High and low sodium intakes are associated with incident chronic kidney disease in patients with normal renal function and hypertension

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The association between salt intake and renal outcome in subjects with preserved kidney function remains unclear. Here we evaluated the effect of sodium intake on the development of chronic kidney disease (CKD) in a prospective cohort of people with normal renal function. Data were obtained from the Korean Genome and Epidemiology Study, a prospective community-based cohort study while sodium intake was estimated by a 24-hour dietary recall Food Frequency Questionnaire. A total of 3,106 individuals with and 4,871 patients without hypertension were analyzed with a primary end point of CKD development [a composite of estimated glomerular filtration rate (eGFR) under 60 mL/min/1.73 m^2 and/or development of proteinuria during follow-up]. The median ages were 55 and 47 years, the proportions of males 50.9% and 46.3%, and the median eGFR 92 and 96 mL/min/1.73 m^2 in individuals with and without hypertension, respectively. During a median follow-up of 123 months in individuals with hypertension and 140 months in those without hypertension, CKD developed in 27.8% and 16.5%, respectively. After adjusting for confounders, multiple Cox models indicated that the risk of CKD development was significantly higher in people with hypertension who consumed less than 2.08 g/day or over 4.03 g/day sodium than in those who consumed between 2.93–4.03 g/day sodium. However, there was no significant difference in the incident CKD risk among each quartile of people without hypertension. Thus, both high and low sodium intakes were associated with increased risk for CKD, but this relationship was only observed in people with hypertension.

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Chronic kidney disease (CKD) is a major risk factor for cardiovascular disease and death.[1,2] Blood glucose control and hypertension management are strategies that have been applied to prevent the development and progression of CKD. Nonetheless, the prevalence of CKD is rapidly increasing worldwide. Because established CKD is an irrecoverable condition, identifying modifiable factors and applying early interventions are crucial for reducing the burden of CKD.

Dietary sodium intake has been repeatedly reported to have an influence on cardiovascular risk factors and outcomes in several patient groups. A high sodium diet is known to aggravate hypertension,[3–5] and studies have shown high sodium intake to be also associated with an increased incidence of cardiovascular diseases.[6–13] However, restriction in dietary sodium intake also activates the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system.[14–16] Aggravation of insulin resistance has also been reported in subjects consuming low dietary sodium.[17] Accordingly, a recent investigation showed that survival of patients with type 1 diabetes can be reduced not only by high urinary sodium excretion but also low excretion.[13]

As hypertension is a major risk factor for CKD,[18] the clear connection between sodium intake and blood pressure also links dietary sodium to CKD.[19–21] However, its association with renal function is less well investigated and confounding. Although several studies have shown that high dietary sodium intake increases the risk of CKD development or progression,[13,22–25] some results failed to find significant connections to renal outcome.[22,26–30] In addition, although the adverse effects of increased dietary sodium on cardiovascular outcomes are more prominent in subjects with hypertension than in those without,[4,8,9] influence of hypertension on the relationship between sodium intake and CKD development is not known.

Therefore, in order to investigate whether dietary sodium intake affects CKD development, this study assessed a prospective community-based cohort of subjects with normal renal function with and without hypertension.

RESULTS

Baseline characteristics

The baseline characteristics of subjects with and without hypertension are shown in Tables 1 and 2, respectively. The median (range) of the subjects' ages were 55 (47–63) and 47 (43–56) years; the numbers of male subjects were 1581 (50.9%) and 2255 (46.3%); and the median (range) of estimated glomerular filtration rates (eGFRs) were 92 (81–100) and 96 (84–105) ml/min per 1.73 m^2 in subjects with and without hypertension, respectively. The average (range) dietary intake of sodium were 2.93 g (2.08 g–4.03 g) in subjects with hypertension and 2.93 g (2.09 g–3.95 g) in subjects without hypertension.

Stratification into quartiles was done according to the amount of dietary sodium intake for subjects with and without hypertension. The proportions of participants with diabetes did not differ, and eGFRs were comparable in each quartile group with and without hypertension. When comparisons were made among the dietary sodium intake quartile groups of subjects with and without hypertension, participants in the higher sodium intake groups tended to

Table 1 | Baseline characteristics of subjects with hypertension

Variables[a]	Total (*N* = 3106)	Quartiles of dietary sodium intake (g/d)				*P*
		Q1 (*N* = 777) <2.08	Q2 (*N* = 776) 2.08–2.93	Q3 (*N* = 777) 2.93–4.03	Q4 (*N* = 776) >4.03	
Dietary composition						
Na intake (g/d)	2.93 (2.08, 4.03)	1.56 (1.20, 1.82)	2.53 (2.32, 2.74)	3.40 (3.14, 3.67)	5.02 (4.44, 6.05)	<0.001
Demographic data						
Age (yr)	55 (47, 63)	57 (49, 64)	55 (47, 63)	54 (46, 62)	55 (46, 62)	<0.001
Male (%)	1581 (50.9)	295 (38.0)	382 (49.2)	444 (57.1)	460 (59.3)	<0.001
SBP (mm Hg)	134 (126, 146)	136 (126, 148)	134 (126, 146)	134 (126, 144)	134 (126, 146)	0.17
DBP (mm Hg)	90 (84, 96)	90 (84, 94)	90 (84, 96)	90 (84, 96)	90 (84, 98)	0.07
BMI (kg/m^2)	25.4 (23.2, 27.4)	25.0 (22.8, 27.3)	25.5 (23.4, 27.5)	25.5 (23.4, 27.3)	25.5 (23.5, 27.4)	0.04
Waist-to-hip ratio	0.92 (0.87, 0.96)	0.92 (0.87, 0.97)	0.91 (0.86, 0.96)	0.91 (0.86, 0.96)	0.92 (0.88, 0.96)	0.01
Education (%)						<0.001
Low	1310 (42.5)	397 (51.8)	323 (41.7)	291 (37.6)	299 (38.9)	
Intermediate	675 (21.9)	160 (20.9)	181 (23.4)	158 (20.4)	176 (22.9)	
High	1098 (35.6)	210 (27.4)	270 (34.9)	324 (41.9)	294 (38.2)	
Income (%)						<0.001
Low	1325 (43.3)	401 (52.1)	320 (41.9)	287 (37.5)	317 (41.5)	
Intermediate	847 (27.7)	208 (27.0)	223 (29.2)	203 (26.5)	213 (27.9)	
High	890 (29.1)	161 (20.9)	221 (28.9)	275 (35.9)	233 (30.5)	
Married (yes)	2750 (88.9)	659 (84.8)	688 (88.9)	701 (90.6)	702 (91.3)	<0.001
Ever drink (%)	1695 (54.8)	351 (45.4)	427 (55.2)	456 (58.8)	461 (59.6)	<0.001
Ever smoke (%)	1310 (42.5)	249 (32.4)	307 (39.8)	354 (45.9)	400 (52.1)	<0.001
Exercise (MET, k)	8.8 (4.8, 16.4)	8.0 (4.4, 16.4)	8.5 (4.9, 16.1)	8.8 (5.0, 15.9)	10.0 (5.4, 17.1)	<0.001
Comorbidities (%)						
Diabetes	598 (19.3)	157 (20.2)	145 (18.7)	166 (21.4)	130 (16.8)	0.11
Dyslipidemia	97 (3.1)	22 (2.8)	24 (3.1)	30 (3.9)	21 (2.7)	0.56
CVD[b]	130 (4.2)	40 (5.1)	37 (4.8)	26 (3.3)	27 (3.5)	0.19
Laboratory parameters[c]						
Na (mmol/l)	143 (142, 144)	143 (141, 144)	143 (141, 144)	143 (142, 144)	143 (142, 144)	0.49
BUN (mg/dl)	14.1 (11.9, 16.7)	14.1 (11.7, 16.5)	14.1 (11.9, 16.7)	14.0 (11.8, 16.6)	14.2 (12.0, 16.9)	0.35
Creatinine (mg/dl)	0.8 (0.7, 1.0)	0.8 (0.7, 0.9)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	0.8 (0.7, 1.0)	<0.001
eGFR (ml/min per 1.73 m^2)	92 (81, 100)	93 (81, 100)	92 (81, 101)	92 (80, 100)	93 (81, 101)	0.72
Hemoglobin (g/dl)	13.8 (12.7, 14.9)	13.4 (12.5, 14.6)	13.9 (12.8, 14.9)	14.0 (12.8, 15.1)	14.0 (12.9, 15.1)	<0.001
Glucose (mg/dl)	84 (79, 93)	83 (77, 92)	84 (79, 92)	86 (80, 95)	85 (79, 93)	0.001
HbA1c (%)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.0)	5.7 (5.4, 6.1)	5.7 (5.4, 6.0)	0.86
Albumin (g/dl)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.4)	4.2 (4.1, 4.5)	4.2 (4.1, 4.4)	0.08
Cholesterol (mg/dl)	193 (171, 218)	192 (170, 217)	193 (170, 217)	197 (173, 223)	190 (170, 215)	0.79
Triglyceride (mg/dl)	153 (112, 212)	146 (109, 199)	152 (111, 204)	159 (113, 228)	156 (115, 223)	<0.001
HDL-C (mg/dl)	43 (37, 49)	43 (37, 49)	43 (37, 50)	43 (37, 49)	43 (37, 49)	0.91
LDL-C (mg/dl)	115 (93, 137)	116 (93, 138)	115 (94, 139)	118 (95, 139)	111 (90, 134)	0.03
CRP (mg/l)	0.16 (0.08, 0.27)	0.16 (0.08, 0.26)	0.15 (0.08, 0.26)	0.17 (0.08, 0.31)	0.16 (0.08, 0.27)	0.66

BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; Na, sodium; Q, quartile; SBP, systolic blood pressure.

[a]All continuous variables are expressed as median (25th, 75th percentiles). The values expressed as mean and SD can be found in Supplementary Table S1.

[b]A history of cardiovascular disease was defined as the composite of myocardial infarction, congestive heart failure, coronary artery disease, peripheral artery disease, and/or cerebrovascular accident.

[c]*P* for trend was conducted by using the Jonckheere-Terpstra test.