

# 学位論文の要旨

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学位論文名 Effect of Salt Intake on Blood Pressure in Patients Receiving Antihypertensive Therapy: Shimane CoHRE Study

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## 論文内容の要旨

### **INTRODUCTION**

Hypertension is the most prevalent lifestyle-related disease in the world, with the number of hypertensive patients being one billion worldwide, including 40 million in Japan. Hypertension is a well-known risk factor for stroke, cardiac disease, and kidney disease, all of which may reduce life expectancy. However, it has been reported that 50% of Japanese patients on antihypertensive drugs do not reach their target BP. Although lifestyle modification is also important for patients on antihypertensive therapy, patients may rely too much on their medication and disregard instructions about lifestyle modification, resulting in a low proportion of patients achieving an appropriate BP despite drug treatment. The most important lifestyle factor with an influence on BP is salt intake. Therefore, we hypothesized that salt intake could have a significant influence on BP, even among patients taking antihypertensive medications. In this cross-sectional study, we showed that salt intake (estimated from spot urine) was correlated with BP in patients on antihypertensive therapy.

### **MATERIALS AND METHODS**

A total of 1501 consecutive participants (571 men and 930 women) were recruited from among persons undergoing health screening examinations in rural areas of Shimane Prefecture during 2012. Participants were limited to the age range between 40 and 74 years. Information about physical activity, smoking, drinking, and use of antihypertensive medications was obtained by interview, and the actual medications were confirmed by checking prescriptions. After

excluding 5 subjects with a history of treatment for renal disease, the remaining 1496 participants were divided into groups with or without antihypertensive medication. This yielded a group of hypertensive subjects on medication (treated subjects: N=491) and a group of normotensive or hypertensive subjects without medication (untreated subjects: N=1005). The International Standardized Physical Activity Questionnaire was employed to assess 24-hour physical activity and the exercise count (ex) was calculated according to the method reported previously.

Participants were categorized into two groups (low and high physical activity groups) based on the median exercise count (56 ex/week). Habitual smokers and habitual drinkers were defined as persons who smoked at least 1 cigarette/day and persons who drank at least 20g of ethanol/day, respectively. Systolic BP and diastolic BP (SBP and DBP) were measured by standard methods. A venous blood sample was collected from each subject after an overnight fast. Triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by standard enzymatic methods. Sodium and creatinine were measured in spot urine collected at the health screening examination, and 24-hour urinary sodium excretion was estimated with the formula proposed by Tanaka et al .

Correlations between BP and other continuous variables were analyzed by calculating Spearman's rank correlation coefficients. The influence of categorical parameters on BP was determined by Student's t-test. Multiple regression analysis was performed to assess the influence of each variable on BP. Written informed consent was obtained from each participant.

The study protocol was approved by the ethics committee of Shimane University.

## **RESULTS AND DISCUSSION**

There was no significant difference of estimated salt intake between the untreated and treated subjects. Individuals with low physical activity were slightly, but significantly, more prevalent among the treated subjects, and there were no significant differences of smoking and drinking habits between the two groups. Twenty-three of the treated subjects were using diuretics. Since these drugs could cause overestimation of the salt intake if they were prescribed temporally, we compared the estimated salt intake between subjects with and without diuretics. The estimated salt intake of the subjects using diuretics was  $10.5 \pm 3.1$  g/day (N=23), which was not significantly different from that of subjects without diuretics ( $9.6 \pm 2.5$  g/day; N=305,  $p=0.1$ ).

Therefore, we included all of the treated subjects in the following analyses. Univariate analysis showed a significant positive correlation between salt intake and SBP/DBP in both the treated and the untreated subjects. Multiple linear regression analysis was performed using the parameters that showed a significant correlation with BP in univariate analysis to find variables with an independent influence on SBP or DBP. The results showed that salt intake was

independently associated with SBP and DBP in the untreated subjects (SBP:  $\beta=1.45\pm0.26$ ,  $p<0.001$ , DBP:  $\beta=0.52\pm0.16$ ,  $p=0.001$ ). Even in the treated subjects, salt intake had an independent association with SBP together with age and BMI (SBP:  $\beta=0.75\pm0.27$ ,  $p=0.01$ ).

This result seemed to be robust because analysis after excluding the 23 subjects using diuretics also revealed a positive correlation between salt intake and SBP ( $\beta=0.72\pm0.28$ ,  $p=0.01$ ).




Female sex had a significant negative influence on DBP despite no significant effect on SBP, so we assessed the effect of sex on pulse pressure by multiple linear regression analysis. As expected, female sex had a significant positive influence on pulse pressure in both the treated and the untreated subjects (the treated:  $\beta=-4.36\pm1.42$ ,  $p=0.002$ , the untreated:  $\beta=-4.17\pm0.90$ ,  $p<0.001$ ) The effect of salt intake on pulse pressure was also significant.

In the present study, we showed that salt intake estimated from the sodium concentration in spot urine was positively correlated with SBP in subjects on antihypertensive therapy. Accordingly, it may be important to control salt intake in hypertensive patients receiving the pharmacotherapy to ensure that their treatment is effective. Multiple linear regression analysis confirmed that female sex had a strong positive influence on pulse pressure. This observation is interesting when we consider the relationship of pulse pressure to arterial stiffness in the elderly. However, as multiple factors are known to influence pulse pressure, further evaluation will be necessary to clarify the pathophysiological significance of the larger pulse pressure observed in women of our study population. While the present study provided epidemiological evidence of a positive correlation between salt intake and BP in subjects on antihypertensive therapy, it has limited clinical applicability because the method of estimating salt intake used in this study is not reliable enough to assess salt intake of individual patients. Probably because of this limitation, the correlation between SBP and estimated salt intake was only modest. Therefore, it would be necessary to confirm the present results by using 24-hour urine data before the clinical application is considered.

## **CONCLUSION**

We showed that salt intake estimated from a spot urine sample had an independent influence on SBP and pulse pressure in patients on antihypertensive therapy. Careful control of salt intake may be important to achieve better therapeutic outcomes in treatment of hypertension.

論文審査及び最終試験又は学力確認の結果の要旨

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論文審査の結果の要旨

高血圧は様々な臓器障害を引き起こすためその治療は重要である。しかし降圧剤服用者の中で血圧コントロールが出来ているものは4割程度であり決して良いとはいえない。高血圧の最大のリスクとして過剰な食塩摂取が挙げられるが、申請者らは降圧剤服用者の血圧コントロールにも食塩摂取が重要であるとの仮説を立て、降圧剤服用者の一日食塩摂取量が血圧に影響を与えているかどうかを明らかにする目的で研究を行った。この研究は、島根大学疾病予知予防プロジェクト Shimane CoHRE Study の一つとして行ったものである。2012年の3自治体での特定健診受診者1496名（男570名、女926名）を対象とし、一日食塩摂取量は随時尿を用いてTanakaら(2002)の推定式にて算出した。単回帰分析で、降圧剤服用群・非服用群両群にて、食塩摂取量は収縮期血圧と正の有意な関係が認められた。これは、重回帰分析において年齢、性別、BMI、身体活動量などの交絡因子を調整した後も有意であった（非服用群：非標準化係数  $1.45 \pm 0.26$ ,  $p < 0.001$ ；服用群：非標準化係数  $0.75 \pm 0.27$ ,  $p = 0.01$ ）。さらに、脈圧との重回帰分析においても食塩摂取量は降圧剤非服用、服用両群において有意な正の関係を示した。以上の結果から、降圧剤服用者においても食塩摂取量は収縮期血圧および脈圧に影響を与える独立因子であることが明らかとなり、降圧剤服用者の血圧コントロールに降圧剤服用と並行した減塩が効果的である可能性が示唆された。従来の疫学研究では、集団全体の平均血圧をわずか2 mmHg低下させることで脳卒中死亡が6%低下すると言われていた。本研究は降圧剤服用者でも減塩によってより良い血圧コントロールを可能とし、ひいては高血圧合併症を減らすことが出来ることを示唆する意義ある研究である。

最終試験又は学力の確認の結果の要旨

申請者は、地域住民1496名を対象としたコホート研究において一日の塩分摂取量と血圧との関連について詳細な解析を行い、何らかの降圧剤服用例においても塩分摂取量が収縮期血圧および脈圧と密接な関連があると報告した。高血圧治療における生活習慣改善の重要性をあらためて示唆する貴重な研究である。申請者は、高血圧に関する知識も十分で今後の研究ビジョンも有しており学位授与に値すると判断する。  
(主査 石橋 豊)

申請者は降圧療法をしていても食塩制限を軽視すれば降圧治療が標的 blood pressure まで降圧できにくいとの仮説を横断解析データから推測した。降圧療法の目標 blood pressure 達成率に食塩摂取量の問題を挙げている点は重要な点と考える。多変量ロジスティック回帰分析を中心にした統計解析が必要と考える。今後の研究発展に期待する。  
(副査 大平明弘)

申請者は、島根大学疾病予知予防プロジェクトの一環として行われた地域住民に対するコホート研究において、塩分摂取量と収縮期血圧の間に独立した正の相関があることを示し、降圧剤服用者においても減塩が重要であることの根拠を示した。学位審査において質疑応答も的確で、学位授与に値すると判断した。  
(副査 織田禎二)

(備考) 要旨は、それぞれ400字程度とする。