学 位 論 文 の 要 旨

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学　位　論　文　名　Frequency of Alcohol Drinking Modifies the Associations of Salt Intake With Blood Pressure and Albuminuria: A 1-year Observational Study

発　表　雑　誌　名
（巻，初頁～終頁，年）　別紙のとおり
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論 文 内 容 の 要 旨

INTRODUCTION

The salt sensitivity of blood pressure is characterized by the blood pressure response to salt intake. The salt-sensitive subjects will sustain an increase in blood pressure with salt loading and a decrease in blood pressure with salt depletion. Besides physiological, genetic, demographic, and environmental factors, dietary factors play a pivotal role in salt sensitivity. The previous study reported that salt sensitivity was more common in heavy alcoholics than in non-drinkers. However, in the general population, the effect of drinking alcohol on salt sensitivity remains unclear.

Albuminuria, one of the essential characteristics of chronic kidney disease, is a strong prognostic factor for cardiometabolic diseases. Among dietary factors, salt plays a vital role in the incidence of albuminuria. Although alcohol drinking was also identified as a risk factor for albuminuria in a large prospective cohort study, few studies have assessed the effect modification of alcohol drinking on the association between salt intake and albuminuria.

The present 1-year observational study aimed to evaluate the clinical impact of drinking frequency on the associations of salt intake with blood pressure and albuminuria in employees at a pharmaceutical company in Japan.

MATERIALS AND METHODS

The present study included 507 employees at a pharmaceutical company in Japan who underwent annual health checkups in both 2017 and 2018. After excluding 55 employees with self-reported hypertension and 1 pregnant female, 451 employees were included in the study to assess the association between salt intake and blood pressure. Additionally, we excluded three employees

with self-reported kidney disease and evaluated the association between salt intake and albuminuria in 448 employees. The study protocol was approved by the ethics committee of the Health and Counseling Center, Osaka University.

The baseline variables measured in 2017 included age; sex; drinking frequency; smoking status; current treatment for hypertension, dyslipidemia, and diabetes; history of kidney disease; body mass index; systolic and diastolic blood pressure; hemoglobin A1c; serum concentrations of total cholesterol, triglyceride, and creatinine; and urine concentrations of albumin, sodium, and creatinine. Urinary levels of albumin, sodium, and creatinine were measured using single-spot urine specimens. Albuminuria was assessed using the urinary albumin-to-creatinine ratio (UACR). To estimate 24-hour sodium excretion, Tanaka's equation was used. Salt intake (g/day) was calculated by multiplying 24-hour sodium excretion (mEq/day) by 0.0585. Estimated glomerular filtration rate (eGFR) was calculated using a three-variable equation modified for Japanese patients. Drinking frequency was classified by the question "How often do you drink alcoholic beverages?" with responses of rarely, occasionally, or daily.

To assess the associations of changes in salt intake with changes in blood pressure and albuminuria, we calculated the differences in salt intake between 2017 and 2018 (Δsalt intake = salt intake in 2018 − salt intake in 2017). The outcome measures were the differences in blood pressure and albuminuria between 2017 and 2018. We calculated Δsystolic blood pressure (ΔSBP), Δdiastolic blood pressure (ΔDBP), and ΔLog UACR as follows: ΔSBP = SBP in 2018 − SBP in 2017, ΔDBP = DBP in 2018 − DBP in 2017, ΔLog UACR = Log UACR in 2018 − Log UACR in 2017.

Baseline characteristics stratified on drinking frequency were compared using ANOVA, the Kruskal-Wallis test, or chi-square test, as appropriate. The associations of Δsalt intake with ΔSBP, ΔDBP, and ΔLog UACR were assessed using simple linear regression models and multivariable linear regression models adjusting for the baseline variables, including age, sex, smoking status, drinking frequency, current treatment for dyslipidemia and diabetes, body mass index, systolic blood pressure (if ΔSBP and ΔLog UACR), diastolic blood pressure (if ΔDBP), total cholesterol, triglycerides, hemoglobin A1c, eGFR, UACR (if ΔLog UACR), and salt intake. The effect modification between Δsalt intake and drinking frequency was assessed by incorporating their interaction term into the multivariable-adjusted model. P for interaction < 0.1 was regarded as statistically significant. To clarify their interaction, the associations of Δsalt intake with ΔSBP, ΔDBP, and ΔLog UACR were assessed in three subgroups stratified on drinking frequency. Continuous variables are expressed as the mean ± standard deviation or median (interquartile range), as appropriate. Statistical significance was set at $P < 0.05$, unless otherwise specified.

RESULTS AND DISCUSSION

The baseline characteristics of 448 employees were as follows: age, 45 (39–51) years; men, 70%; body mass index, 22.1 ± 2.8 kg/m^2; SBP, 118 ± 12 mmHg; eGFR 78 ± 11 mL/min/1.73m^2; UACR 29 (19–52) mg/gCr, salt intake 8.4 ± 1.8 g/day.

Multivariable-adjusted linear regression models showed significant associations of Δsalt intake with both ΔSBP and ΔDBP (per 1 g/day of Δsalt intake, adjusted β 0.92 [95% confidence interval 0.46, 1.39] for ΔSBP; 0.50 [0.17, 0.83] for ΔDBP). The interactions between drinking frequency and Δsalt intake were statistically significant (P for interaction = 0.028 and 0.006 for ΔSBP and ΔDBP). A subgroup analysis clarified a drinking frequency-dependent association between Δsalt intake and ΔSBP (adjusted β 0.19 [−0.73, 1.12], 0.84 [0.14, 1.53], and 1.78 [0.86, 2.69] in rare, occasional, and daily drinkers, respectively). A similar association between Δsalt intake and ΔDBP was observed (adjusted β −0.24 [−1.02, 0.54], 0.67 (0.18, 1.16), 0.95 [0.38, 1.51], in rare, occasional, and daily drinkers, respectively). Regarding the association between changes in salt intake and albuminuria, a multivariable-adjusted model showed a significant association between Δsalt intake and ΔLog UACR (per 1 g/day of Δsalt intake, adjusted β 0.16 [95% confidence interval 0.14, 0.19]) and a significant interaction between drinking frequency and Δsalt intake (P for interaction = 0.088). The association between Δsalt intake and ΔLog UACR was enhanced by drinking frequency in a dose-dependent manner (adjusted β 0.13 [0.06, 0.19], 0.16 [0.12, 0.20], and 0.20 [0.13, 0.27] in rare, occasional, and daily drinkers, respectively).

The present study revealed that drinking frequency modified salt sensitivity, which was the association between the change of salt intake and that of blood pressure. Moreover, drinking frequency was also enhanced the association between salt intake and albuminuria. One of the mechanisms of salt sensitivity is the impairment of nitric oxide (NO)-dependent vascular relaxation by decreasing NO in the vascular endothelium due to the suppression of endothelial nitric oxide synthase (eNOS). Alcohol suppresses the expression of eNOS and impairs endothelial function. Thus, alcohol-induced vasodysfunction may contribute to enhanced salt sensitivity. Regarding the association between salt sensitivity and salt-induced albuminuria, an Italian trial reported that urinary albumin levels significantly increased after salt loading in salt-sensitivity subjects but not in salt-resistant subjects. These results imply that alcohol-enhanced salt sensitivity possibly augments salt-induced albuminuria. Further studies are essential to clarify the effect modification of alcohol consumption with salt sensitivity and salt-induced albuminuria.

CONCLUSION

The findings of the present studies showed that a higher frequency of alcohol drinking enhanced the deleterious effect of salt intake on blood pressure and albuminuria. These results indicate that drinkers would obtain a higher benefit from salt restriction in regard to decreasing blood pressure and albuminuria.

別紙

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論　　文　　名	1. Drinking frequency modifies an association between salt intake and blood pressure: A cohort study 2. Frequency of alcohol drinking modifies the association between salt intake and albuminuria: a 1-year observational study
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