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Alcohol Consumption Can be a “Double-Edged Sword” for Chronic Kidney Disease Patients

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Excessive drinking of alcohol is becoming a worldwide problem, and people have recognized that there exists a close relationship between chronic kidney disease (CKD) and alcohol consumption. However, there are many inconsistencies between experimental and clinical studies on alcohol consumption and kidney damage. The possible reason for this contradictory conclusion is the complex drinking pattern of humans and some bio-activators in wine. In addition, the design itself of the clinical studies can also produce conflicting interpretations of the results. Considering the benefits of light-to-moderate alcohol consumption, we recommend that CKD patients continue light-to-moderate drinking, which is beneficial to them. Because alcohol consumption can lead to adverse events, we do not advise non-drinkers to start to drink. Although light-to-moderate alcohol consumption may not pose a risk to patients with CKD, the patients' condition needs to be considered. Consumption of even small amounts of alcohol can be associated with increased death risk. Additional clinical and experimental studies are needed to clarify the effect of alcohol on the kidneys and alcohol consumption on CKD patients.

MeSH Keywords: **Alcohol Drinking • Drinking Behavior • Polyphenols • Reactive Oxygen Species • Renal Insufficiency, Chronic**

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Background

As early as thousands of years ago, humans had mastered the primitive aspects of brewing technology. Nowadays, many forms of ethyl alcohol are available, such as beer, wine, vodka, and other spirits, and these have become very popular among adults. However, excessive alcohol consumption has become a worldwide problem. The World Health Organization estimates that more than 55% of adults consume alcohol, and 140 million people worldwide have alcoholism [1,2]. In fact, alcoholism is a serious problem in Asia, where 10.6–23.67% of men and 1.84–5.3% of women have a history of excessive alcohol consumption [3–9].

Another noteworthy problem is alcohol consumption in patients with chronic kidney disease (CKD). In recent years, CKD has become one of the most serious global public health problems. Recent studies estimated that CKD affects about 119.5 million people worldwide [10,11]. Some clinical studies show that alcohol consumption is an important issue in patients with CKD; approximately 20–36% of patients consume alcohol either occasionally or daily, and the approximate percentage of heavy drinkers among patients with CKD is 10% [10,12–14].

Age, diabetes, hypertension, hyperlipidemia, and smoking are traditional risk factors of cardiovascular disease in patients with CKD [15–17]. In addition, many studies have suggested that alcohol consumption can also affect the prognosis of patients with CKD. For example, the prognosis of light-to-moderate drinkers differs from that of heavy drinkers. Patients who are drinking more red wine may also benefit from its cardiovascular protective effects. Therefore, the influence of drinking on patients with CKD cannot be simply attributed to the effects of ethanol and its metabolites on the kidney; the influence of other bioactivators in alcohol and the effects of drinking on other body systems should be also considered [7,18–20].

It is interesting that many experimental studies have confirmed the damage caused by ethyl alcohol to glomeruli and renal tubules. However, some clinical studies have shown that moderate alcohol consumption is associated with lower occurrence of CKD, and alcohol consumption can alleviate the decline in kidney function. Numerous clinical studies have failed to reach a consistent conclusion regarding alcohol consumption and prognosis in patients with CKD.

In this review, we focused on the effect of ethyl alcohol on the kidneys and the effect of drinking on patients with CKD, and summarized the clinical and experimental studies. We analyzed and compared the advantages and disadvantages of alcohol consumption for patients with CKD and the contradictions in existing studies, and we hope to provide some information for clinical decision-making and policy formulation.

Effects of Ethanol on the Kidneys

Metabolic process of ethyl alcohol and the role of the kidney

In general, the proximal part of the small intestine is the main site for alcohol absorption. Additionally, the stomach, large intestine, esophagus, and even the mouth can absorb small amounts of ethyl alcohol [21].

Although most of the alcohol is metabolized in the liver, the kidneys are equally important in the metabolism and excretion of ethyl alcohol. Some enzymes that are necessary for ethanol metabolism, such as alcohol dehydrogenase, CYP2E1, and CYP24A1, have been found in the kidneys [22,23]. Furthermore, approximately 10% of ingested ethanol is excreted by the kidneys in its original form [21]. Therefore, excessive alcohol consumption places a major strain on the normal metabolic processes of the kidneys. For example, alcohol can induce the production of reactive oxygen species/reactive nitrogen species (ROS/RNS), which can result in oxidative stress in the kidneys, leading to potential renal injury resulting from hemodynamic disorders and inflammation [24–28].

Alcohol consumption and inflammation

In general, excessive alcohol consumption leads to liver damage [29]. However, some studies have found that ethanol can directly cause kidney damage, independent of liver damage [28,30,31]. Latchoumycandane et al. found that the effects of excessive ethanol metabolism alone are sufficient to significantly damage kidney function, without heavy liver dysfunction. Moreover, ethanol-induced kidney injury correlates with leukocyte infiltration and activation without oxidative ethanol catabolism by CYP2E1 [28].

A follow-up study by Latchoumycandane et al. indicated that infiltration of neutrophil myeloperoxidase and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase type 2 have critical roles in kidney structural damage and dysfunction associated with long-term alcohol consumption in mice [27]. Notably, leukocyte infiltration is related to prolonged and extensive ethanol exposure. Alcohol consumption for more than 4 weeks causes inflammatory injury in the kidney [25,32], and these conditions are not observed if alcohol consumption is for <2 weeks [33]. Nevertheless, Yuan et al. found that ethyl alcohol did not increase inflammatory cytokines in mice, but suppressed inflammation-related damage in bilateral renal ischemia reperfusion mice [20]. Even though the exact role of the inflammatory response is not clear, it has a critical role in alcohol-induced kidney injury.

Oxidative damage after chronic ethanol administration

Physically, the kidneys have several enzymes with antioxidant capacities, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase, which can balance various oxidative processes. Several studies have demonstrated that alcohol consumption increases ROS generation, which contributes to lipid peroxidation and damages antioxidant capacity [34,35].

In the kidneys, ROS is generated via both enzymatic and non-enzymatic processes [22,23,27,32,36,37]. In pathophysiological conditions, ROS, such as O_2^- , may react with nitric oxide (NO) to produce $ONOO^-$, which is a highly oxidizing compound that reacts with biological molecules, causing lipoperoxidation [25,38,39] and oxidation of proteins [40], cytomembrane, and DNA [32,37] in the kidneys. In addition, Das et al. reported that alcohol consumption impairs the ability of CAT to catalyze the decomposition of H_2O_2 in the kidneys [41]. This subsequently promotes the conversion of H_2O_2 to the more reactive hydroxyl radicals, which cause damage in antioxidant capacities and mitochondria in renal cells [34,42,43]. Samadi et al. also suggested that ethanol induces depression of nephrin and podocin in podocytes, which contributes to renal injury and proteinuria and is mediated by oxidative stress [44].

Unlike previous reports, some researchers indicated that ethyl alcohol pretreatment can improve renal antioxidant activities and capacity. Yuan et al. found that a small amount of ethanol pretreatment can increase the activities of inducible nitric oxide synthase and SOD in the kidneys, which ameliorated oxidative stress in an bilateral renal ischemia reperfusion simulation model as a compensatory mechanism [20]. Other research also reported that 5 weeks of ethanol exposure can improve CAT activities in the renal cortex in rats. Nevertheless, before rats received large doses of ethanol in their drinking water, they had a 3-week transition period with low concentrations of ethanol [37]. We think that the enhancement of CAT activities may not come from high concentration of ethanol, but rather from the compensatory improvement of antioxidant capacity after the intervention with low-concentration ethanol in the early stage.

Therefore, the effect of ethanol on renal antioxidant capacity varies with the concentration of ethanol and the duration of stimulation. In general, ethanol causes oxidative stress-related damage in the kidneys, but sometimes, in some conditions, it also improves the antioxidant capacity of the renal cells. Unfortunately, we only know that low-concentration ethanol can improve renal antioxidant capacity, but the exact dose and period are still unclear.

Effects of chronic alcohol consumption on the renin-angiotensin system (RAS), hypertension, and abnormal hemodynamics in the glomeruli

The glomeruli are sensitive to fluctuations of systemic blood pressure (BP), and the RAS is the most important BP control system in the kidneys. However, long-term alcohol consumption can activate the RAS and enhance sympathetic nervous activity, which elevates the systemic BP and destroys the normal structure of the glomeruli. Furthermore, this change is irreversible, and the renal structure cannot return to normal once ethanol stimulation is stopped [26,45].

NO is a free gaseous signal molecule produced by the NOS family, including neuronal NO synthase (nNOS), inducible NO synthase (iNOS), and endothelial NO synthase (eNOS), and it plays an important role in hemodynamics regulation. In general, NO is generated by mesangial cells and renal tubular epithelial cells, and it plays an important role in the regulation of glomerular and medullar hemodynamics and renin release. Although different studies have shown opposite results for the effects of NO and NOS activity with alcohol consumption [19,39,46,47], they came to a similar conclusion that NO and NOS play important roles in glomerular endothelial cell injury. In addition, long-term alcohol consumption decreases prostaglandin E2 in the kidney, which can release anti-inflammatory cytokines and dilate the afferent arteriole to increase glomerular blood flow, which causes kidney dysfunction and glomerular destruction [24].

Therefore, the interaction of RAS overactivity, hypertension, NO, and prostaglandin E2 deficiency under the influence of alcohol consumption cause abnormal hemodynamics in the glomeruli, which result in an adverse effect on the kidney morphological structure and renal function.

Abnormal immunoreaction and renal tubular dysfunction to alcohol consumption

Some abnormal immunological responses play a crucial role in glomerulonephritis; however, some studies have found that alcohol consumption can cause an abnormal immunoreaction, and the immunocomplex deposition in the glomeruli may be a cause of renal injury and nephropathy [48–50]. Kaartinen et al. found that an abnormal immunoreaction may be related to acetaldehyde, the first metabolite of ethanol, which can form covalent adducts with different proteins to activate the immune response [49].

In addition, long-term alcohol consumption can lead to injuries of renal tubules [1,2,30,39,51]. Na^+K^+ -ATPase present on the proximal tubular epithelial membrane is important for tubular reabsorption. However, recent studies have demonstrated

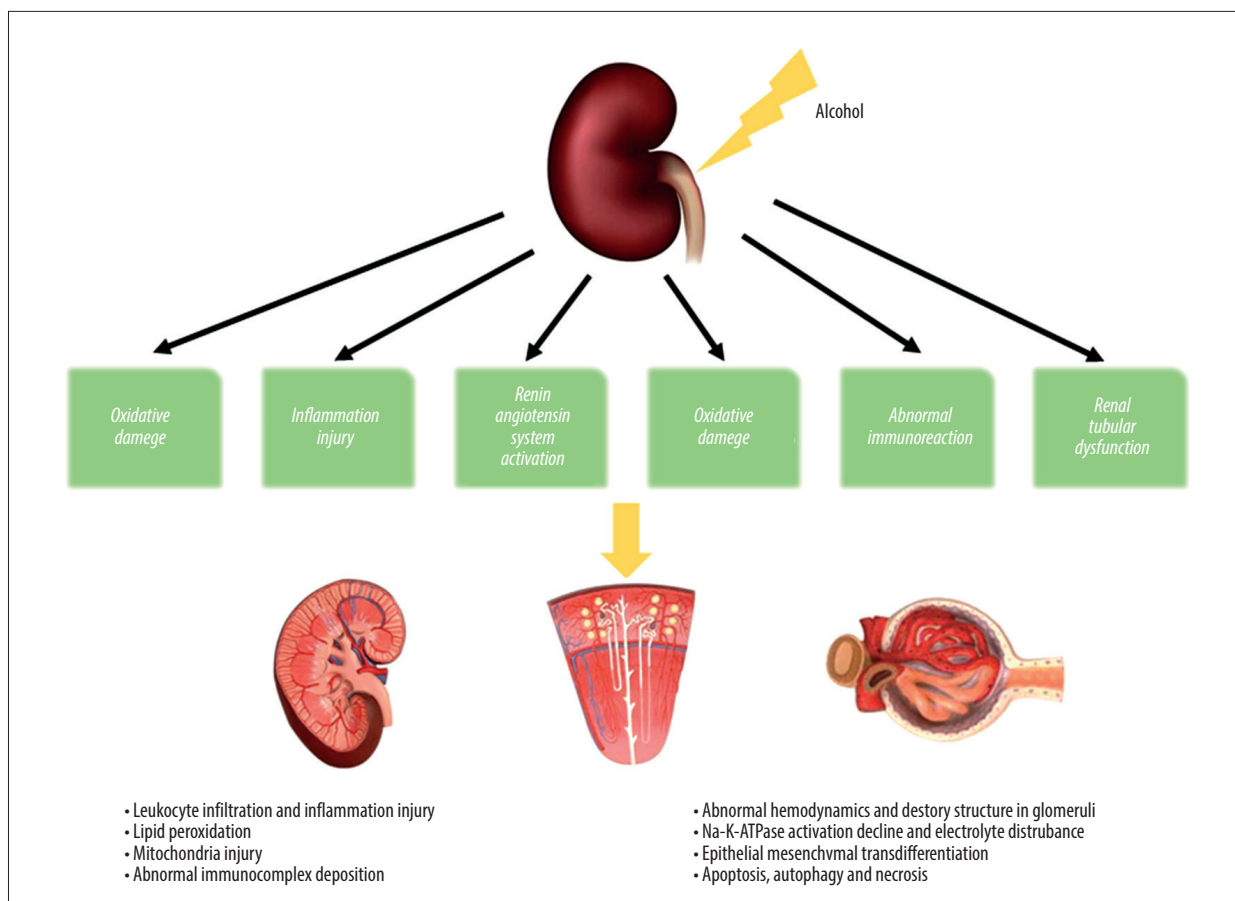


Figure 1. The possible mechanism of alcohol-induced renal injury.

that its activity is decreased by ROS and lipid peroxidation with the consumption of ethyl alcohol [22,41,52]. However, the effect of ethanol on renal tubule function is not limited to sodium ions. Diuresis by inhibiting vasopressin release [53] and impairing acid secretion have also been discovered in alcoholics. In addition, hypokalemia, hyponatremia, hypomagnesemia, hypocalcemia, hypophosphatemia, and metabolic acidosis mixed with volume-contracted metabolic alkalosis are common in long-term alcohol consumption.

Moreover, alcohol-induced renal tubular dysfunction is also reflected in vitamin reabsorption disorders. Subramanian et al. proved that chronic alcohol consumption can significantly inhibit carrier-mediated thiamin and biotin transport across the renal brush border membrane and basolateral membrane [54,55].

Other effects of ethanol on the kidneys

Some studies found that ethanol has an influence on renal damage, such as apoptosis and epithelial mesenchymal transdifferentiation. Nesreen and Sayed discovered that alcohol consumption significantly increased renal caspase3, caspase8, and caspase9 activity, and ethanol toxicity can increase the

ratios of Bax and Bcl-2 in kidney tissues compared to a control group [24,25]. This indicates that long-term ethyl alcohol consumption can activate both intrinsic and extrinsic pathways of apoptosis in the kidneys (Figure 1). However, other studies found that long-term alcohol consumption aggravates renal fibrosis, which may be related to epithelial mesenchymal transdifferentiation and fibrosis induced by ethanol [33,47,56].

Kidney injury secondary to alcohol hepatitis, cirrhosis, and other conditions

Kidney injury secondary to alcoholic hepatitis and cirrhosis is common among hospitalized patients [57,58]. Although patients with alcoholic hepatitis and cirrhosis are asked to stop drinking, the factors that cause kidney injury often persist. Alcoholic hepatitis and cirrhosis are associated with hypotension and vasodilation, which can overcome renal blood flow autoregulation, and these patients are prone to acute kidney injury (AKI) and tubular necrosis [59]. In patients with cirrhosis, the spontaneous bacterial peritonitis and sepsis always further aggravate the inflammation in the body; bacterial endotoxins and cytokines, such as TNF- α and IL-6, are closely related to acute/chronic kidney injury and albuminuria [60,61].

Moreover, alcoholic hepatitis and cirrhosis patients are susceptible to renal dysfunction caused by nephrotoxic drugs [62,63].

Therefore, the effect of ethanol on the kidney is beyond our original understanding. Alcohol can not only directly damage the kidney, but also causes renal dysfunction by damaging other organs. In addition, some studies proved that alcohol consumption aggravates kidney injury in diabetic nephropathy rats [64]. Hepatorenal syndrome, which is secondary to alcoholic hepatitis [65], and acute kidney injury, secondary to rhabdomyolysis, also cannot be ignored [46].

Association Between Alcohol Consumption and Chronic Kidney Disease

Effects of alcohol consumption on CKD incidence

Many studies have confirmed that unhealthy diet and lifestyle can cause various diseases, and heavy alcohol consumption is one of the important factors [66]. As an influential factor of many chronic diseases, alcohol consumption has been increasingly studied in recent years. Many studies have shown that alcohol consumption is related to cardiovascular disease, urinary protein, and CKD [3,6,16,45,66–69]. This review focused on 21 clinical studies of the relationship between alcohol consumption and CKD, including 13 cohort studies and 8 cross-sectional studies. The characteristics of the study design and other details of these studies are presented in Table 1.

However, reports on the effects of alcohol consumption on healthy people have not been consistent, with some studies suggesting that alcohol consumption leads to albuminuria and decreased glomerular filtration rate, but others finding the opposite. Shankar et al. found that chronic alcoholism is associated with CKD [70], which is consistent with results from previous studies [71,72]. In their study, excessive alcohol consumption is associated with a higher odds ratio of CKD than in the abstainer. Other studies also found a higher association between heavy drinking and albuminuria or CKD, particular among young and middle-aged men [4,67,73,74]. However, Kimura et al. found a U-shaped and J-shaped association between alcohol consumption and the incidence of proteinuria in men and women, respectively. Then, they identified the anti-proteinuric effect of 15–30 g/day (moderate) alcohol consumption [3]. Another study suggested that light wine consumption or moderate alcohol consumption is associated with lower prevalence of albuminuria and CKD compared to abstinence [15,75,76]. Interestingly, some researchers think that moderate alcohol consumption may be an indicator of social integration and overall well-being, which are good for health [77].

However, the effect of alcohol consumption on estimated glomerular filtration rate (eGFR) is different from that of albuminuria. White et al. [74] found that ethanol intake has an inverse, approximately linear, relationship with the risk of onset of eGFR <60 mL/min/1.73 m². The same relationship between frequency of drinking and CKD is also found in healthy Japanese, Koreans [7,9,16,78,79], and others [73,80–82]. The same result also was confirmed among both African and Caucasian men and women. Hu and colleagues found that alcohol consumption may lower the risk of developing CKD, and the protective effect persisted even with heavy drinking [83]. This may be because alcohol consumption lowers the risk of type 2 diabetes and rise in serum high-density lipoprotein, which are closely related to CKD. Although the exact cause of this contradictory result is unknown, it could be related to their clinical research design [74].

Influence of alcoholism on the prognosis of patients with CKD

Although many studies have shown that alcoholism causes proteinuria and increases the risk of CKD in healthy people, other studies have also shown that alcohol consumption is one of the protective factors for patients with CKD. Migliori et al. [84] observed a decrease of inflammatory parameters in patients with CKD after consuming extra-virgin olive oil and white wine, due to the simple phenol that inhibits activity on pro-inflammatory cytokines. The same cardiovascular protective effects are found in red wine [15]. However, some researchers observed that the protective effect of alcohol consumption on patients with CKD is not limited to red wine, and the protective effect of alcohol consumption in patients with CKD is more obvious with the increase of alcohol consumption [13]. Persistent alcohol consumption remained significantly associated with a lower risk of all-cause mortality in patients with CKD [12]. Although alcohol consumption leads to hypertriglyceridemia in patients with CKD, which is associated with low eGFR and albuminuria, daily alcohol intake still reduces the risk of disease progression [5]. Other studies discovered that heavy drinking cannot further reduce CKD risk, which enforces the hypothesis that moderate alcohol consumption is best for patients with CKD [85–87]. Light alcohol consumption in women and moderate alcohol consumption in men are associated with improved indices of eGFR in patients [50].

In contrast, Menon et al. could not find any adverse or beneficial effects of alcohol consumption on kidney function in the elderly [88]. A Japanese cohort study also found that CKD is an independent risk factor for higher rates of stroke in men and women. Furthermore, moderate alcohol consumption appears to be harmful in patients with CKD because it increases the incidence of cerebral hemorrhages [14,89].

Table 1. Characteristics of the clinical studies on alcohol consumption and chronic kidney disease.

| Author and tear of publication | Study design | Eligible criteria | Number of the patients | Age | Race | Gender | Follow-Up Period | The Exact Definition of Alcohol Intake | Conclusion |
|--------------------------------|----------------------------|--|------------------------|--|---|-------------------------------|--------------------------------|--|--|
| Hu EA, et al. 2019 [83] | Cohort study | 45–64 years; black and white; available data for all the variables included in the analysis; free of CKD at baseline | 12692 | 45–64 years | 9656 white and 3036 black | 7089 women and 5603 men | Median 24 years | never drinkers; former drinkers; ≤1 drink/week; 2–7 drinks/week; 8–14 drinks/week; ≥15 drinks/week | Consuming a low or moderate amount of alcohol may lower the risk of developing CKD |
| Umesawa M, et al. 2018 [16] | Retrospective cohort study | Free from kidney disease or CKD at the first checkup | 153007 | 40–74 years | Japanese | 94005 women and 41002 men | 10 years | Never; occasional; every day | Daily alcohol intake was negatively associated with risk for CKD in both women and men |
| Pan C, et al. 2018 [67] | Retrospective cohort study | Alcohol abuse and personal history of alcoholism, and exclude the patients with an established diagnosis | 11639 | 42.90±12.75 years | Taiwanese | 2608 women and 9031 men | 6.47±3.80 years | All patients were heavy drinkers with alcohol dependence syndrome | Patients with alcohol use disorder have a higher risk of CKD |
| Kimura Y, et al. 2018 [3] | Retrospective cohort study | Free from kidney disease or CKD at the first checkup | 177572 | Median 66 years in men and 66 years in women | Japanese | 88925 women and 88647 men | Median 1.8 years | Rare drinkers; occasional drinkers; daily drinkers with ethanol intake ≤19; 20–39; 40–59; ≥60 g/day | Moderate alcohol consumption was associated with lower risk of proteinuria in both males and females. Females with ≥60 g/d of alcohol consumption were at higher risk of proteinuria, whereas males were not |
| Jespersen T, et al. 2018 [15] | Cross-sectional study | Age ≥21 years; completed the food frequency questionnaire; available data for all the variables included in the analysis | 5852 | ≥21 years | U.S. population | 2779 men and 3073 women | – | None; light (<1 glass/day); moderate (1 glass/day) | Light wine consumption is associated with lower prevalence of CKD and a lower odd of CVD in those with CKD in the U.S. population |
| Bundy JD, et al. 2018 [12] | Cohort study | Mild to moderate CKD on the basis of an eGFR entry criterion of 20–70 ml/min per 1.73 m ² | 3939 | 21–74 years | Non-Hispanic white 1638; Non-Hispanic black 1650; Hispanic 497; other 154 | 1778 women and 2161 men | Maximum duration of 10.9 years | User or nonuser | Drinking is associated with lower risk of all-cause mortality among patients with CKD |
| Tsuruya K, et al. 2017 [5] | Cohort study | Without history of renal diseases | 117279 | 39–74 years | Japanese | 47737 men and 69542 women | 2 years | Every day; sometimes; rarely | Daily drinking reduces the risk of CKD |
| Matsumoto A, et al. 2017 [117] | Cross-sectional study | Age ≥40 years; available data for all the variables included in the analysis | 292013 | ≥40 years | Japanese | 117 692 men and 174 321 women | – | Rare; occasional; ethanol intake ≤ 19 g/d; ethanol intake 20–39 g/d; ethanol intake 40–59 g/d; ethanol intake ≥ 60 g/d | Mild to moderate alcohol consumption might be associated with a lower risk of CKD |

Table 1 continued. Characteristics of the clinical studies on alcohol consumption and chronic kidney disease.

| Author and year of publication | Study design | Eligible criteria | Number of the patients | Age | Race | Gender | Follow-Up Period | The Exact Definition of Alcohol Intake | Conclusion |
|--------------------------------|-----------------------|--|------------------------|-----------------|--|-----------------------------|-------------------|--|---|
| Lin M, et al. 2016 [4] | Cross-sectional study | Without estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m ² and/or urinary albumin creatinine ratio ≥30 mg/mmol | 15390 | 40–65 years | Chinese | 5396 males and 9994 females | – | Never; past (past drinking for 4–6 months); current (<210 g/week, 210–420 g/week, ≥420 g/week for men, <140 g/week, 140–280 g/week, ≥280 g/week for women) | Heavy alcohol intake was associated with an elevated risk for renal hyper filtration |
| Shirai Y, et al. 2016 [7] | Cross-sectional study | Age 29–80 years; without current or history of CKD | 9388 | 29–80 years | Japanese | 6343 men and 3045 women | – | Drinking frequency: 0, 2, 3–4, 5–6, and 7 days/week. Amount of alcohol consumption: 0, <20, 20–40, 40–60, and >60 g/day for men and 0, <10, 10–20, 20–30, and >30 g/day for women. | In men, negative and positive linear relationships with drinking habits were found for CKD risks and mean eGFR, respectively. But there was a lack of a relationship in women |
| Dunkler D, et al. 2016 [75] | Cohort study | Middle-aged adults with type 2 diabetes but without severe albuminuria | 6916 | Median 66 years | White 4699; Asian 1173; Native Latin 650; Others 394 | 2209 female and 4707 males | 5.5 years | No; moderate; heavy drinker | It is lower risk for CKD in individuals with moderate alcohol than non-drinkers |
| Koning SH, et al. 2015 [80] | Cohort study | Free of CKD at baseline and available data for all the variables included in the analysis | 5476 | 48.4±11.7 years | Unclear | 2881 female and 2595 male | Median 10.2 years | Non-drinker; occasional(<10 g/week); light (10–69.9 g/week); moderate (70–210 g/week); heavier(>210 g/week) | Alcohol consumption was consistently inversely associated with the risk of CKD |
| Kanda E, et al. 2015 [8] | Cohort study | Healthy people without CKD | 7473 | 38.8±10.5 years | Japanese | 5572 male and 1901 female | 3 years | No alcohol consumed; 20–140 g of alcohol/week; >140 g of alcohol/week | Light drinking and high exercise frequency were associated with the increased risk of loss of kidney function in male |
| Dunkler D, et al. 2014 [77] | Cohort study | Patient with diabetes but without macroalbuminuria | 6972 | Median 66 years | Caucasian | 4743 male and 2229 female | 5.5 years | Moderate (1–12 drinks/week for women and 1–18 drinks/week for men); heavy alcohol intake (>12 drinks/week for women, and >18 drinks/week for men) | Drinking moderately had a significantly reduced risk of CKD compared with nonusers |

Table 1 continued. Characteristics of the clinical studies on alcohol consumption and chronic kidney disease.

| Author and tear of publication | Study design | Eligible criteria | Number of the patients | Age | Race | Gender | Follow-Up Period | The Exact Definition of Alcohol Intake | Conclusion |
|--------------------------------|-----------------------|---|------------------------|---|---------------------------|-----------------------------|------------------|--|---|
| Kim NH, et al. 2014 [9] | Cross-sectional study | Age ≥40 years; available data for all the variables included in the analysis; free of CKD at baseline | 5251 | ≥40 years | South Korean | 2386 male and 2865 female | – | Abstinence; moderate drinking (women, 0.1–19.99 g/day; men, 0.1–39.99 g/day), and heavy drinking (women, ≥20 g pure alcohol/day; men, ≥40 g pure alcohol/day). Binge drinking (men, ≥60 g pure alcohol/day; ≥48 g/day for women) | Alcohol consumption was inversely associated with a reduction in eGFR in Korean men |
| Hsu YH, et al. 2013 [13] | Cross-sectional study | eGFR >30 ml/min/1.73 m ² , and available data for all the variables included in the analysis | 27253 | 58.82±12.04 years of men and 57.18±11.59 years of women | Taiwanese | 15 353 women and 11 900 men | – | Non-drinkers, occasional drinkers, or frequent drinkers | Alcohol consumption was inversely associated with stage 3 CKD in Taiwanese men |
| Funakoshi Y, et al. 2012 [79] | Cross-sectional study | Available data for all the variables included in the analysis; free of CKD at baseline | 9196 | 57.9±5.1 years | Japanese | Men | – | Non-drinkers; 1–2/week; 3–4/week; 5–6/week; everyday | It is inverse association between frequency of drinking alcohol and CKD in apparently healthy men |
| Buja A, et al. 2011 [90] | Cohort study | 65–84 years old | 3404 | 65–84 years | Italians | 1619 women and 1785 men | Mean 3.5 years | For men (lifelong abstainers; former drinkers); ≤12 g/d; 13–24 g/d; 25–47 g/d; >48 g/d); for women (lifelong abstainers; former drinkers; ≤12 g/d; 13–24 g/d; and >24 g/d) | Moderate quantities of alcohol are not injurious to renal function in elderly men |
| Menon V, et al. 2010 [88] | Cohort study | Age ≥65 years and available data for all the variables included in the analysis | 4343 | ≥65 years | 3765 white and 578 others | 2586 female and 1757 male | Mean 5.6 years | None, former, <1 drink, 1–6 drinks, 7–13 drinks and ≥14 drinks/week | Moderate alcohol consumption has neither adverse nor beneficial effects on kidney function in senior |
| White SL, et al. 2009 [74] | Cohort study | Age ≥25 years and available data for all the variables included in the analysis | 6259 | ≥25 years | Australians | 2810 males and 3449 females | 5 years | Non-drinker; light; moderate; heavy drinker | Moderate-heavy alcohol consumption may be an important modifiable risk factor for albuminuria in the general population |
| Shankar A, et al. 2006 [70] | Cross-sectional study | Age 43–84 years and available data for all the variables included in the analysis | 4898 | 43–84 years | 98% Caucasians | 2744 women and 2154 men | – | None; <1 servings/week; 2–4 servings/week, 5–6 servings/week, 1–3 servings/day; ≥4 servings/day | Heavy drinking is associated with CKD |

Influence of sex, age, primary diseases and other confounding factors

Sex, age, primary diseases, initial GFR, individual differences, and dietary structure can all influence the results of a study. Although associations between alcohol consumption and CKD risk did not show significant interactions with age, sex, smoking, hypertension, or hypercholesterolemia [80], many studies still found that the effect of alcohol consumption on CKD varies with sex [13,14,76,90], as it appears that sex may be a significant determinant of the effects of alcohol on GFR [50,91].

One of the reasons for this sex difference might be the different pharmacokinetics of ethyl alcohol between men and women. Since women, with a lower proportion of body water, have a smaller distribution volume for alcohol, they are more likely to have a higher concentration of alcohol in the blood than men. Moreover, women with a lower activity of gastric alcohol dehydrogenase have lower gastric first-pass metabolism of alcohol, which also leads to a higher concentration of alcohol than in men [92]. Since women have a higher blood concentration of alcohol, they may be more sensitive to alcohol than men [3,50,90]. At the same time, the difference in the actual amounts of alcohol consumption [79] between men and women causes this sex difference. Men generally drink more than women, and men have higher rates of alcoholism than women. Furthermore, the cardiovascular-protective effects of estrogen [91,93] should not be overlooked.

Age, primary diseases, initial eGFR, and individual differences can also affect the prognosis of patients with CKD and interfere with the effects of alcohol on the kidneys [7,10,67,94]. Since aging, metabolic diseases, and hypertension impair kidney function, they can also influence the effect of ethanol on the kidneys. Thus, the risk of kidney damage from alcohol increases with age, metabolic diseases, hypertension, and initial eGFR. However, Buja et al. suggested an inverse linear relationship between moderate alcohol consumption and the risk of age-related loss of renal function [90]. Although moderate alcohol consumption contributes to increased insulin sensitivity [95,96] and delays the progression of diabetes [77,97], the prognosis of such patients differs from non-diabetic but moderate drinking patients with CKD. This indicates that moderate drinking may be beneficial for patients with CKD, but it is not enough to offset the adverse effects of metabolic disease on these patients.

Genetic and individual differences sometimes need to be taken into account [78]. As known, alcohol tolerance varies greatly from person to person, and some nations consume more alcohol than others. Although studies on individual differences in alcohol consumption and CKD are limited, existing studies have found that individual variation in an alcohol

dehydrogenase gene may play a role [98], but more studies are needed to confirm these findings.

Special Benefits and Confounding Factors of Alcohol Consumption

Some special bioactivators in alcohol

Ethyl alcohol and water are the main ingredients of alcohol beverages, but we cannot ignore other bioactivators in liquors, such as polyphenols. Red wine is one of the most abundant sources of polyphenols [99], and a glass of red wine contains about 100 mg of polyphenols [100], which is the reason for the French Paradox phenomenon (low incidence of cardiovascular diseases while consuming a diet rich in saturated fat) and the Mediterranean diet advantage (rich in fruits and wine, it was shown to protect against the coronary diseases) [42].

Although there has long been controversy about the renal-protective effect of alcohol consumption on kidney injury, the renal-protective effects of polyphenols and other bioactivators from wine has been demonstrated in many studies [15,95,97,101–103]. These include anthocyanins, which are the main polyphenols in red grapes, and resveratrol, which is the most famous polyphenolic compound found in red wine [104]. They have been demonstrated to have ROS scavenging, anti-platelet, anticancer, anti-inflammatory, antidiabetic, antibacterial, antiaging, and cardiovascular and renal-protective effects [105–112]. Moreover, other bioactivators in red wine, excluding resveratrol, and those in white wine, also have the function of ROS scavenging and renal protection [7,84,113].

However, we should be aware that alcohol also can contain harmful substances. Sanoff et al. found that consumption of a homemade alcohol, prepared by an unregulated process in Nicaragua, may be related to kidney injury among the local residents, which may related to pesticides or heavy metals contamination [114].

Drinking patterns and associated effects

Drinking pattern is another factor that can influence the effects of alcohol consumption in patients with CKD. Unlike experimental studies, human drinking patterns are fraught with uncertainty. Drinking patterns irregularly vary among people, especially among those who drink occasionally. There are still big questions about whether occasional heavy drinking causes kidney damage and whether occasional light drinking still has a renal-protective function. Umehara et al. analyzed the relationship between different drinking patterns (never, occasional, and every day) and CKD prognosis, and they discovered that daily alcohol intake is negatively associated with the risk for

CKD in both women and men [16]. However, their results did not consider the relationship between frequency and total alcohol consumption; someone may drink more alcohol on one occasion than another's total intake for 1 week, which may also affect the analysis of the results.

Although the Japanese government has clearly defined the classification of alcohol consumption – 20 g ethanol/day as moderate intake; ≥ 40 g ethanol/day as the volume related to increased risks of lifestyle-related diseases; ≥ 60 g ethanol/day as excessive intake – and a lower volume is recommended for women than for men, it does not consider the drinking patterns. However, clinical research shows the amounts and patterns of alcohol consumption both affect eGFR in patients with CKD [7].

Specific effects of drinking patterns have been demonstrated in a study of ischemic heart diseases [76]. This meta-analysis found a significant difference when comparing episodic heavy drinkers with moderate regular drinkers; the former increases the risk of ischemic heart diseases [115]. There is a lower risk of ischemic heart disease for moderate drinkers without heavy drinking occasions and a higher risk for drinkers with the same average amount who engaged in heavy episodic drinking [76]. Moreover, the harmful effect of episodic heavy drinking seems to be more obvious in people with light alcohol consumption, and it may be related to a rise in platelet reactivity and thrombosis after binge drinking [9].

Potential confounding factors of alcohol consumption

Alcohol consumption is a factor that can interfere with the prognosis of patients with CKD; however, it is not the only factor responsible for this effect. Many factors associated with alcohol consumption, such as smoking, drug abuse, use of nonsteroidal anti-inflammatory drugs, high-fat diet, coffee, and energy drinks, also interfere with the prognosis of these patients [67].

These unhealthy behaviors are very common among alcoholics; for example, people tend to smoke when they are drinking and eat calorie-dense and hypersaline foods. Bundy et al. found that illicit drug use is associated with a higher risk of CKD aggravation and all-cause mortality, while smoking is associated with a higher risk of all-cause mortality than in non-smokers [12].

Moreover, smoking increases the oxidative stress injury caused by drinking to various organs [116], and it worsens the renal injury caused by alcohol abuse in patients with CKD [70]. According to some studies, alcohol consumption was inversely associated with the risk of a low eGFR in male and female non-smokers, but they did not observe any benefit in female smokers [117]. Current smoking may modify the potential benefits of light-to-moderate alcohol consumption [85], and heavy drinking combined with daily smoking appears to be associated with various chronic diseases [6].

Other studies found that alcohol combined with energy drinks, caffeine, or soft drinks can disturb the physiological redox reaction and cause lipoperoxidation in the liver and nephrotoxicity [30,118]. Furthermore, drinkers often like to eat more pickled food and eat less vegetables and fruits, which increases the consumption of salt and cholesterol [119]. Hu et al. found that people who consume high levels of alcohol may have poorer-quality diets than never drinkers and light-to-moderate drinkers; however, the protective effects of alcohol consumption are not offset by their unhealthy diets [83]. A relatively low incidence of cardiovascular disease was found in middle-aged French men, despite a relatively high dietary intake of saturated fats. Subsequent research suggests that it is potentially attributable to the consumption of red wine, which contains various polyphenols and has various protective effects [42,120], and we believe the same protective effects can be seen in patients with CKD.

Abstinence and the “sick quitters” hypothesis

Abstinence is one of the characteristics of human drinking habits; many doctors will encourage patients to stop drinking, which may be good for their health [121]. As for the kidney damage caused by alcohol, some studies discovered that the patients' renal function recovered after abstinence [1]. However, others also found that abstinence cannot completely repair the kidney injury [26]. Unfortunately, existing clinical studies have not analyzed why some patients with CKD give up drinking and the influence of giving up drinking on the prognosis of these patients.

The “sick quitters” hypothesis means the higher risk of CKD in non-drinkers was not attributed to “giving up drinking.” Patients who give up drinking may do so because they were diagnosed with CKD and other diseases. Since many of the recent clinical studies are observational studies, the “sick quitters” hypothesis is always difficult to clarify. However, some studies confirm that long-term alcohol consumption is not related to eGFR decrease, and light-to-moderate drinking is inversely associated with the risk of CKD after all non-drinkers and former drinkers were excluded at baseline or during follow-up from their studies [80,88].

Therefore, we need more evidence to determine whether abstinence can relieve and heal the kidney damage caused by long-term alcohol consumption and the effects of alcohol abstinence on the prognosis of patients with CKD.

Limitations of Existing Studies

Although there have been many clinical studies on alcohol consumption and CKD, most have some limitations that could cause misinterpretation of the results and conclusions.

First, many studies are based on patients' routine health check-ups, as annual health examinations do not allow researchers to evaluate any fluctuation in serum creatinine and other biomarkers. Moreover, many patients were excluded from the long-term observational studies because they did not attend routine annual health checkups. Although the researchers do not analyze the reasons why people are lost to follow-up, we cannot ignore the possibility that some patients were diagnosed with CKD and had begun regular medical treatment in another medical center. We also realize that previous studies did not include an adequate number of heavy drinkers, especially female heavy drinkers. Therefore, the relationship between heavy alcohol consumption and CKD may be affected by this sampling bias [16,79,117].

Second, the proteinuria detection and diagnosis of CKD can also affect the credibility of the conclusion. In most studies, proteinuria was detected by a single measurement using a dipstick test. Although studies have proven that even a single dipstick indication of proteinuria is a significant risk for CKD and ESRD [122], a single dipstick detection can be biased by numerous confounders. In other studies, the researchers used serum creatinine or eGFR to ascertain the kidney function of patients; however, they are not ideal in many drinkers, especially in those with extremely low or high muscle mass due to chronic alcoholism [123]. Moreover, different equations of eGFR calculation (Cockcroft-Gault equation, the Modification of Diet in Renal Disease equation, and the Chronic Kidney Disease Epidemiology Collaboration equation) may result in different eGFR despite using the same serum creatinine value [67,74,124].

Third, in most studies, patients' alcohol consumption data were obtained by a fixed self-administered questionnaire, and this method lacks quantitative measurement. This self-report is susceptible to under-reporting and underestimates the patients' alcohol consumption [12,13,117].

Conclusions

In summary, there is no exact evidence that alcohol consumption aggravates the state of CKD or increases all-cause mortality in CKD, and the protective effect of abstinence on such patients is unclear. Although many studies stated that people should not start drinking for any reason, and alcohol

consumption can increase disease risk [125], we also cite many studies demonstrating the protective effects of light-to-moderate alcohol consumption in our review.

In view of the protective effect of moderate alcohol consumption on cardiovascular diseases, we consider that light-to-moderate alcohol consumption may not have adverse effects. Thus, current alcohol consumers can continue to enjoy light-to-moderate drinking and benefit from it. However, as alcohol consumption can lead to adverse events, such as hypertension, cerebral hemorrhage, alcohol addiction, and tendencies toward violence, clinicians should not advise non-drinkers to start drinking.

Although light-to-moderate alcohol consumption may not pose a risk to patients with CKD, the patients' condition needs to be considered. Many patients with CKD often have other comorbidities, such as diabetes, coronary heart disease, stroke, and other serious chronic diseases. For these patients, drinking alcohol may further increase their risk of death. In addition, alcohol consumption can contribute to volume overload, hypertension, and electrolyte disorder between hemodialysis sessions in hemodialysis patients, which also should not be ignored. So, alcohol consumption can be a double-edged sword for patients with CKD, and any policy regarding alcohol consumption for them must be very cautious.

Drinking is a complex social activity, and the results of many studies on the effect of alcohol consumption on CKD may be affected by many confounding factors. This makes it difficult for us to obtain reliable evidence to support our conclusions. More clinical and experimental studies are needed to confirm the effect of alcohol consumption on CKD. Additionally, the drinking pattern, integral dose of alcohol consumption, differences in alcohol beverages, and various concomitant factors should be considered, as they have a significant influence on the effects of alcohol consumption.

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Conflict of interest

None.

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