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COMMENTARY

Impact of mild-to-moderate alcohol consumption and smoking on kidney function

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It has been noted that modifiable lifestyle factors, such as alcohol,[1] smoking,[2] sleep and exercise, contribute to progression of chronic kidney disease (CKD).[3] Excessive alcohol consumption can lead to a variety of adverse effects, including liver disease, heart failure, increased cancer risk, neurologic complications and unintentional injuries. Balanced against these deleterious effects is the observation that compared to abstinence or heavy drinking, moderate alcohol intake may have health benefits, particularly in regard to cardiovascular disease (CVD)[4] and type 2 diabetes;[5] however, its association with the risk of CKD had received considerably less attention. Recently, the relationship between an amount of alcohol consumption and incident CKD has been investigated in longitudinal observational studies. In a community-based followed-up study carried out in Japan, compared with abstention, alcohol consumption of <20 g per day was associated with a decreased risk of developing a positive dipstick proteinuria in men, with a similar trend in women, during annual examinations for 10 years among 123 764 Japanese adults.[6] Most recently, in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective population-based cohort in the Netherlands, alcohol consumption was inversely associated with the risk of development of CKD during four serial follow-up examinations (median 10.2 years) among 5476 participants aged 28–75 years who were free of CKD at baseline.[1]

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In Japan, alcohol was one of the nine target areas included in the 'National Health Promotion Movement in the 21st Century (Healthy Japan 21)' launched in 2000.[7] Its basic policy was to promote the following: (1) early detection and treatment of heavy drinking, (2) prevention of alcohol-drinking by minors and (3) dissemination of knowledge about alcohol and health. With regard to point (3), on the basis of a study that had targeted Japanese men aged between 40 and 59 years,[8] and a meta-analysis of surveys that had targeted Westerners,[1] a drinking level considered to be 'moderate' was set as an average daily intake of about 20 g of pure alcohol (with a smaller amount for women).[9] In contrast, Healthy Japan 21 defines a person as a heavy drinker with an alcohol problem if he/she drinks about 60 g of pure alcohol (540 ml on a seishu-converted basis) per day.[9] In contrast, smoking has been previously shown to be associated with progression of CKD.[2,3] Further, joint exposure to both current smoking and heavy drinking has been associated with higher odds of CKD than their individual effects.[10] However, the association of smoking and mild-to-moderate alcohol consumption on kidney function is not entirely clear.

In this issue of *Hypertension Research*, Matsumoto *et al.*[11] demonstrate a relationship between mild-to-moderate alcohol consumption and a lower prevalence of proteinuria in non-smokers, but not in smokers, using the data from the cross-sectional survey of 292 013 individuals undergoing the Specific Health Check and Guidance in Japan. They evaluated the drinking and smoking habits of the participants by a self-reported questionnaire and categorized alcohol consumption as follows: drink score (0) rare,[1] occasional,[2] ethanol intake $\leqslant 19$ g per day,[3] ethanol intake 20–39 g per day,[4] ethanol intake 40–59 g per day[5] and ethanol intake $\geqslant 60$ g per day. Furthermore, they defined kidney dysfunction, one of the outcomes, as an eGFR <60 ml min^{-1}/1.73 m^2 because recent reports have demonstrated that an eGFR <60 ml min^{-1}/1.73 m^2 is a risk factor for CVD and end-stage renal disease (ESRD), resulting in the establishment of CKD stage 3a. They assessed proteinuria (defined as 1+ or more urinary protein by dipstick test) as the other outcome.

In the results, mild-to-moderate alcohol consumption was associated with a lower incidence of proteinuria in non-smokers, and this finding was consistent with previous publications (Figure 1). However, in smokers, the association of alcohol with proteinuria was not observed. Furthermore, alcohol consumption was inversely associated with the risk of decreased estimated glomerular filtration rate (eGFR), but in female smokers, the association between mild-to-moderate alcohol consumption and a lower prevalence of eGFR <60 ml min^{-1}/1.73 m^2 was not observed (Figure 1). The reason might be that uric acid and past history of kidney disease were slightly higher in female smokers than non-smokers.

The possible mechanism of effects of alcohol consumption to prevent CKD is explained as follows:

- Moderate consumption may be associated with increased insulin sensitivity, high-density lipoprotein (HDL) and plasma concentration of endogenous tissue-type plasminogen activator,[12] thereby protecting against atherosclerosis.
- Alcohol acutely increases urine production, most likely through inhibition of the

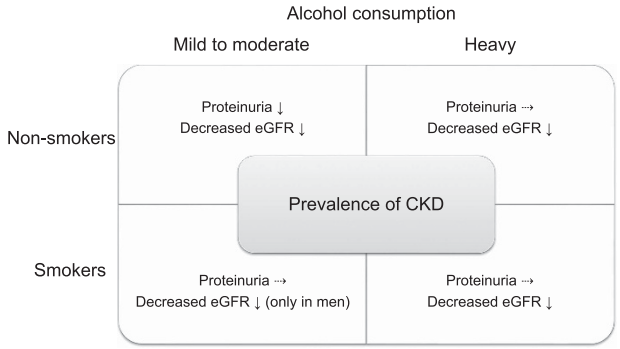

Figure 1 Summary of the results of the association of alcohol consumption and smoking with the prevalence of chronic kidney disease (CKD). Mild-to-moderate alcohol consumption was associated with a lower incidence of proteinuria in non-smokers, but in smokers, the association of alcohol with proteinuria was not observed. Furthermore, alcohol consumption was inversely associated with the risk of decreased eGFR, but in female smokers, the association between mild-to-moderate alcohol consumption and a lower prevalence of estimated glomerular filtration rate (eGFR) <60 ml min^{-1}/1.73 m^2 was not observed. Down arrow: significant lower prevalence of proteinuria or decreased eGFR (eGFR <60 ml min^{-1}/1.73 m^2) compared with a drink score of (0) rare. Dashed arrow: not significant compared with a drink score of (0) rare.

release of arginine vasopressin (antidiuretic hormone).[13]

- Ethanol at low concentrations (0.02–0.1 mmol ml^{-1}) protected murine glomerular podocytes through alcohol dehydrogenase (ADH) and 20-hydroxyeicosatetraenoic acid (20-HETE).[14] Additionally, 20-HETE, an arachidonic acid metabolite generated by CYP4a12a, blocked the ethanol-induced cytoskeletal derangement and superoxide generation. In contrast, ethanol at high concentrations (0.4 mmol ml^{-1}) altered the actin cytoskeleton, induced CYP2e1, increased superoxide production and inhibited ADH gene expression.[14] These findings are suggesting that ethanol may positively and negatively affect several metabolites and signaling pathways involved in regulating glomerular barrier function.

As for gender differences, it has been reported that estrogen affects the glomerular and vascular remodeling and induces cardiorenal protection.[15] Estrogen prevents CKD progression by lowering the cardiovascular stress response to adrenergic stimuli. Moreover, it has been reported that testosterone induces apoptosis in proximal tubule cells. Alcohol consumption increases the estrogen level in females and decreases testosterone levels.[16] These findings suggest that alcohol consumption may modify the effect of sex hormones on the loss of kidney function. In Japan, alcohol consumption in males was higher than that in females, and therefore, the renoprotective effect of alcohol might lead to improvement in kidney function in males compared with females.

Smoking induces CVD through several key mechanisms. One important mechanism is that the nicotine from cigarette smoke induces sympathetic nervous system activation, which results in coronary vasoconstriction.[17] Other mechanisms include endothelial dysfunction, the lowering of the zinc serum/urine quotient, insulin resistance and oxidative stress.[17,18] Therefore, smoking might have modified the potential benefits of alcohol to prevent CKD.

Alcohol also has an adverse effect on driving safety and can increase liver dysfunction, heart failure and some cancers; therefore, the results regarding alcohol intake should be interpreted carefully. Nevertheless, in non-smokers, mild-to-moderate alcohol consumption may not need to be prohibited, at least regarding its effects on kidney function. Further studies are needed to better understand the effects of alcohol consumption on kidney function in patients with CKD.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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