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Impact of Excess Salt Intake on Plasma Brain Natriuretic Peptide Levels in a Japanese General Population with Chronic Kidney Disease

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ABSTRACT

Background: Both subtle elevation of B-type natriuretic peptide (BNP) and a decrease in estimated glomerular filtration ratio (eGFR) were reported to be related to the development of cardiovascular disease in apparently asymptomatic populations. However, the relationship between excess salt intake, eGFR and BNP in the general population remains to be determined.

Methods and Results: This community-based cross sectional study enrolled individuals over 40 years old (n = 3115) in Takahata, Japan. There were 206 subjects with chronic kidney disease (CKD) (eGFR < 60 mL/min/1.73m^2). Plasma BNP levels were higher in subjects with CKD than in those without CKD. However, subjects with CKD had a lower salt intake, higher systolic blood pressure and higher plasma renin activity (PRA) than subjects without CKD. There was a greater increase in BNP levels with salt intake in CKD subjects compared to those without CKD. PRA was significantly suppressed by excess salt intake in both groups. Multivariate analysis showed that salt intake was an independent risk factor for elevated BNP levels in CKD subjects, but not in those without CKD.

Conclusions: Excess salt intake is an independent risk factor for elevated plasma BNP levels, especially in subjects with CKD. These results suggest that sodium restriction for prevention of future cardiovascular events may be more important in subjects with CKD than in those without CKD.

Key words: B-type natriuretic peptide, salt intake, chronic kidney disease, myocardial damage, blood pressure

Introduction

It is well known that dietary sodium restriction lowers blood pressure and can prevent hypertension. Many observational studies have shown a close correlation between sodium intake and blood pressure[1, 2]. Meta-analyses of randomized trials of sodium restriction in people with and without hypertension have supported these observational findings[3, 4]. Recent evidence suggests that long-term interventions aimed at reduction of sodium

intake may reduce the risk of cardiovascular disease (CVD) [5, 6].

A graded association between glomerular filtration rate (GFR) and cardiovascular deaths was demonstrated with a subtle decrease in GFR (<60-80 mL/min/1.73m^2), which increased the independent risk of death, acute cardiovascular events, hospitalization and cardiovascular complications following myocardial infarction[7, 8]. Even micro-albuminuria, in the absence of an apparent decrease in renal function or diabetes mellitus, is a predictor for CVD and death[9].

Increased salt intake elevates systemic and glomerular pressure and increases the risk of adverse renal events such as proteinuria, absence of nocturnal decrease in blood pressure with decrease in renal function, and end stage renal dysfunction[10].

Plasma B-type natriuretic peptide (BNP) levels are extremely low in healthy individuals. Plasma BNP is an important marker for heart failure in clinical practice, because BNP levels increase in early stage heart failure before the onset of symptoms, and also reflect disease severity. The measurement of plasma BNP levels has important implications for assessing the condition of patients with heart failure[11, 12].

Heart-type fatty acid-binding protein (H-FABP) is a low molecular weight (14-15 kDa) cytoplasmic protein involved in the transport of long-chain fatty acids in cardiomyocytes. H-FABP is rapidly released into the circulation when the myocardium is injured. We and others have demonstrated that H-FABP is a promising marker for latent myocardial damage and the prognosis of patients with chronic heart failure[13, 14].

There have been a few reports on the impact of salt intake on plasma BNP levels in subjects with chronic kidney disease (CKD). Excess salt intake was shown to cause hypertension, renal dysfunction and myocardial injury[15-17]. In addition, plasma BNP levels were not increased after short-term sodium loading in healthy subjects[18]. However, little is known about the relationship between long-term excess salt intake and plasma BNP levels in the general population. In the present study, we investigated the impact of excess salt intake on plasma BNP levels and H-FABP levels in a general population with CKD.

Methods

Study population

This study was part of the ongoing molecular epidemiological study utilizing the regional characteristics of the 21st Century Center of Excellence (COE) program and the global COE program in Japan. Details of the study methodology have been described elsewhere[19].

The survey population for this community-based study was the general population, aged 40 to 87 years, of Takahata town (total population 26,026) in northern Japan. This region has a resident population of 15,222 adults over the age of 40 years (7,109 men, 8,113 women). From June 2004 through November 2005, 1,394 men and 1,771 women (a total of 3,165 subjects) agreed to participate in the study. The total participation rate was 20.5% (19.4% of men, 21.4% of women). The study was approved by the institutional ethics committee and all participants gave written informed consent. Fifty subjects were excluded from the present analysis because of incomplete data. In total, 3,115 subjects were entered into the final statistical analysis. There were 1,380 men (44.3%) and 1,735 women (55.7%). The mean age was 63 years.

Measurements

A self-report questionnaire was used to document medical history, current medications and clinical symptoms. Systolic and diastolic blood pressures were measured using a mercury manometer, with the subject in a sitting position after at least 5 min of rest. Hypertension was defined as a systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of anti-hypertensive medication. Diabetes mellitus was confirmed either by self-reported physical diagnosis or by a fasting plasma glucose level >126 mg/dL or a HbA1c (JDS) value ≥6.5%. Hypercholesterolemia was confirmed by a serum total cholesterol concentration ≥220 mg/dL and/or the use of anti-hyperlipidemic medication. The urine albumin-

creatinine ratio (UACR) was measured in a single spot urine specimen collected in the early morning. The urine albumin concentration was determined by immunoturbidimetry. Albuminuria was defined as UACR >30 mg/g•Cr. CKD was defined as an estimated GFR (eGFR) <60 mL/min/1.73m^2.

Serum creatinine (SCr) was measured by an enzymatic method. The GFR was estimated using the Japanese version of the equation used in the Modification of Diet in Renal Disease (MDRD) study (20). Salt intake was estimated from a single urine sample, using the formula of Kawasaki: 24 h urinary Na (mEq/day) = 16.3 square root of X_{Na}, where X_{Na} = second morning voiding urine $(SMU)_{Na}$ /SMU_{Cr} x predicted 24 h urinary Cr excretion[21].

Plasma BNP concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co. Ltd., Tokyo, Japan). The analytical range of the assay was 4-2000 pg/mL. H-FABP levels were measured using a two-step sandwich enzyme-linked immunosorbent assay (ELISA) kit (MARKIT-M H-FABP, Dainippon Pharmaceutical Co Ltd, Tokyo, Japan). The cut-off value for BNP was determined as the mean + 1 SD, which was 78.8 pg/mL[22].

Statistical analyses

Student's t-test was used to evaluate the significance of differences in mean values and chi-square test was used to evaluate differences in proportions. The non-parametric Mann-Whitney U-test and Kruskal-Wallis test were used for parameters that were not normally distributed. Study participants were divided into two groups: the CKD group and those without CKD. The influence of salt intake on plasma BNP levels was analyzed in each group. Logistic regression analysis was performed to identify independent predictors of high BNP level in the general population. Variables identified as significant in the univariate analysis were entered into the multivariate analysis. Data are expressed as mean ± SD. A significant difference was defined as $P < 0.05$.

Results

The characteristics of the study subjects are shown in Table 1. There were 206 subjects with CKD

Table 1. Comparison of characteristics between non-CKD subjects and CKD subjects

	All	Non-CKD	CKD	p value
n	3115	2909	206	-
Age (years)	63.0 ± 10.3	62.5 ± 10.1	70.8 ± 8.5	<0.05
Male, N (%)	1380 (44.3)	1279 (44.0)	101 (49.0)	<0.05
BMI (kg/m^2)	23.5 ± 3.2	23.5 ± 3.2	24.1 ± 3.5	<0.05
Salt intake (g/day)	12.4 ± 3.4	12.6 ± 3.4	10.6 ± 3.0	<0.05
Systolic BP (mmHg)	134.2 ± 15.9	133.9 ± 15.9	138.8 ± 14.8	<0.05
Diastolic BP (mmHg)	79.3 ± 10.0	79.2 ± 10.1	79.9 ± 9.7	N.S.
Serum albumin (g/dl)	4.5 ± 0.3	4.5 ± 0.3	4.5 ± 0.3	N.S.
SCr (mg/dl)	0.68 ± 0.22	0.65 ± 0.13	1.04 ± 0.61	<0.05
HL, N (%)	1042 (33.5)	972 (33.4)	70 (34.0)	N.S.
DM, N (%)	240 (7.7)	212 (7.3)	28 (13.6)	<0.05
Hemoglobin (g/dl)	13.7 ± 1.5	13.7 ± 1.4	13.5 ± 1.6	<0.05
Albuminuria (mg)	9.3 (6.0, 18.3)	9.1 (5.9, 17.5)	14.9 (7.1, 51.5)	<0.05
UACR (mg/g)	9.75 (5.06, 22.6)	9.62 (5.04, 21.8)	13.63 (5.71, 55.3)	<0.05
eGFR (ml/min/1.73 m^2)	81.3 ± 16.4	83.4 ± 14.7	51.4 ± 8.3	<0.05
Uric acid (mg/dl)	5.1 ± 1.4	5.0 ± 1.3	6.0 ± 1.5	<0.05
PRA (ng/ml/h)	0.9 (0.4, 1.8)	0.8 (0.4, 1.7)	1.2 (0.4, 2.7)	<0.05
ACE (IU/L)	14.8 ± 5.1	14.8 ± 5.1	14.7 ± 5.9	N.S.
BNP (pg/ml)	19.0 (10.3, 34.5)	18.6 (10.1, 33.5)	28.7 (14.6, 66.9)	<0.05
H-FABP (ng/ml)	3.4 (2.6, 4.5)	3.3 (2.5, 4.3)	5.6 (4.1, 7.0)	<0.05

Nonparametric variables are expressed as median with range (25th, 75th)

CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; SCr, serum creatinin; HL, hyperlipidemia; DM, diabetes mellitus; UACR, urine albumin-creatinine ratio; eGFR, estimated glomerular filtration ratio; PRA, plasma renin activity; ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; H-FABP, heart type fatty acid binding protein.

among the 3,115 participants. Both non-CKD and CKD subject were divided into two subgroups based on BNP levels (Table 2). The CKD subjects with high BNP were older and had a higher salt intake, lower total protein, lower hemoglobin concentration, lower plasma renin activity (PRA) and higher prevalence of albuminuria compared to those with low BNP. However, there was no difference of salt intake between non-CKD subjects with low or high BNP levels.

Salt intake in subjects with CKD

Participants were divided into three groups based on their eGFR (≥90, 60-89, <60 mL/min/1.73m^2). As shown in Figure 1, plasma BNP levels increased with increasing salt intake in CKD subjects, whereas excess salt intake had less influence on plasma BNP levels in subjects without CKD. Univariate logistic regression analysis showed that increased age, low total protein, low low-density

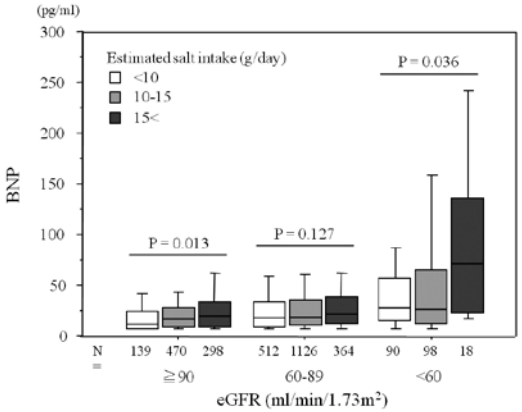

Figure1. Excess salt intake increased plasma BNP levels in subjects with CKD.
Abbreviations are as indicated in Table 1. A box plot displays the median, quartiles, and 10%tile and 90%tile observation for each group. Kruskal Wallis was used to evaluate differences.

Table 2. Comparison of characteristics between non-CKD subjects and CKD subjects with low or high BNP

	All		Non CKD		CKD	
BNP	Low	High	Low	High	Low	High
n	2914	201	2750	159	164	42
Age(years)	62.4±10.2	71.3±7.8 ‡	62.0±10.1	70.2±7.9 ‡	69.6±8.7	75.5±5.3 ‡
Men,N(%)	1284(44.1)	96(47.8)	1204(43.8)	75(47.2)	80(48.8)	21(50.0)
BMI(kg/m^2)	23.5±3.2	23.2±3.5	23.5±3.2	23.1±3.5	24.2±3.4	23.7±3.6
Saltintake(g/day)	12.4±3.4	12.6±3.8	12.5±3.4	12.8±3.8	10.3±2.8	11.8±3.8 †
HT,N(%)	1573(54.0)	145(72.1)	1452(52.8)	108(67.9) ‡	121(73.8)	37(88.1)
SystolicBP(mmHg)	133.9±15.8	138.5±16.4 ‡	133.7±15.9	138.1±16.0 ‡	138.5±14.0	139.9±18.0
DiastolicBP(mmHg)	79.2±10.0	80.0±10.5	79.2±10.1	80.2±10.4	80.0±9.3	79.4±11.1
Totalprotein(g/dl)	7.5±0.4	7.3±0.5 ‡	7.5±0.4	7.3±0.5 ‡	7.6±0.4	7.2±0.6 ‡
Serumalbumin(g/dl)	4.5±0.2	4.4±0.4 ‡	4.5±0.2	4.4±0.3 ‡	4.5±0.3	4.4±0.4 †
HL,N(%)	1110(38.1)	55(27.4) †	1043(37.9)	43(27.0) †	67(40.9)	12(28.6)
DM,N(%)	220(7.5)	20(10.0)	201(7.3)	11(6.9)	19(11.6)	9(21.4)
Hemoglobin(g/dl)	13.7±1.4	13.2±1.7 ‡	13.8±1.4	13.4±1.6 †	13.7±1.4	12.6±1.9 ‡
CKD,N(%)	164(5.6)	42(20.9) ‡	-	-	-	-
Albuminuria(mg/day)	27.6±93.6	96.3±430.3 ‡	25.0±84.0	40.0±101.9 †	71.8±188.5	309.2±896.9 †
UACR(mg/g•Cr)	9.4(4.9,21.2)	19.5(8.1,59.6) ‡	9.4(4.9,20.8)	17.0(7.6,46.2) ‡	10.5(5.3,36)	51.4(14.7,205) ‡
SCr(mg/dl)	0.7±0.2	0.8±0.6 ‡	0.6±0.1	0.7±0.1	1.0±0.2	1.3±1.2 †
eGFR(ml/min/1.73m^2)	81.8±16.1	73.4±19.2 ‡	83.5±14.8	80.6±13.8 †	52.7±6.8	46.5±11.6 ‡
Uricacid(mg/dl)	5.0±1.3	5.3±1.5 †	5.0±1.3	5.1±1.4	6.0±1.5	6.2±1.4
PRA(ng/ml/h)	0.9(0.4,1.8)	0.6(0.3,1.1) †	0.9(0.4,1.7)	0.6(0.3,1.0) †	1.5(0.5,2.9)	0.7(0.2,1.6) †
ACE(IU/L)	14.8±5.1	15.0±6.2	14.8±5.0	15.1±5.8	14.6±5.5	14.9±7.4
BNP(pg/ml)	17.7(9.8,30.4)	111.4(88.8,162.1) ‡	17.6(9.6,30.1)	107.8(87,147.1) ‡	23.3(11.5,35.1)	141.1(107.5,196.8) ‡
H-FABP(ng/ml)	3.3(2.5,4.4)	4.3(3.4,5.9) ‡	3.3(2.5,4.3)	4.0(3.2,5.1) ‡	5.3(3.8,6.7)	6.5(4.9,8.4) ‡
PriorCVDepisode,N(%)	90(3.1)	15(7.5) ‡	84(3.1)	13(8.2) ‡	6(3.7)	2(4.8)

Non normal distribution variables are expressed as median with range (25th, 75th)
BMI, body mass index; HT, hypertension; BP, blood pressure; HL, hyperlipidemia; DM, diabetes mellitus; CKD, chronic kidney disease; UACR, urine albumin-creatinine ratio; SCr, serum creatinine; eGFR, estimated glomerular filtration ratio; PRA, plasma renin activity; ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; H-FABP, heart type fatty acid binding protein; CVD, cardio vascular disease; †, P<0.05 vs. subject with low BNP; ‡, P<0.001 vs. subject with low BNP.

lipoprotein (LDL) cholesterol and low hemoglobin concentrations, low eGFR, albuminuria, and high salt intake were significantly associated with high plasma BNP levels in CKD subjects (Table 3). In the case of subjects without CKD, increased age, high systolic blood pressure, low total protein and LDL cholesterol concentrations, and hemoglobin concentrations, low PRA, low eGFR, and high prevalence of albuminuria were associated with high BNP levels. Prior CVD history was associated with high plasma BNP levels in subjects without CKD but not CKD subjects.

Multivariate logistic regression analysis showed that low serum total protein concentration, increased age, albuminuria and high salt intake were independently associated with high plasma levels of BNP in CKD subjects (Table 4). The odds ratio for the association between a 5 g per day increase in salt intake and high BNP levels was 1.92 (95%C.I., 1.00-3.86). On the other hand, in subjects without CKD, increased age, low total protein and low LDL cholesterol concentrations, low PRA

Table 3. Univariate logistic regression analysis for high plasma BNP levels in non-CKD and CKD subjects

	Non-CKD			CKD		
	OR	95% CI	p value	OR	95% CI	p value
Age (per 10 years increase)	2.61	2.16-3.11	<0.001	2.86	1.63-4.81	<0.001
Gender (men)	1.15	0.83-1.58	0.403	1.05	0.53-2.07	0.888
Salt intake (per 5 g/day increase)	1.11	0.86-1.40	0.387	2.23	1.28-4.01	0.006
BMI (per 1 increase)	0.97	0.92-1.02	0.175	0.95	0.86-1.05	0.321
Systolic BP (per 10 mmHg increase)	1.22	1.10-1.34	<0.001	1.11	0.82-1.34	0.583
Diastolic BP (per 10 mmHg increase)	1.11	0.90-1.34	0.225	0.91	0.66-1.34	0.722
Total protein (per 1SD increase)	0.68	0.58-0.80	<0.001	0.42	0.28-0.64	<0.001
Uric acid (per 1SD increase)	1.13	0.96-1.31	0.147	1.11	0.79-1.54	0.570
LDL-C (per 1SD increase)	0.75	0.55-0.74	<0.001	0.55	0.40-0.74	0.005
Hemoglobin (per 1g/dl increase)	0.84	0.75-0.93	0.001	0.62	0.49-0.79	<0.001
eGFR (per 10 ml/min/1.73m^2 increase)	0.91	0.74-1.00	0.013	0.45	0.31-0.66	<0.001
PRA (per 1 increase)	0.73	0.62-0.87	<0.001	0.85	0.71-1.02	0.080
Current smoking	0.86	0.61-1.23	0.413	1.22	0.58-2.56	0.594
Albuminuria	1.88	1.32-2.69	<0.001	3.77	1.87-7.63	<0.001
Prior CVD episode	2.85	1.55-5.23	<0.001	1.32	0.26-6.77	0.742

LDL-C, low-density lipoprotein cholesterol; other abbreviations as in Table 2

Table 4. Multivariate logistic regression analysis for high plasma BNP levels in non-CKD and CKD subjects

non-CKD subjects	Odd Ratio	95% CI	p value
Age (per 10 years increase)	2.44	1.95-3.02	<0.001
Systolic BP (per 10 mmHg increase)	1.08	0.97-1.22	0.163
Total protein (per 1SD increase)	0.73	0.61-0.88	<0.001
LDL-C (per 1SD increase)	0.79	0.66-0.94	0.008
Hemoglobin (per 1 g/dl increase)	0.96	0.85-1.10	0.571
eGFR (per 10 ml/min/1.73m^2 increase)	0.94	0.83-1.06	0.348
PRA (per 1SD increase)	0.58	0.41-0.83	0.003
Albuminuria	1.48	1.00-2.18	0.047
Prior CVD episode	2.71	1.42-5.18	0.003

CKD subjects	Odd Ratio	95% CI	p value
Age (per 10 years increase)	2.27	1.34-4.81	0.005
Total protein (per 1SD increase)	0.56	0.36-0.87	0.010
LDL-C (per 1SD increase)	0.76	0.46-1.19	0.229
Hemoglobin (per 1 g/dl increase)	0.93	0.68-1.28	0.669
eGFR (per 10 ml/min/1.73m^2 increase)	0.62	0.37-1.04	0.072
Albuminuria	2.59	1.09-6.15	0.031
Salt intake(per 5 g/day increase)	1.92	1.00-3.86	0.047

Abbreviations as in Table 2, 3.

and albuminuria, but not high salt intake, were independent risk factors for high BNP levels (Table 4). CKD subjects with an excess salt intake had a higher prevalence of hypertension, higher UACR and lower PRA than those with a moderate salt intake (Table 5). There were greater increases in plasma BNP levels in CKD subjects with an excess salt intake (>15 g/day) compared to those with a moderate salt intake (≤15 g/day).

Figure 2 shows that BNP and H-FABP increased with advancing renal dysfunction. CKD subjects with an excess salt intake showed a greater increase in BNP levels than those with a moderate salt intake, while excess salt intake did not alter BNP levels in subjects without CKD (Figure 2A). CKD subjects with an excess salt intake showed a slight but not significant increase in H-FABP levels compared to those with a moderate salt intake (Figure 2B).

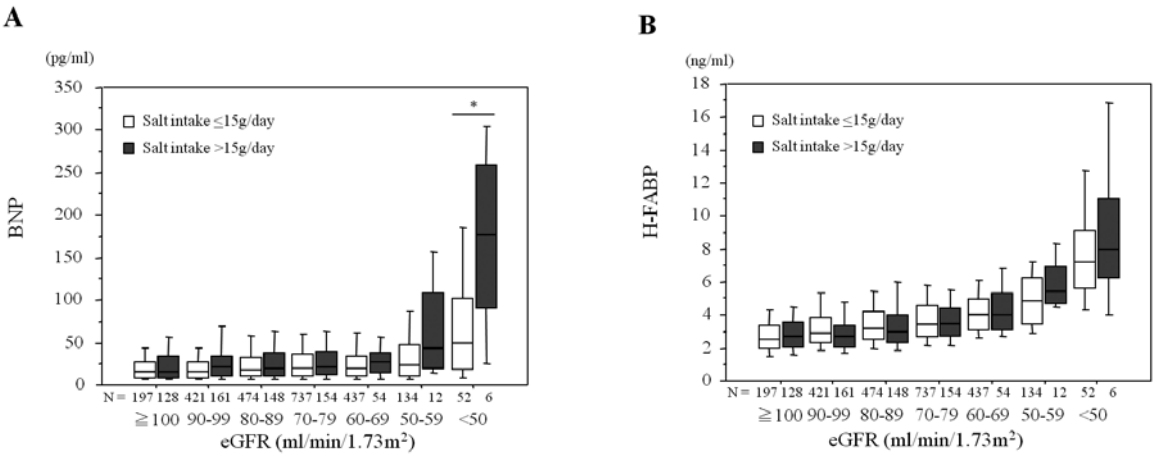

Figure 2. Excess salt intake induced greater myocardial damage in subjects with CKD.
A) Impact of excess salt intake and eGFR on plasma BNP levels. B) Impact of excess salt intake and eGFR on serum H-FABP levels. Abbreviations are as indicated in Table 1; *p <0.05 vs. subject with salt intake <15g/day.

Table 5. Characteristics of 3 CKD groups based on amount of salt intake

		Salt intake			
	All	< 10 g/day	10-15 g/day	> 15 g/day	P value
n	206	90	99	17	-
Age (years)	70.8 ± 8.5	71.4 ± 8.4	69.7 ± 8.8	72.9 ± 5.7	0.273
BMI (m/kg^2)	24.1 ± 3.5	23.5 ± 3.5	24.7 ± 3.3	24.6 ± 3.4	0.036
Salt intake (g/day)	10.6 ± 3.0	7.9 ± 1.5	12.0 ± 1.4	16.6 ± 1.6	<0.001
HT, N (%)	158 (76.7)	62 (68.9)	79 (80.6)	16 (94.1)	0.034
Systolic BP (mmHg)	139 ± 14.8	135 ± 13.1	141 ± 15.9	144 ± 12.7	0.005
Diastolic BP (mmHg)	80 ± 9.7	78 ± 9.0	81 ± 9.5	84 ± 12.0	0.024
HL, N (%)	79 (38.3)	34 (37.8)	42 (42.9)	3 (17.6)	0.140
DM, N (%)	28 (13.6)	14 (15.6)	12 (12.2)	2 (11.8)	0.782
SCr (mg/dl)	1.04 ± 0.60	1.03 ± 0.58	1.04 ± 0.68	1.01 ± 0.17	0.475
eGFR (ml/min/1.73m^2)	51.4 ± 8.3	51.0 ± 8.6	51.8 ± 8.5	52.2 ± 5.8	0.667
UACR (mg/g • Cr)	13.6 (5.7, 55.3)	9.4 (4.6, 34.8)	16.4 (7.5, 99.5)	59.3 (10.4, 168.9)	0.007
Uric acid (mg/dl)	6.0 ± 1.4	6.1 ± 1.7	6.0 ± 1.2	5.9 ± 1.2	0.915
PRA (ng/ml/h)	1.2 (0.4, 2.7)	1.5 (0.7, 3.7)	1.1 (0.4, 2.3)	0.6 (0.3, 1.7)	0.007
ACE (IU/L)	14.7 ± 5.9	14.8 ± 6.0	15.2 ± 5.3	12.0 ± 8.3	0.288
BNP (pg/ml)	28.7 (14.6, 66.9)	28.1 (15.2, 58.3)	27.2 (12.5, 65.7)	71.7 (24.2, 135.4)	0.036
H-FABP (ng/ml)	5.6 (4.1, 7.0)	5.3 (3.7, 7.0)	5.8 (4.1, 6.8)	6.3 (4.7, 7.6)	0.277
Prior CVD episode, N (%)	8 (3.9)	3 (3.3)	4 (4.0)	1 (5.9)	0.878

Nonparametric variables are expressed as median with range (25th, 75th). Abbreviations as in Table 2, 3

Discussion

Subjects with CKD had higher plasma BNP and serum H-FABP levels than subjects without CKD. Multivariate analysis revealed that salt intake was an independent risk factor for elevated BNP levels in CKD subjects but not those without CKD.

Excess salt consumption and hypertension

Although salt intake has recently decreased in Japan, it is still higher than that of other developed countries[23]. Average salt intake in Japan was 11.4 g/day in men and 9.8 g/day in women according to the National Health and Nutrition Survey 2008[24]. An intimate relationship between dietary salt and blood pressure was identified by the worldwide INTERSALT survey[25], and increased dietary salt is known to have adverse effects on the cardiovascular system independently of blood pressure. As shown in Table 1, subjects with CKD had a higher prevalence of hypertension and a lower salt intake than those without CKD. Subjects with CKD and hypertension might be strongly recommended for sodium restriction by their doctors. It has also been reported that dietary salt intake is positively related to left ventricular mass[26]. Several studies showed the effects of dietary salt on cardiac damage independently of blood pressure[27, 28]. Many reports have suggested an optimal cut off value for BNP, for identification of heart disease, of 50 to 130 pg/mL or greater[22]. In the present study, we determined the cut-off value for BNP as the mean + 1 SD, which was 78.8 pg/mL. There are many confounding factors influencing plasma BNP levels, including left ventricular wall stress, neurohumoral factors, aging, anemia, and renal disease. An excess salt intake was reported to increase circulating blood volume, blood pressure and high afterload, which increase BNP levels[29]. We observed a large impact of excess salt intake on plasma BNP levels in CKD subjects, but not in subjects without CKD (Figure 1). The CKD subjects may have high plasma BNP levels because of volume overload[30] and low excretion of BNP[31] as well as cardiac damage. Multivariate analysis revealed that excess salt intake was an independent risk factor for elevation of plasma BNP in CKD subjects. The odds ratio for elevation of BNP in CKD subjects was 1.92 per 5 g/day increase in salt intake. Surplus salt is adequately excreted by the kidney if renal function is normal; therefore subjects without CKD would not have high plasma BNP levels[32].

Influence of salt intake on chronic kidney disease

There is increasing evidence from animal experiments that salt increases reactive oxygen species within the vasculature and renal cortex, which may be associated with the development of interstitial fibrosis and progressive renal dysfunction[33]. As shown in Table 5, CKD subjects with an excess salt intake had greater UACRs than CKD subjects with a moderate salt intake. This result suggested that excess salt intake is probably associated with the development of microalbuminuria.

Excess salt intake induces myocardial damage

H-FABP is rapidly released into the circulation when the myocardium is injured[34]. We reported that H-FABP is a sensitive marker of ongoing myocardial damage[35]. We observed elevation of H-FABP, as well as plasma BNP levels, with decreasing eGFR (Figure 2B). The increase in H-FABP levels tended to be greater in CKD subjects with an excess salt intake than in those with a moderate salt intake, whereas there were no statistical significance between subjects with and without CKD because of limited number of CKD subjects. These results suggest that the impact of excess salt intake on left ventricular dysfunction and myocardial damage may be augmented by renal insufficiency. Animal experiments also showed that chronic salt loading or uninephrectomy caused myocardial damage[36]. Since BNP is a cardiac neurohormone that has cardioprotective effects such as vasodilatation, and suppression of renin-angiotensin aldosterone activation, sympathetic nerve activity and cardiac hypertrophy[36, 37], BNP levels may increase in response to myocardial damage as well as volume overload resulting from excess salt intake. A previous study showed that plasma BNP levels

provided strong predictive information about the future onset of heart failure and mortality in the general population[38].

In conclusions, excess salt intake is an independent risk factor for elevated plasma BNP levels in subjects with CKD. Sodium restriction for prevention of future cardiovascular events may be more important in subjects with CKD than in those without CKD.

Limitations

There are limitations to this study. First, we did not measure aldosterone which is influenced by salt intake[39]. Second, detailed information about the types of anti-hypertensive drugs being used was not available. Some reports indicated that angiotensin converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARB) increase plasma renin activity[40]. Administration of anti-hypertensive drugs such as diuretics, ACE-I and ARB may influence sodium excretion. Third, poor medication compliance might be associated with elevation of BNP levels in subjects with CKD and hypertension who cannot obey sodium restriction diet. However, there were no data about medical compliance in the present study. Finally, since the salt sensitivity of the Japanese is relatively high[41], salt sensitivity may have influenced the results of the present study. However, we did not assess salt sensitivity in this study. Further studies might be required to clarify the points.

Conclusion

Excess salt intake may augment myocardial damage in subjects with CKD. Optimal sodium restriction is required to prevent cardiovascular disease, especially in subjects with CKD.

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