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Chronic Alcohol Intake is a Possible Risk Factor for Kidney Injury

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Abstract

The tradition of imbibing alcoholic beverages can be traced back to ancient civilizations. Alcohol abuse is a major contributor to mortality, societal issues, and a strain on the healthcare system in the United States. Alcohol abuse impacts more than 29 million individuals and results in over 140,000 deaths each year in the United States. Long-term alcohol consumption is a well-established factor that increases the risk of tissue damage. Both acute and chronic alcohol intake can adversely affect renal function, particularly in the presence of hepatic illness. Scientists have observed that alcohol can cause alterations in the structure and function of the kidneys, leading to a decreased ability to maintain proper fluid and electrolyte balance in the body. Chronic drinkers may suffer from decreased amounts of vital electrolytes in their blood and significant disturbances in the body's acid-base equilibrium. In addition, drinking can disrupt the hormonal processes that regulate kidney function. Persistent alcohol consumption worsens liver disease, causing additional injury to the kidneys by compromising their ability to balance salt and fluid levels, which might potentially result in sudden kidney failure. The correlation between chronic alcohol intakeD and kidney damage is fascinating yet contentious, as the molecular pathways behind alcohol-induced kidney impairment remain little comprehended. Existing epidemiological research have yielded ambiguous results, and there is a scarcity of experimental evidence that directly establishes a causal relationship between alcohol use and kidney injury. This review investigates the potential correlation between chronic alcoholism and the risk of renal injury.

Keywords: Alcohol Abuse; Alcohol Intake; Kidney Injury; Oxidative Stress

Abbreviations

CKD: Chronic Kidney Disease; ESRD: End-Stage Renal Disease; CVD: Cardiovascular Diseases; ROS: Reactive Oxygen Species; RAAS: Renin-Angiotensin-Aldosterone System.

Introduction

Alcohol usage is a substantial menace to worldwide health. In 2016, an estimated 2.3 billion individuals, accounting for 43% of the global population, engaged in alcohol consumption. Out of these, around 40% (almost 1 billion individuals) were classified as strong episodic drinkers. During the last twenty years, the amount of alcohol consumed per person has risen from 5.5 to 6.4 liters of pure alcohol. Within the Asian population, 57% of males and 29% of females partake in alcohol use. The preferred choice of beverage is liquor, which makes up 88% of the total consumption. Multiple epidemiological studies emphasize the intricate correlation between alcohol use and cardiovascular diseases (CVD). More precisely, people who used small to moderate quantities of alcohol had a decreased chance of developing cardiovascular disease, but those who drank heavily had an increased risk of death [1].

Chronic kidney disease (CKD) is a medical condition characterized by substantial alterations in kidney function and/or structure. The signs of chronic kidney disease (CKD) usually do not manifest until the disease has progressed to advanced stages, which makes it more challenging to implement early preventative measures. Previous research indicates that the worldwide occurrence of chronic kidney disease (CKD) is estimated to be 13.4%, affecting a population of 49 to 71 million individuals who eventually develop end-stage renal disease (ESRD). The number of individuals diagnosed with CKD in China is around 119.5 million, resulting in a prevalence rate of 10.8%. Studies conducted on mice have demonstrated that the administration of ethanol can negatively affect kidney function by causing inflammatory injury, oxidative damage, activation of the renin-angiotensin system, and aberrant immunological responses [1].

Nevertheless, epidemiological research yield inconclusive results regarding the influence of alcohol use on renal function. Several research suggest that consuming a moderate amount of alcohol is linked to a reduced occurrence of chronic kidney disease (CKD), however other investigations have reported conflicting findings. Significantly, investigations in this field have predominantly been carried out in particular areas of China [1].

Alcohol Abuse and Kidney Disorders

Cardiovascular disorders such as hypertension and ischemic heart disease, together with diabetes microvascular consequences, are widely recognized as significant risk factors for the onset of chronic kidney diseases (CKD). Excessive alcohol consumption is a contributing factor to the development of cardiac problems. Chronic heavy drinkers are at a greater risk compared to those who consume alcohol in small to moderate quantities drinks [2-5].

Several study reports and meta-analysis studies suggest that prolonged and excessive alcohol intake increases the likelihood of developing chronic kidney disease (CKD). These investigations have established a correlation between excessive alcohol use and an increased likelihood of developing proteinuria, end-stage renal disease (ESRD), and chronic kidney disease (CKD). The combined risk ratios for chronic kidney disease (CKD), proteinuria, and end-stage renal disease (ESRD) in individuals with high alcohol consumption were 0.83, 0.85, and 1.00, respectively. These findings indicate a reduced or absent risk of kidney disease in individuals who consume alcohol heavily [6].

Additional research has yielded similar results, indicating that the occurrence of renal disease is equivalent or may be lower in individuals who use large amounts of alcohol (more than 210g per week) compared to those who consume moderate amounts (70-210g per week) [7-12]. Conversely, certain studies indicate that excessive alcohol use may result in unfavorable consequences for individuals with chronic kidney disease (CKD) [13-15]. Both Japanese Yamagata K, et al. [12] and Italian Buja A, et al. [7] cohort studies have found a U-shaped relationship between alcohol use and the incidence of proteinuria. The conflicting results may be attributed to several variables, including the varying impact of different alcoholic beverages on renal function or the diverse drinking habits observed across different nations. Moreover, the reliance on self-reported data regarding drinking patterns and alcohol consumption may add potential bias into certain findings. Parekh RS, et al. [16] discovered that individuals who consume large amounts of alcohol frequently provide inaccurate information about their alcohol use.

Potential Mechanistic Understanding of Alcoholic Kidney Damage

There is data, both direct and indirect, that supports multiple potential pathways kidney damage due to alcohol intake. The detrimental effects of alcohol are attributed to either the alcohol itself or the excessive amounts of by products produced during its metabolism, such as acetaldehyde, NADH, and free radicals. These alcohol-induced pathological changes in cells are linked to organ damage and can potentially contribute to kidney injury. Moreover, intricate interplay among several organs might intensify and worsen the progression of renal illness in patients with alcohol use disorder.

Oxidative Stress

It refers to an imbalance between the productions of reactive oxygen species (ROS) and the ability of the body to neutralize or detoxify these harmful molecules.

Free radicals, which are produced during the process of alcohol metabolism, have the potential to harm cells unless they are counteracted by antioxidants. Oxidative stress arises when the body's ability to eliminate free radicals lags behind their production rate, and it plays a pivotal role in alcohol-induced tissue damage. Research suggests that alcohol-induced damage to organs, such as the liver [17], heart [18,19], and kidneys [20], leads to the production of reactive oxygen species (ROS) through different processes. The mechanisms that produce ROS include both nonenzymatic activities, such as faults in the mitochondrial electron transport chain [21,22], and enzymatic processes involving enzymes like NADPH oxidases [23] and CYP2E1 [24].

CYP2E1 plays a crucial role in the development of renal damage caused by alcohol consumption. Alcohol is mostly

broken down by the liver enzyme alcohol dehydrogenase. However, long-term ingestion of ethanol causes the activation of CYP2E1 in both the liver and kidneys. It is worth mentioning that the increase in CYP2E1 activity is significantly greater in the kidneys than in the liver [25,26]. The notable increase in CYP2E1 expression in the kidneys results in oxidative stress, causing modifications to phospholipids in cell membranes. These altered phospholipids have the ability to stimulate neutrophil granulocytes, a kind of immune cell, which intensifies oxidative stress and establishes a self-perpetuating loop [20].

Research suggests that drinking alcohol may increase the activity of enzymes from the nitric oxide synthase family in the kidneys, which can produce free radicals [27]. Nitric oxide synthase facilitates the production of nitric oxide, which, when present in excessive amounts, can interact with other molecules to produce free radicals, resulting in kidney tissue harm [28,29]. Tirapelli LF, et al. [27] showed that ethanol consumption leads to an elevation in the expression of two nitric oxide synthases. Nevertheless, the precise method by which ethanol increases the expression of these enzymes, either directly or indirectly, is still uncertain.

One concept posits that ethanol's effect on the digestive system may induce the release of toxins from the intestines into the circulation, which in turn may stimulate the production of nitric oxide synthase. Another hypothesis suggests that these enzymes may experience uncoupling as a result of oxidation or a shortage of vital coenzymes, resulting in an increased generation of free radicals.

Uncoupling leads to the generation of detrimental reactive oxygen species (ROS), such as the superoxide anion, instead of the vasorelaxant nitric oxide that is important for regulating proper blood flow in the kidney. In addition to oxidative stress, recent research indicates that nonoxidative processes also contribute to alcohol-induced organ damage. More precisely, the process of ethanol metabolism produces fatty acid ethyl esters in different organs, which might cause harm to those organs that is associated to ethanol use [30]. Calabrese V, et al. [31] noted a substantial rise in the concentrations of fatty acid ethyl esters caused by ethanol. The heart had the greatest levels, followed by the kidney, brain, and liver.

During the process of ethanol metabolism, significant quantities of acetate are generated and integrated into acetyl-coenzyme-A, a crucial component for the metabolism of proteins, lipids, and carbohydrates. This results in a systematic alteration of metabolic processes. Protein acetylation, which refers to the attachment of an acetyl group to a protein, is essential for controlling mitochondrial functions such fatty acid metabolism and antioxidant defense [32]. The balance between lysine acetylation and deacetylation of important proteins, like the master regulator of mitochondrial biogenesis called PGC-1 alpha, is known to have a role in triggering a metabolic switch in situations of excessive or insufficient nutrition [33-35].

Recent studies have demonstrated that ethanol causes an increase in the acetylation of mitochondrial proteins in the kidney. This increase in acetylation may disrupt the functioning of specific mitochondrial proteins that are responsible for alcohol metabolism or protection against oxidative stress, such as superoxide dismutase 2, aldehyde dehydrogenase 2, and glutathione peroxidase. The process of hyperacetylation may play a crucial role in the development of ethanol-induced mitochondrial dysfunction in the kidneys [36].

Alcohol-Induced Gastrointestinal Harm and Renal Injury

Alcohol-induced damage to the intestines and the resulting increased movement of bacterial endotoxin are important factors in both the beginning and advancement of alcoholic liver injury, as well as in the development of other disorders associated to alcohol [37,38]. The specific impact of alcohol-induced endotoxin release on the development of kidney damage in individuals with alcoholism has not been thoroughly investigated. It is possible that the stimulation of the body's natural immune system, caused by endotoxins released from a weakened gut barrier, may have a significant impact on the development of kidney damage caused by myoglobin.

Prolonged alcohol intake causes substantial harm to various organs, perhaps worsening the adverse impact of ethanol on the kidneys. Ethanol significantly triggers the development of the microsomal ethanol oxidation system (CYP2E1), resulting in the generation of reactive oxygen species as secondary products. Alcoholic steatohepatitis may be caused by higher gastrointestinal permeability and exposure to endotoxins, leading to an increased load of immunoglobulin A (IgA). The excessive accumulation of IgA, resulting from increased production in the intestines and decreased removal by the liver, may result in the deposition of IgA in the kidneys, which could potentially lead to glomerulopathy. Renal microcirculatory alterations in advanced liver cirrhosis may result in the development of hepatorenal syndrome [39].

IgA glomerulonephritis is a common form of primary glomerulonephritis that occurs globally. It is characterized by acute kidney inflammation caused by an immune response involving IgA. This kidney disease, which is associated with IgA, presents clinical symptoms of renal damage and has

the potential to advance to renal failure. Empirical research indicates that excessive alcohol use can trigger IgA kidney disease. Moreover, there is evidence suggesting that liver damage caused by alcohol, namely advanced liver cirrhosis, might result in hepatorenal syndrome. This disease is characterized by a decrease in kidney function due to decreased circulation. The precise causes of hepatorenal syndrome are not well comprehended, but it is likely that the disrupted equilibrium between vasoconstrictor and vasodilator variables has a substantial impact [39].

Alcoholic Skeletal Myopathy and Renal Damage

In severe cases of chronic alcohol consumption, individuals commonly experience a range of muscle symptoms including difficulties with walking, muscle cramping, soreness, and a loss in muscle mass. These muscle deficits happen regardless of peripheral neuropathy, starvation, or obvious liver illness. Chronic alcoholic myopathy is a condition where muscle mass can drop by up to 33%, making it the most common skeletal muscle ailment in developed countries. It affects approximately 50% of individuals who overuse alcohol [40].

While a definitive correlation between acute alcoholic myopathy and kidney injury has not yet been established, recent studies suggest a possible association. Although the precise mechanism of alcoholic myopathy is not fully understood, disruptions in mitochondrial-related energy equilibrium are likely to play a role in muscle cell dysfunction [41]. Occasionally, individuals who are chronically malnourished due to alcoholism may develop a condition called acute alcoholic myopathy, also referred to as alcoholic rhabdomyolysis. This condition can result in either reversible or irreparable acute kidney impairment [42-45].

Multiple investigations have established a connection between rhabdomyolysis and myoglobin poisoning, which can lead to acute kidney injury. This provides evidence for a potential link between alcohol use, alcohol-related acute myopathy, and kidney damage. For example, Belliere J, et al. [46] established a correlation between rhabdomyolysis and an excessive infiltration of macrophages in the kidney. This infiltration resulted in the activation of pro-inflammatory markers and subsequent damage to the organ. Plotnikov EY, et al. [47] demonstrated that myoglobin-induced oxidative stress causes damage to mitochondria isolated from rat kidneys. This suggests that rhabdomyolysis and myoglobin toxicity can lead to kidney oxidative stress by causing injury to mitochondria.

Alcoholic Cardiomyopathy and Renal Injury

Multiple epidemiological studies have demonstrated that moderate alcohol consumption can have a positive impact on cardiovascular health by decreasing the likelihood of developing coronary heart disease [48,49]. Nevertheless, excessive alcohol use has been associated with the onset of nonischemic dilated cardiomyopathy [50] and substantially increases the likelihood of experiencing sudden cardiac death [51]. Cardiorenal syndrome [52] refers to the impairment of kidney function caused by chronic or sudden heart failure. This syndrome encompasses intricate renal pathophysiological reactions, such as tissue edema, ischemia damage, peripheral vasoconstriction, and the stimulation of the renin-angiotensin-aldosterone system (RAAS), which controls blood circulation [53]. Excessive activation of the renin-angiotensin-aldosterone system (RAAS) worsens oxidative stress in individuals with persistent alcoholism [54]. Hence, oxidative stress not only causes renal failure but also plays a role in the advancement of chronic heart failure, leading to a harmful cycle in alcohol-related cardiovascular problems [55,56].

Conclusion

Chronic alcohol abuse or alcohol use disorders are a significant public health concern due to their detrimental effects on multiple organs in the human body. Alcohol can have a direct or indirect impact on the body, leading to damage in many organs. The detrimental consequences of alcohol arise either from the alcohol itself or from the excessive byproducts generated during its metabolism, such as acetaldehyde, NADH, and free radicals. The cellular pathophysiological alterations caused by alcohol are associated with organ damage and can potentially lead to kidney impairment. Moreover, intricate interplay across various organs can exacerbate and worsen the progression of renal pathology in patients with alcohol use disorder. Subsequent research efforts should investigate these theories to acquire a more profound comprehension of alcoholic kidney injury.

Conflict of Interest

None.

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