Research Article

The association between dietary sodium intake and adiposity, inflammation, and hormone markers: A preliminary study*

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ABSTRACT

Purpose: Excess intake of sodium is a major diet-related risk factor for human diseases including hypertension and cancer as well as obesity and inflammation. However, findings are still controversial, and evidence is lacking in Koreans. Therefore, for better understanding of the role of dietary sodium intake in disease etiology, this study investigated the effects of dietary sodium intake on adiposity, inflammation, and hormones in Koreans. **Methods:** A total of 80 males and females joined the study. The general characteristics and dietary intake data were investigated by trained interviewers using a questionnaire and 24-h dietary recall, respectively. For the markers of adiposity, body weight, body mass index, percent of body fat, visceral fat area, and waist and hip circumference were measured. For the inflammation and hormone markers, leptin, adiponectin, insulin, tumor necrosis factor-α, and interleukin-6 were also analyzed. **Results:** Multivariate linear regression analyses suggested that dietary sodium intake was not associated with adiposity. However, dietary sodium showed a significant association with insulin level: Plasma insulin concentration increased with sodium intake independent of other dietary intake or percent of body fat ($\beta = 0.296$, adjusted $r^2 = 0.276$, $p < 0.01$). Other markers for inflammation and hormonal responses were not associated with dietary sodium intake. **Conclusion:** Findings suggested that dietary sodium intake may be a critical modifying factor in the level of plasma insulin. However, it showed a limited effect on obesity and other inflammation markers and hormone levels. These findings should be confirmed in larger, well-designed investigations.

KEY WORDS: dietary sodium intake, insulin, inflammation, obesity, body mass index

Introduction

Excess intake of dietary sodium is a major health issue worldwide. Many studies have provided evidence that high dietary sodium affects blood pressure and susceptibility for cardiovascular disease and cancer.[1-5] The role of dietary sodium in each disease etiology may vary, but the findings from the National Health and Nutrition Examination Survey in the United States were that excess intake of dietary sodium is responsible for a 20% greater risk of all-cause mortality.[6,7]

Excess sodium intake is also observed to be associated with obesity. Greater sodium intake was often accompanied by increased body weight.[8,9] This may be simply due to the amount of body fluid retained by the sodium. However, high sodium intake also correlated with consumption of high energy density foods including soft drinks.[10,11]

Furthermore, although there are inconsistencies, dietary sodium intake was associated with body mass index (BMI) and overweight.[7,12] This suggests that dietary sodium plays an intricate physiological role in obesity as well as human metabolism.

Recent studies reported that excess sodium intake may affect innate immunity. In murine explants, high sodium diet was associated with tissue inflammation and autoimmune disease.[13,14] Findings from human studies were consistent with these reports in that sodium intake correlated with changes in inflammatory markers including tumor necrosis factor-α (TNF-α) and adiponectin.[15-17] Obesity is considered a low grade of chronic inflammation. Therefore, the increased adipocytes associated with dietary sodium intake may lead to the production of adipokines, which initiate inflammation-related pathophysiological responses.[18,19] Additionally, few studies reported that dietary sodium

intake was associated with insulin level and that abundant dietary sodium increased insulin resistance, key markers for inflammation and endocrine metabolism.[20-22] In line with these findings, although some evidence suggested that the inflammation responses by sodium level may be obesity independent, we still could not dismiss the potential links underlying dietary sodium, obesity, inflammation, and hormone metabolism.

Korea has among the highest sodium consumption worldwide. Reducing the dietary sodium intake by 3 grams is expected to decrease incidence of hypertension, cardiovascular disease, gastric cancer, and kidney disease, resulting in savings of 12.6 trillion won in health costs.[23] Therefore, public health campaigns and nutritional education programs actively aim to reduce national dietary sodium intake. A decreasing trend in sodium intake is evident recently,[24] but little is known regarding the relationship of dietary sodium with obesity and other inflammation and hormonal markers in a Korean population. Therefore, to better understand the role of sodium intake in human health and disease, with this study, we investigated the effects of dietary sodium intake on adiposity as well as inflammation and hormonal responses.

Material and Methods

Study subjects

This cross-sectional study is a part of the research project The Development of a Sodium Adaptation Index Based on the Dietary Habits of Koreans: A Survey. Details of the project were described elsewhere.[25] Briefly, the male and female participants were recruited from Gwangju area, Korea, from May 2014 to April 2015. Participants were limited to individuals aged 19 to 69 years who had not been diagnosed with hypertension, heart failure, diabetes, renal disease, or cancer. Individuals were also excluded who were taking any medicine or who were pregnant or lactating. Lastly, subjects who reported any severe recent change in diet or lifestyle habits were not included in this study.

The Institutional Review Board of Kyungbuk National University approved the study protocols (KNU 2014-0053), and all actual procedures were performed in accordance with the allowed guidelines. All participants provided written informed consent prior to the commencement of the study.

Data collection

We asked volunteers to answer a questionnaire designed to obtain their sociodemographic and lifestyle information. Trained investigators asked each subject's smoking status, household income, education level, and general physical activity level.

Trained research scientists also collected anthropometrical data. Body weight and height were determined using a weight and height measurement tool (HM-201, Panix, Seoul, Korea). BMI was computed as follows: weight (kg) divided by the square of the height (m). For the waist and hip circumference, a measuring tape was used. Percent body fat and visceral fat area were measured with a body composition analyzer (InBody720, Biospace Co. Seoul, Korea).

We collected dietary intake data using 24-h dietary recall. Specifically, a professional dietitian interviewed each participant on the first day of the study. Dietary intake for target nutrients including sodium potassium and total energy intake were estimated by Computer Aided Nutritional Analysis program (CAN-Pro) version 4.0 (Korean Nutrition Society, Seoul, Korea)

Blood sample and biochemical data collection

Based on a literature review, we selected body weight, BMI, percent body fat, visceral fat area, and waist and hip circumference as adiposity markers. We also selected, leptin, adiponectin, insulin, TNF-α and interleukin-6 (IL-6) as inflammation and hormone response markers.

Blood samples were taken by venipuncture after a minimum of 12 hours of fasting. Serum plasma or whole blood samples were aliquoted and stored at -80℃ until the assay. We analyzed leptin, adiponectin, TNF-α, C-reactive protein (CRP), and IL-6 using modified enzyme immunoassay with the following commercial kits (BioVendor R&D, Brno, Czech Republic): human leptin ELISA, human adiponectin ELISA, human TNF-alpha ELISA, human CRP ELISA and human IL-6 ELISA. We prepared the samples following the manufacturer's instruction and performed tests with the Multiskan EX ELISA reader (Thermo Electron Corporation, Shanghai, China).

Statistical analysis

Data on continuous variables are presented as means ± standard deviations, and categorical variables exhibited as number of subjects and percent. We energy adjusted

the dietary intake variables before the statistical analysis with Willet's residual method. We primarily conducted Pearson's correlation coefficient analyses to screen for potential associations among the variables with respect to diet, anthropometry, and biochemical markers. We then ascertained the effects of dietary sodium intake on those variables using separate linear regression tests in the presence or absence of covariates. We determined covariates for the models such as age, sex, total energy, and potassium intake. We only added lifestyle covariates (smoking status, household income, educational and general physical activity level) to the models when the ANOVA results for each lifestyle factor were statistically associated with each target variable. We tested for multicollinearity among the covariates prior to the multiple linear regression tests using the condition index (all variables < 90). We used Bonferroni-corrected p values for multiple comparisons. We conducted all statistical analyses using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and considered a two-sided $p < 0.05$ statistically significant.

Results

Table 1 displays the general characteristics of the study participants. The mean age of the subjects was 43.3 ± 14.5 years, and there were equal numbers of males and females, 40 each. Total daily sodium intake of the study subjects was $3,960.1 \pm 1,824.3$ mg/day, and this was not different from the average intake for Koreans whom we investigated earlier. Mean calorie intake was $1,862.9 \pm 556.9$ kcal/day. The majority of subjects were nonsmokers (71.3%) and college graduates (55.0%). They also had

monthly incomes of less than 2,000,000 won (67.3%) and did not engage in heavy physical activity (70%). The mean BMI was 22.44 ± 3.01, and 18.3% of subjects were obese (BMI > 25, n = 15). The Pearson's coefficient correlation analysis showed that sodium intake was not correlated with energy intake, BMI, or other investigated variables (data not shown), with the exception of insulin concentration ($r = 0.410$, $p < 0.001$).

We established linear regression models to verify whether sodium intake affected body size, adiposity, hormones, and inflammation in the presence and absence of covariates (Table 2). The statistical results with respect to body size measurement revealed that dietary sodium intake was not associated with body weight, BMI, percent of body fat, visceral fat area, or waist or hip circumference. The regression models for adiposity, inflammation markers, and hormones, however, suggested that higher dietary sodium intake increased the insulin level (model 1: $\beta = 0.301$, adjusted $r^2 = 0.168$, Bonferroni-corrected $p < 0.001$), and this association held when we adjusted for other dietary and lifestyle factors (model 3: $\beta = 0.295$, adjusted $r^2 = 0.230$, Bonferroni-corrected $p = 0.011$). We did not observe these effects of dietary sodium intake on leptin, adiponectin, TNF-α, or IL-6.

Blood insulin level might be associated with other adiposity and dietary intake factors. Therefore, in order to verify clearer associations between dietary sodium intake and insulin, we established a regression model that incorporated percent body fat and total carbohydrate and fat intake. We found that a significant positive association between dietary sodium and insulin level was retained after we adjusted for those factors (model 2: $\beta = 0.296$, adjusted $r^2 = 0.276$).

Table 1. General characteristics of study participants

	Total subjects (n = 80)
Age (years)	43.33 (14.46)
Sex (n, %)	
Males	40 (50)
Females	40 (50)
Smoking status	
Never	57 (71.25)
Former	17 (21.25)
Current	6 (7.5)
Household income (10,000 Korean won)	
200 or less	49 (61.25)
200~400	24 (30.0)
400 or more	7 (8.75)

Values in the brackets denote percent of subjects or otherwise means ± standard deviations.

Table 1. General characteristics of study participants (continued)

	Total subjects (n = 80)
Education level	
Middle school graduate or less	12 (15.0)
High school graduate	24 (30.0)
College graduate or more	44 (55.0)
General physical activity	
Light (retirees, office workers, homemakers doing simple chores)	56 (70.0)
Moderate (teachers, retailers, manufacturers, homemakers)	20 (25.0)
Heavy (laborers, farmers, builders, athletes, etc.)	4 (5.0)
Dietary intake	
Total energy (kcal/day)	1,862.9 ± 556.9
Sodium (mg/day)	3,960.1 ± 1,824.3
Potassium (mg/day)	2,636.2 ± 923.8
Fat (g/day)	47.08 ± 17.53
Carbohydrate (g/day)	284.7 ± 47.88
Body size measurement	
Weight (kg)	61.89 ± 9.98
Body mass index (kg/m^2)	22.44 ± 3.01
Percent body fat, %	25.81 ± 7.80
Visceral fat area (cm^2)	77.92 ± 32.63
Waist circumference (cm)	80.82 ± 8.69
Hip circumference (cm)	95.04 ± 5.51
Inflammation and hormone markers	
Leptin (ng/dL)	4.14 ± 3.38
Adiponectin (μg/dL)	8.29 ± 4.70
Insulin (uIU/ml)	1.83 ± 1.39
TNF-α (pg/ml)	9.78 ± 2.77
Interleukin-6 (pg/ml)	0.78 ± 1.05

Values in the brackets denote percent of subjects or otherwise means ± standard deviations.

Table 2. Association of dietary sodium intake with measures of body size and inflammation and hormone markers

	Model 1[1]			Model 2[2]			Model 3[3]		
	Standardized beta coefficient	Standard error	R^2	Standardized beta coefficient	Standard error	Adjusted R^2	Standardized beta coefficient	Standard error	Adjusted R^2
Body size measurements									
Weight (kg)	0.536	0.616	0.010	0.267	0.554	0.236	0.419	0.519	0.380
Body mass index (kg/m^2)	0.194	0.185	0.014	0.123	0.184	0.135	0.111	0.178	0.202
Percent body fat, %	0.271	0.484	0.004	0.359	0.374	0.434	0.196	0.363	0.501
Visceral fat area (cm^2)	1.596	2.020	0.008	0.900	1.459	0.507	1.554	1.405	0.554
Waist circumference (cm)	0.691	0.534	0.021	0.562	0.528	0.087	0.596	0.496	0.227
Hip circumference (cm)	0.445	0.338	0.022	0.422	0.353	-0.017	0.436	0.341	0.090
Inflammation and hormone markers									
Leptin (ng/dL)	-0.058	0.225	0.001	-0.009	0.209	0.196	-0.001	0.209	0.200
Adiponectin (μg/dL)	-0.449	0.323	0.032	-0.204	0.324	0.083	-0.252	0.323	0.177
Insulin (uIU/ml)	0.301[***]	0.084	0.168	0.327[***]	0.087	0.172	0.295[***]	0.085	0.230
TNF-α (pg/ml)	0.265	0.184	0.033	0.212	0.193	0.000	0.212	0.193	0.000
Interleukin-6 (pg/ml)	0.031	0.070	0.003	0.020	0.073	0.012	0.020	0.073	0.010

Dietary sodium intake (g/day) was adjusted for total energy intake using Willet's residual method prior to the analyses.
1) Model 1: crude model   2) Model 2: adjusted for age, sex, total energy and potassium intake   3) Model 3: adjusted for age, sex, total energy and potassium intake, smoking status, household income, education level and general physical activity, as appropriate
[***] $p < 0.001$, Bonferroni-corrected $p < 0.05$

Table 3. Dietary sodium intake as an independent prediction marker for insulin with adjustment for adiposity and diet factors

Regression models	Standardized beta coefficient	Standard error	Adjusted R^2	95% confidence limit
Insulin				
Model 1[1]	0.295**	0.085	0.230	(0.124, 0.466)
Model 2[2]	0.295**	0.084	0.289	(0.127, 0.464)

1) Model 1: adjusted for age, sex, total energy and potassium intake, and level of general physical activity 2) Model 2: adjusted for age, sex, total energy and potassium intake, general physical activity, percent of body fat, and total carbohydrate and fat intake
** $p < 0.01$

Discussion

Excess dietary sodium intake is a critical health issue in Korea. Studies have suggested that increased sodium intake is associated with risk of obesity and inflammation response as well as hypertension and cancer. However, the precise mechanisms of dietary sodium in disease risk are not fully understood. For this reason, it is necessary to collect more comprehensive evidence to evaluate the role of dietary sodium in human metabolism.

In this study, we evaluated the effects of dietary sodium intake on body size and adiposity in addition to hormones and inflammation response. Among the examined variables, only insulin level was associated with dietary sodium intake: Plasma insulin increased with higher sodium intake. Associations between dietary sodium intake and insulin sensitivity or resistance have been observed in previous studies. Although some controversies exist, observational and intervention studies have found that low dietary intake was associated with decreased insulin resistance.[20] A number of possible mechanisms have been proposed for the association, including that lower sodium intake decreases leptin, which reduces abdominal fat cells, resulting in lower adiposity and insulin resistance.[26] A second proposition is that lower intake of dietary sodium modifies the expression of glucose transporter type-4 protein in adipocytes and may therefore improve insulin sensitivity.[27] A final proposed mechanism is that low sodium intake alters the level of angiotensin II, which regulates insulin activity.[28] These proposed mechanisms all suggest that lower dietary sodium intake is associated with human glucose and insulin metabolism and could further help to prevent diabetes mellitus and metabolic syndrome. In the present study, we did not assess insulin resistance because we had limited information on blood glucose level. However, the increased insulin levels with higher sodium intake could be evidence for an association between sodium and insulin resistance. The multiple study findings all suggest the importance of reducing dietary sodium intake for human health.

Earlier studies reported that dietary sodium intake was associated with body size including body weight, BMI, and overweight,[7,8] and additional evidence has suggested that increased sodium intake could alter markers for inflammation responses.[12,29] In the current study, however, dietary sodium intake did not show a significant influence on body weight, BMI, percent body fat, visceral fat area, or waist or hip circumference, and these insignificant associations held even when we considered total energy and dietary intake and lifestyle factors. These limited associations could have resulted from the obesity levels of the study participants. Because chronic inflammation responses could be mediated by obesity status, we intended to perform additional analyses according to obesity level to more precisely verify the associations among dietary sodium, adiposity and inflammation response. However, there were only 15 obese subjects in the study, and therefore, we could not perform the subgroup analyses. High dietary sodium intake and obesity could have shown clear correlations with our study variables, but the subjects did not show extreme sodium intake or high BMI, and this might have been responsible for the minimal association between dietary sodium intake and obesity and inflammation markers. Lastly, the subjects joined the study voluntarily, so they may have been more concerned about their health, diet, and lifestyles than the general population. In short, the study findings did not show clear associations between diet and our examined variables.

For this study, we comprehensively investigated the relationships between dietary sodium intake, adiposity, and inflammation. The study provided preliminary evidence of an association between sodium intake and insulin level but with the limitation discussed above that our study sample was relatively small. A larger study cohort could give better statistical power for the findings. Additionally, there were sex-specific differences in diet and intake, but we could not perform stratified analyses because of the limited numbers of subjects. We therefore considered

covariates in the statistical models, but we could not dismiss potential underlying effects. Therefore, our findings should be confirmed in larger, well-designed studies.

In conclusion, our study exhibited that dietary sodium intake was not associated with body size but it did significantly affect plasma insulin level. Considering the importance of insulin for presenting diabetes mellitus and metabolic diseases, this preliminary evidence supports the idea that reducing dietary sodium is a critical diet-related factor in improving public health.

Summary

Excess intake of sodium is observed to be a major risk factor in many human diseases, and furthermore, the association between immune responses and sodium intake has been of interest as a potential underlying mechanism of obesity. In this Korean study, we examined the effects of dietary sodium intake on adiposity, inflammation, and hormone markers. Among the examined variables using multivariate linear regression analyses, plasma insulin was the sole marker associated with sodium intake; plasma insulin was higher with higher sodium intake, and this association was independent of other dietary intake and overweight. This increase of insulin level with increased sodium intake could be evidence for a relationship between sodium and insulin resistance. The current study did not exhibit any associations between dietary sodium and obesity or inflammation responses, but it did provide evidence that reducing dietary sodium intake could be effective for preventing diabetes mellitus and other metabolic disorders.

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