol, consumption, harmful effects, awareness

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INTRODUCTION

Alcohol or ethanol is the most commonly abused drug among youth[1]. Globally, adverse utilization of alcohol results in approximately 2.5 million deaths each year. Alcohol abuse is a major and increasingly attributable risk factor for mortality and morbidity worldwide. A World Health Organization (WHO) report states that per capita global consumption of alcoholic beverages in 2010 was equal to 6.2 litres of pure alcohol consumed by each individual aged 15 years or older. Approximately 2.3 million people die each year due to the adverse and harmful use of alcohol, accounting for approximately 3.8% of all deaths globally[2,3].

The purpose of this review is to promote awareness and significance of a broad range of different organ injuries induced by alcohol that highlights the physiological processes of organ damage. Specifically, it focuses on the effects of alcohol on cardiovascular system, liver, adipose tissue, skeletal muscle, brain, water and electrolyte metabolism and endocrine system[4].

EFFECT OF ALCOHOL ON CARDIOVASCULAR SYSTEM:

From over the last three decades, various epidemiologic studies had revealed data that showed complex associations between alcohol utilization and cardiovascular conditions such as hypertension, peripheral arterial disease, coronary heart disease, cardiomyopathy and stroke. Specifically, such associations are strongly modulated by the amount and pattern of alcohol consumption[5]. In contrast to high alcohol intake which has a detrimental effect on cardiovascular health, chronic low alcohol has been shown to have a beneficial effect[6]. Both men and women who consume 1-3 drinks a day have a 10% to 40% lower risk of coronary heart disease than those who abstain[7].

Effect of alcohol on blood pressure:

Adults consuming low-to-moderate amounts of ethanol each day typically has no acute (i.e., short-term) or substantial impact on blood pressure (BP) or hemodynamics. However, data from various studies suggest that binge drinking (more than 5 standard drinks in a single occasion) is associated with temporary increase in BP that ranges from 4 to 7 mmHg for systolic BP and 4 to 6 mmHg for diastolic BP[5].

The World hypertension League (WHL) supposed that the relatively greater effect of alcohol on systolic blood pressure compared with diastolic blood pressure might indicate an imbalance between central nervous system (CNS) factors influencing cardiac output and the peripheral vascular effects of alcohol. Ethanol diminishes the baro reflex by interacting with receptors in the brain stem, i.e. rostral ventrolateral medulla (RVLM) and nucleus tractus solitarii (NTS)[8]. Findings

from this study revealed that ethanol reduction was associated with a significant reduction in mean (95% confidence interval) systolic and diastolic blood pressures of -3.31 mmHg and -2.04 mmHg respectively[9].

A study showed that the alcohol treated rats had an increased sympathetic activity as there occurred a decrease in heart rate in alcohol treated rats when compared to control rats during β-adreno-receptor blockade with propranolol. Such increased sympathetic activity is consistent with impairment of the baro-receptors that, upon activation, inhibit the sympathetic nervous system[10,11,12,13].

Alcohol treated rats showed blood vessels constriction due to increased shifts in the binding of the calcium ion (Ca^{2+}) in arteries and arteriolar smooth muscle cells results in increased sensitivity to endogenous vasoconstrictors[9,14].

Alcoholic myopathy in heart and skeleton muscles:

Excessive use of alcohol affects not only the striated muscles of the myocardium, but also to the skeleton. Electromyography showed that most patients who are chronic alcoholics have some abnormality in skeletal muscle, and almost have histologic changes of varying severity. Because skeletal and cardiac muscles are similar in many respects, it is reasonable to presume that the mechanisms that underlie alcohol-induced injury are similar in both[15,16].

In alcoholic myopathy and cardiomyopathy, preclinical (asymptomatic), acute (occasional binge drinking) and chronic (daily) forms are recognized. In cardiomyopathy chronic alcohol abuse on many occasions results in irreversible congestive failure and in chronic myopathy insistent weakness or recurrent acute episodes of myoglobinuria are not unusual. Histologically, the skeletal muscle and heart might exhibit necrosis of myofibers, interstitial fibrosis and acute and chronic inflammation, depending on the stage of myopathy[17].

Alcohol and Peripheral artery disease (PAD):

Peripheral arterial disease is a type of an atherosclerotic disease in the lower extremities which is characterized by periodic claudication with pain at posterior cruris and discomfort. Various anomalies of smooth muscle cells, vascular endothelial cells and platelets are involved in its pathogenesis[18]. Data on ethanol use and atherosclerosis are scarce[19]. Lower extremity arterial disease (LEAD) is one of the most common complications of diabetes and might harms the peripheral arteries through multiple pathways. It was reported that alcohol consumers with PAD have a lower mortality than patients with PAD who did not consume alcohol. The prevalence of LEAD ranges from 16.9 to 23.8%. In United States approximately 10 million men and women suffer from LEAD, and in Chinese patients with diabetes older than 50 years[20].

The Edinburgh Artery Study (EAS) supported the useful effect of alcohol, as there was a positive association between the amount of alcohol intake and the ankle brachial index. In the Physician's Health Study (PHS), regular drinkers showed a 26% lower incidence of peripheral arterial disease compared with non-drinkers after adjustment for confounding factors. Similar results were also shown in the Atherosclerosis Risk in Communities (ARIC) study and Framingham Heart Study (FHS)[21].

There is relatively little investigation on the relationship of moderate alcohol consumption with risk of Abdominal Aortic Aneurysm (AAA). In an analysis of male smokers, there was a finding of U-shaped relationship, with relative risks for AAA of 0.74 (95% CI, 0.49–1.13) among alcohol consumers of up to 15 g of alcohol per day and 0.60 (95% CI, 0.36– 1.02) among consumers of 16 to 30 g of alcohol per day[22].

EFFECT OF ALCOHOL ON BRAIN:

Alcohol-related brain damage (ARBD):

Some people continuously drink much higher amounts than the recommended limits of alcohol. For men, such excessive drinking could mean > 50 units/week, and for women, greater than 35 units/week. Drinking at these high levels not only poses high risk to someone's health but it can increase the risk of becoming addicted. Drinking at such high levels over many years directly damages the brain tissue and in some people causing alcohol-related brain damage (ARBD)[23, 24].

ARBD is defined as chronic decline in thinking or memory caused by excessive alcohol consumption and a lack of thiamine (vitamin B1). Vitamin B1 is needed to provide energy to the body. It is especially important for brain because they use so much energy. Regular heavy alcohol consumption over time damages nerve cells because alcohol is a toxin. It also causes chemical changes and the shrinkage of brain tissue. The second way that alcohol misuse leads to ARBD is by causing vitamin B1 deficiency. Alcohol can also cause ARBD through repeated head injuries because people who misuse alcohol are more prone to falls and getting into fights. Finally, heavy consumption damages blood vessels and is linked to raise cholesterol levels, high blood pressure and an increased risk of strokes and heart attacks. All of these conditions can damage the brain. The most common form of ARBD is alcoholic dementia which may also be called alcohol-related dementia. ARBD also includes Korsakoff's syndrome, which is also called Korsakoff's psychosis[25].

Effects of ethanol on GABA receptors:

Alcoholism is associated with short and long-term cognitive dysfunction including memory impairment, resulting in substantial disability and cost to society. Thus, understanding how alcohol

impairs cognition is essential for developing treatment strategies to reduce its adverse impact. Memory processing is thought to involve persistent, use-dependent changes in synaptic transmission, and alcohol alters the activity of multiple signalling molecules in synaptic processing, including modulation of the gamma-aminobutyric acid (GABA) and glutamate transmitter systems that mediate most fast inhibitory and excitatory transmission in the brain. Different combinations of subunits markedly influence pharmacological and physiological properties, and alcohol promotes the actions of GABA at some $GABA_A$ receptors. Early studies suggested that alcoholic effects are most prominent at receptors expressing γ2L subunit that has a site for phosphorylation by protein kinase C (PKC), and mice with targeted deletions of the γ-isoform of PKC have reduced ethanol sensitivity[26].

Alcohol related dementia:

It is well established that prolonged and excessive use of alcohol can lead to irreversible damage to the structure and function of the brain[27]. Present diagnostic criteria for ethanol-associated cognitive disorders focus on two main syndromes of impairment: alcohol-related dementia (ARD) and WKS (Wernicke-Korsakoff syndrome)[28].

Autopsy evaluations showed that up to 78% of persons with diagnosed alcoholism demonstrate some degree of brain pathology. Neuropathological and Neuroimaging evidence showed prominent white matter loss (in the corpus callosum, prefrontal cortex and cerebellum) and neuronal loss in the hypothalamus, superior frontal association cortex and cerebellum[23,29]. The frontal lobes of individuals with alcoholism is highly susceptible to damage, volume shrinkage, decreased neuron density and altered glucose metabolism and perfusion. Magnetic resonance imaging studies showed early reversibility of white matter shrinkage which is accompanied by clinical improvement in motor and cognitive abilities. The restoration of myelination and axonal integrity are the probable mechanism of recovery after white matter damage, but is vulnerable to repeated disruption if drinking is resumed[30, 31].

Epidemiological results generally have been derived from population studies that relate patterns of alcohol consumption and dementia. Studies have showed a high prevalence of alcohol misuse in patients with dementia (9% to 22%) and high rates of dementia in alcohol abusers (10% to 24%), although most studies did not specify the type of dementia. Prevalence studies of dementia in nursing homes have reported ARD of 10% to 24% of all dementias, which is likely higher than in the general population[32-34].

Table 1 Assessment of Alcohol-Related Dementia[35-37]

Index	Description
High Index of Suspicion	In confused patients with alcohol abuse/disorders and/or dietary deficiency/malnourishment and co-morbid medical illness.
Thorough history taking .	Specially noting the quantity, pattern, duration of alcohol use, frequency and time of last use; attempts at abstinence, number of detoxification attempts and severity of withdrawal symptoms. Detailed history of aphasia, apraxia, amnesia, visuo-spatial deficits and difficulty in daily functioning and its temporal relationship with alcohol use.
Detailed clinical examination	Eliciting dietary deficiency/malnourishment; Oculomotor abnormalities-nystagmus, diplopia, miosis, anisocoria, papilloedema, ophthalmoplegia and retinal hemorrhages; Cerebellar dysfunction (ataxia, nystagmus); Mild memory impairment or delirium; Autonomic disturbances like hypo or hyperthermia, tachycardia, hypotension. Other features like spastic paraparesis, hearing loss, seizures,or acute psychosis.
Investigations	Serum levels of folate, B12, magnesium, calcium and phosphate, complete blood counts; electrolytes; liver function tests; renal function tests; thyroid function tests; coagulation profile; blood sugar level. Raised gamma glutamyl transferase and macrocytosis are useful biological markers of alcohol use. Treatment with thiamine should be started immediately without waiting for the results. Thiamine pyrophosphate levels and erythrocyte transketolase activity may be helpful. Magnetic resonance imaging of brain may support Wernicke encephalopathy's diagnosis.

EFFECT OF ALCOHOL ON LIVER:

Alcoholic Liver Disease (ALD) ranks among the major causes of morbidity and mortality in the world, and affects millions of patients globally each year. ALD is a broad term that includes a spectrum of phenotypes ranging from simple steatosis to steatohepatitis, cirrhosis, progressive fibrosis and hepatocellular carcinoma. Whilst the disease progression is well characterized, currently there is no FDA-approved therapy available to reverse or halt this process in humans[38, 39].

Early-Stage Pathogenesis of ALD:

Steatosis is the first response of the liver in severe alcohol abusers. It is histologically defined as the deposition of fat in hepatocytes (liver cells). Alcohol increases NADH/NAD+ in hepatocytes, thereby interrupt fatty acid oxidation and leading to steatosis development (40). Innate immune signalling has a role in the early stage of ALD with simple steatosis even before the onset of inflammation. Endoplasmic reticulum (ER) stress activates interferon regulatory factor 3 (IRF3) via the adaptor molecule STRING. IRF3 is activated (phosphorylated) with a single exposure to ethanol, preceding the development of inflammation. Hepatocyte-specific IRF3 is required for the

intrinsic (mitochondrial) apoptosis pathway, while Kupffer cell IRF3 deficiency provides only marginal liver damage[41].

Continuous alcohol abuse causes progression to liver cirrhosis and fibrosis, which leads to a high risk of complications (such as variceal bleeding, ascites, hepatic encephalopathy, bacterial infections and renal failure)[42]. Acetaldehyde advances fibrogenesis directly by accelerating the expression of collagen in hepatic stellate cells (HSC). HSCs can also be activated by damaged hepatocytes, neutrophils and activated Kupffer cells through various pro-fibrogenic mediators including interleukin (IL)-8, angiotensin II, transforming growth factor β, platelet-derived growth factor and leptin. The biological actions and activation of these mediators are largely due to reactive oxygen species (ROS)[27-31].

EFFECT OF ALCOHOL ON ADIPOSE TISSUE:

When overall body mass is considered, little effect is seen at lower levels of alcohol intake, whereas most observational studies have shown increased body mass index (BMI) associated with greater ethanol consumption[43,44,45].

Adipose tissue is an organ which stores energy is also found to play a major role in ALD progression by secreting hormones and cytokines known as adipocytokines or adipokines. Alcohol affects the metabolic and innate immune activities of adipose tissue which results in alcohol-induced injury of the tissues[46]. Alcohol intake causes alcoholic fatty liver disease. In animal and human models, ethanol intake causes susceptibility toward non-alcoholic fatty liver disease[47]. Alcohol intake, even at moderate levels, affects the function of adipose tissue[44]. If alcohol misuse and obesity are both present, risk of liver-related mortality and morbidity is increased. Excess ethanol consumption proportionally increases the amount of visceral adipose tissue, similar to changes seen in obesity[48].

Studies on rodents:

Exposure to alcohol up-regulates fatty acid transport proteins, causes accumulation of lipids in the liver, inactivates adipose protein phosphatase 1, induces insulin intolerance, and also upregulates tensin homolog (PTEN) and phosphatase and suppressor of cytokine signalling 3(SOCS3) proteins in mice. Alcohol consumption more than 14 standard drinks are shown to be related to a higher risk of metabolic syndrome[46].

Chronic alcohol consumption activates lipolysis of adipose tissue and promotes the release of free fatty acids. Some circulating levels of free fatty acids might not always reflect this change as they are removed by other tissues like liver and heart. While in-vivo metabolic flux studies using radiolabeled triglycerides showed that chronic alcohol intake increases lipolysis, primary

adipocytes from chronic alcohol-fed rats has shown that basal rates of lipolysis and FFA release were not altered by ethanol feeding[49-52].

EFFECT OF ALCOHOL ON WATER AND ELECTROLYTE METABOLISM:

Ethanol also displays actions on water and electrolyte metabolism. Alcohol ingestion increases urinary excretion. The increase in urine volume seems to be caused by suppression of vasopressin and the intake of fluid. The study was conducted on hypertensive patients for determining the effect of periodic alcohol intake for 1 week on the sodium excretion and urine volume. Urinary sodium excretion diminished in the early phase but increased in the late phase. On day's 3–5 urine volume were increased but not on day 1. The mean BP also diminished in the early phase and then returned toward the baseline levels. The initial BP reduction might mask the alcohol-induced diuresis and causes sodium retention, which might be involved in subsequent BP elevation. It has also been shown that urinary potassium excretion reduces after alcohol ingestion[53,54].

In another study the serum potassium level reduced after a single intake of alcohol. This alteration in serum potassium seems to be intermediated by the sympathetic nervous system, as propranolol attenuated alcohol-induced hypokalemia. Conversely, ethanol increases the urinary excretion of calcium and magnesium. It is possible that calcium and magnesium are exhausted in habitual drinkers, and the alcohol-induced alterations in these minerals may contribute to arrhythmia and BP elevation[55].

EFFECT OF ALCOHOL ON THE ENDOCRINE SYSTEM:

The endocrine system ensures a correct communication between various organs of the body to maintain a stable internal environment. Chronic alcohol use disrupts the communication between nervous, immune system and endocrine and causes hormonal disturbances that lead to serious consequences at behavioural and physiological levels. It is known that ethanol increases plasma renin activity. Ethanol also stimulated the release of adrenocorticotropic hormone, and increases in plasma aldosterone and cortisol were observed after drinking[56].

The level of plasma insulin increases after alcohol intake; however, the change is less than that induced by an isocaloric control drink. It has been shown that a low-to-moderate intake of alcohol enhances insulin sensitivity and reduces the risk of type-2 diabetes mellitus, whereas no risk reduction was observed in consumers of equal to or over 48 g/day[57, 58].

There are several reports showing evidence for the existence of hyperprolactinemia in chronic alcoholic men and women. In a study conducted by European scientists, persistent hyperprolactinemia was observed in 16 chronic alcoholic women during a 6 week treatment trial[59]. Alcohol-induced hyperprolactinemia has also been demonstrated in nonhuman primates and

laboratory animals[60,61]. Alcoholic individuals often show dysregulations of the hypothalamic pituitary-thyroid axis. A significant reduction in T4 and T3 concentrations was observed in the alcoholic groups during withdrawal and early abstinence, compared to non alcoholic healthy groups[62].

Acute and chronic alcohol exposures have both been shown to induce immunosuppression through dysregulation in all branches of the immune system. Alcohol exposure reduces neutrophill (macrophage) infiltration and migration to sites of infection as well as production of new neutrophills in response to infection and their phagocytic activity. Chronic alcohol exposure also decreases monocyte phagocytic activity even though the number of these cells is increased. Furthermore, chronic alcohol exposure decreases the number and activity of dendritic and natural-killer cell (NK-cells)[63-65].

CONCLUSION:

Alcohol is not an ordinary commodity. Its use is diverse and widespread, especially in India and when used above the normal range can results in harmful consequences on different biological organs. Average volumes consumed and patterns and frequency of drinking are three dimensions of alcohol consumption that need to be considered in efforts to reduce the burden of alcohol-related harmful effects, e.g. on cardiovascular system, liver, adipose tissue, skeletal muscle, brain, water and electrolyte metabolism, endocrine system etc. Alcohol is also associated with motor vehicle accidents and a range of other detrimental effects. To reduce such harmful effects, national policies need to be developed to keep track of alcohol consumption and its consequences, and to raise awareness amongst the public. It is up to both citizens and concerned governments to encourage debate and formulate effective public health oriented policies and measures in order to minimize the harm caused by alcohol.

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