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ORIGINAL ARTICLE

Effect of high dietary sodium on bone turnover markers and urinary calcium excretion in Korean postmenopausal women with low bone mass

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BACKGROUND/OBJECTIVES: High salt intake is a well-recognized risk factor of osteoporosis for its modulating effect on calcium metabolism. To understand the effect of dietary sodium on bone turnover, we evaluated the association between urinary sodium excretion and bone turnover markers in Korean postmenopausal women with low bone mass.

SUBJECTS/METHODS: A retrospective review of medical records at a single institution identified 537 postmenopausal women who were first diagnosed with osteopenia or osteoporosis between 2008 and 2013. Subjects were stratified by low (< 2 g/day, $n = 77$), moderate (2–4.4 g/day, $n = 354$) and high ($\geqslant 4.4$ g/day, $n = 106$) sodium excretion. A 24-h urine was collected to estimate sodium, calcium and creatinine. Bone turnover markers and calciotropic hormones were measured in serum. Bone mineral density (BMD) was assessed using dual-energy X-ray absorptiometry.

RESULTS: Sodium intake was positively associated with urinary sodium excretion ($P = 0.006$, $r = 0.29$). Bone turnover markers were significantly higher in the moderate-to-high urinary sodium excretion group ($\geqslant 2$ g/day) than in the low urinary sodium excretion group (< 2 g/day); CTX-I (C-telopeptides of type I collagen) was 21.3% higher ($P = 0.001$) and osteocalcin (OC) was 15.7% higher ($P = 0.004$). Calciotropic hormones and BMD were not significantly different across the sodium excretion groups.

CONCLUSIONS: High urinary sodium excretion ($\geqslant 2$ g/day) increased bone turnover markers in Korean postmenopausal women, suggesting that excessive sodium intake might accelerate bone turnover.

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INTRODUCTION

According to the 2011 Korea National Health and Nutrition Examination Survey (KNHANES V-2), the average daily sodium intake is 6172 mg for males and 4172 mg/day for females.[1] However, World Health Organization (WHO) recommends that adults consume < 2000 mg of sodium per day.[2] Public health implications of high sodium intake have largely focused on cardiovascular end points but have not sufficiently examined other organ systems such as the skeletal system.

The prevalence of osteoporosis among Korean women over 50 years old is 38.7%[3] and is substantively higher than the prevalence of 10% reported by the 2010 and 2012 National Center for Health Statistics in the United States[4,5] and the prevalence of 30% in five European countries (France, Germany, UK, Italy and Spain).[6] One of the important factors leading to this difference could be excessive daily sodium intake among Korean women.

Although the role of calcium in the prevention and treatment of osteoporosis is well established, less emphasis has been placed on factors that may modulate calcium metabolism—such as, sodium.[7,8] The higher sodium intake among Korean women may contribute to their higher rates of osteoporosis because a high-sodium diet induces hypercalciuria and contributes to a negative calcium balance, even with a high-calcium diet.[9] Even though the increased mobilization of calcium stores with high sodium intake may contribute to osteoporosis,[10] there are some controversies; one study shows that sodium excretion has no effect on bone mass,[11] and others suggest a negative correlation between sodium excretion and bone mass.[12,13] Moreover, the association between dietary sodium intake and bone turnover markers has not been studied extensively. One study shows no effect of high sodium intake on serum osteocalcin (OC) or serum C-telopeptides of type I collagen (CTX-I), although reducing sodium intake decreases serum OC by approximately 3%.[14] Laura *et al.* also report that serum propeptide of type I collagen, a bone formation marker, is significantly decreased with a low-sodium diet.[15] Because the effect of excessive sodium intake on bone turnover has not been well established, we aimed to assess changes of bone turnover markers according to the amount of urinary sodium excretion, which is closely associated with dietary sodium intake in Korean postmenopausal women with low bone mass.

MATERIALS AND METHODS

Subjects

We reviewed the medical records retrospectively. Postmenopausal women who were at least 1 year past menopause were included. Participants were first diagnosed with osteopenia or osteoporosis at the health promotion center of the Samsung Medical Center (Seoul, Korea), which is used for medical checkups in the general population, and were subsequently referred to the Division of Endocrinology and Metabolism between March 2010 and March 2013. Dietary sodium and calcium consumption was assessed in 86 subjects using a modified food frequency questionnaire (FFQ) based on the one used in the KNHANES. We classified these subjects

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as the confirmation group, in which we intended to confirm the correlation between dietary sodium intake and urinary sodium excretion. After analyzing this association in the confirmation group, we selected the verification group retrospectively to assess the association between urinary sodium excretion and bone turnover markers. The subjects in the verification group were first diagnosed with osteopenia or osteoporosis at the outpatient clinic of the Department of Endocrinology and Metabolism between March 2008 and March 2013. This population included individuals who visit health promotion center for medical checkups from the general population and subsequently referred and who were referred from the outpatient department of another division. A total of 833 subjects were initially selected for the verification group. Subjects with history of kidney transplantation, primary hyperparathyroidism and rheumatoid arthritis were excluded. Subjects were also excluded if they had taken corticosteroids, estrogen, supplemental calcium, anticonvulsant agents, diuretics such as thiazide within 6 months of the study, bisphosphonates, parathyroid hormone and antihormonal agents for cancer therapy (such as breast cancer). Patients with an estimated glomerular filtration rate < 60 ml/min/1.73 m^2 (according to Modification of Diet in Renal Disease study equation) were also excluded. After exclusion, a total of 537 subjects were analyzed as the verification group, which consisted of Korean women between 41 and 86 years who were at least 1 year past menopause and serum follicle-stimulating hormone levels were >40 mIU/ml. Among them, 68 patients had cessation of menstruation after hysterectomy. This study was approved by the Institutional Review Board at the Samsung Medical Center.

Measurements

Bone formation and resorption biomarkers, calciotropic hormones, such as intact parathyroid hormone and serum 25-hydroxyvitamin D (D2+D3), and baseline serum electrolyte, calcium, phosphorus, magnesium and creatinine were retrospectively obtained from electronic medical records. Blood samples were collected in the morning after an overnight fast of >8 h. All blood samples were obtained at the first visit to the outpatient clinic and before the commencement of osteoporosis or osteopenia treatment. Serum OC, a marker of bone formation, and serum CTX-I, a marker of bone resorption, were measured by electrochemiluminescence immunoassay (Roche Modular Analytics E170 (Roche Diagnostics, Mannheim, Germany)). In our laboratory, the interassay coefficient of variation ranged from 1.8 to 2.3% for OC and 2.6 to 2.9% for CTX-I. Serum bone alkaline phosphatase (ALP), a marker of bone formation, was measured by ELISA (Ostase Bone specific alkaline phosphatase EIA, Immunodiagnostic Systems, IDS, Boldon, UK) and had an interassay coefficient of variation of 3.7–6.4%. Serum parathyroid hormone (PTH) was measured by radioimmunoassay (kit from CIS bio, Automatic Gamma Counter GAMMA-10 2.0, Codolet, France) and had an interassay coefficient of variation of 9.5–11.5%. Serum 25-hydroxyvitamin D was measured by LC-MS/MS (Agilent 6460 triple-quadrupole mass spectrometer (Agilent Technologies, Inc., Santa Clara, CA, USA)) and had an interassay coefficient of variation of 2.8–3.4% for D2 and 3.0% for D3. Baseline bone mineral density (BMD) was measured by dual-energy X-ray absorptiometry using either Lunar Prodigy Advance (448 patients) or Hologic Delphi W (89 patients). In accordance with WHO criteria, osteopenia was defined as a T-score between -1 and -2.5 and osteoporosis as a T-score of < -2.5 for the lumbar spine, femur neck or total hip. The different measurement devices for BMD were adjusted for in the regression analysis of urine sodium excretion and BMD. Current smoking status, coffee intake and age of menopause were obtained by self-report questionnaires.

Assessment of dietary sodium intake in the confirmation group

All subjects in the confirmation group completed the modified FFQ during a health-care examination at the health promotion center on the basis of dietary intake over the previous 3 months. The modified FFQ was composed of 71 questions that assessed consumption frequency of 63 food items in 11 food groups. The detailed contents of food groups and frequency of servings were the same as the FFQ used in the KNHANES.[16] The 'modified FFQ' was used in the Samsung Medical Center to promote better understanding and easier recall of food groups and consumption frequency.

Assessment of sodium excretion

Before the administration of medications for osteoporosis or osteopenia, 24-h urine samples were collected from all patients to estimate urinary sodium, calcium and creatinine excretion. Urine sodium was measured using an ion-selective electrode, calcium was measured using ocresolphthalein complexone method and creatinine was measured by the Jaffe method using the COBAS Integra 800 (Roche Diagnostics). We classified subjects into low (<2 g/day), moderate (2–4.4 g/day) and high sodium excretion groups ($\geqslant$4.4 g/day). Cutoff point of the lower sodium level was chosen on the basis of the recommended daily sodium amount by WHO.[2] Cutoff point of the upper sodium level to delineate between the moderate and high sodium excretion was chosen on the basis of a recent study on sodium intervention.[9]

Statistical analysis

Statistical analyses were performed using SPSS statistics 21.0 (SPSS, Inc. Chicago, IL, USA). Kruskal–Wallis tests were used to analyze the differences in age, years since menopause (YSM), mean urinary calcium excretion and calciotropic hormones across the urinary sodium excretion groups. Mann–Whitney tests were used to compare between pairs of groups when appropriate. Bone turnover markers including serum OC, CTX-I and bone ALP across the urinary sodium excretion groups were assessed using one-way analysis of variance. Bonferroni correction was used in the *post hoc* analysis of the between-group comparisons to account for the number of comparisons performed. An analysis-of-covariance model, including bone turnover markers, urinary sodium excretion and the interaction between the two, was fit to assess the heterogeneity of bone turnover markers levels across YSM duration.[17–19] All other data, which were parametrically distributed and expressed as means and standard deviation (s.d.), were analyzed using analysis of variance. A P-value < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the baseline characteristics of our study population. Among the 86 subjects in the confirmation group, the average daily sodium and calcium intakes were 3465 and 813 mg. Linear correlation between the amount of daily sodium intake (mg/day) and urinary sodium excretion (mg/day) was statistically significant ($P=0.006$, $r=0.29$). Patients in the verification group ($n=537$) were stratified into low ($n=77$), moderate ($n=354$) and high urinary sodium excretion group ($n=106$). Age, YSM, body weight, body mass index, smoking status and coffee intake were similar across these three groups. Baseline sodium excretion/creatinine ratio (mg/g Cr) ($P<0.001$) and calcium excretion/creatinine ratio (mg/g Cr) ($P=0.004$) were higher in the moderate and high urinary sodium excretion groups compared with the low urinary sodium excretion group (Table 2), and the correlation between these two variables was statistically significant ($P<0.001$, $r=0.202$, data not shown). The intact PTH ($P=0.21$) and 25-hydroxyvitamin D ($P=0.794$) were similar across the groups (Table 2). Average baseline serum markers of bone formation and bone resorption were significantly different across the three urinary sodium excretion groups (CTX-I; $P=0.003$, OC; $P=0.001$, bone ALP; $P=0.025$; Table 3). Specifically, serum CTX-I was higher in the moderate and high urinary sodium excretion groups, respectively, than in the low urinary sodium excretion group ($P=0.001$ and $P=0.01$, respectively), as were serum OC ($P=0.001$ and $P=0.043$, respectively) and serum bone ALP ($P=0.015$ and $P=0.009$, respectively) (Figure 1). Serum CTX-I was 21.3% higher ($P=0.001$), serum OC was 15.7% higher ($P=0.004$) and serum bone ALP was 9.5% higher ($P=0.174$) in individuals with sodium excretion $\geqslant 2$ g/day than in those with <2 g/day (Figure 2). Differences in bone turnover markers were maintained even after adjustment for duration of YSM ($P=0.002$ for CTX-1 and $P=0.006$ for OC; Table 3). BMD of the lumbar spine (LS; $P=0.296$), femoral neck (FN; $P=0.969$) and total hip (TH; $P=0.419$) were not different among the urinary sodium excretion groups (Table 4). Urinary sodium excretion and BMD were not significantly associated after adjustment for body weight, YSM, age and BMD device (Lunar versus Hologic) (LS; $P=0.743$, FN; $P=0.299$, TH; $P=0.155$, data not shown).

Table 1. Baseline characteristics of the study population

	Confirmation group (n = *86*)	*Verification group* (n = *537*)			
		Low excretion (*< 2 g/day*) (n = *77*)	*Moderate excretion* (*2–4.4 g/day*) (n = *354*)	*High excretion* (*⩾4.4 g/day*) (n = *106*)	P-*value*[a]
Age (years)	58 ± 6	58 (55–66)	59 (54–63)	60 (54–64)	0.575
Median years since menopause (years)	8.5 (5–12)	8.5 (4–18)	9.0 (5–17)	10.0 (5–13)	0.978
Height (cm)	157.3 ± 5.2	152.4 ± 4.6	155.3 ± 5.3	156.0 ± 4.8	< 0.001
Weight (kg)	52.8 ± 7.5	50.3 ± 7.1	53.4 ± 6.6	55.1 ± 6.5	0.068
BMI (kg/m^2)	21.4 ± 2.9	21.7 ± 3.0	22.2 ± 2.8	22.6 ± 2.3	0.068
Current smoking status	1 (1.1%)	0 (0%)	3 (0.8%)	1 (0.9%)	0.7
Coffee drinking status (> 2 cups/day)	—	8 (10.3%)	39 (11%)	6 (5.6%)	0.265

Abbreviation: BMI, body mass index. Data are presented as mean ± s.d., median (interquartile range) or number (%). [a]Differences across the three sodium excretion groups.

Table 2. Sodium and calcium excretion and calciotropic hormones stratified by baseline sodium excretion

	n	*Baseline*		
		Median	*Interquartile range*	P-*value*[a]
Sodium excretion (mg/g creatinine)				
< 2 g/day	77	2617.5	2015.2–3288.4	< **0.001**
2–4.4 g/day	354	3915.9	3354.9–4568.6	
⩾ 4.4 g/day	106	5589.9	4836.5–6439.5	
Calcium excretion (mg/g creatinine)				
< 2 g/day	77	188.3	127.9–298.8	**0.004**
2–4.4 g/day	354	219.5	156.3–307.6	
⩾ 4.4 g/day	106	251.4	176.1–328.3	
PTH (pg/ml)				
< 2 g/day	77	36.2	26.2–46.6	0.21
2–4.4 g/day	354	33.2	24.7–42.7	
⩾ 4.4 g/day	106	32.3	24.0–43.0	
25-hydroxyvitamin D (ng/ml)				
< 2 g/day	77	18.6	13.3–26.4	0.794
2–4.4 g/day	354	18.6	12.7–26.3	
⩾ 4.4 g/day	106	19.3	13.6–25.6	

Abbreviation: PTH, parathyroid hormone. Bold entries are significant values of $P < 0.05$. [a]*P*-values for differences across the three sodium excretion groups.

DISCUSSION

Although the WHO recommends that adults consume < 2000 mg of sodium per day,[2] the 2011 data from Korea National Health and Nutrition Examination Survey (KNHANES V-2) show that the average Korean adult intakes 5158 mg sodium per day,[1] which is much higher compared with the 3436 mg reported in the United States,[20] 3900–4200 mg in Central Europe and Middle East/North Africa and 3400–3800 mg in Western Europe and Australia/New Zealand.[21] Actually, most Korean food and condiments are high in salt. Despite recommendations to reduce sodium intake,[2,22] salt consumption still exceeds physiologic need for sodium. This excessive intake of sodium is associated with adverse clinical outcomes and has been a significant health issue worldwide.[23]

Our analysis of the confirmation group confirmed the positive correlation between dietary sodium intake (mg/day) and urinary sodium excretion (mg/day) ($P = 0.006$). The quantity of sodium in a 24-h urine specimen is similar to the quantity of sodium ingested in the absence of hydration disorders or a large change in volume load.[24] The correlation coefficient we found was similar to that of a previous study on sodium and calcium intake in postmenopausal women.[13] We observed a significant increasing urinary calcium excretion in excessive urinary sodium excretion groups (⩾2 g/day, $P = 0.004$), which supports observations from cross-sectional and cohort studies.[12,25–27] We then analyzed baseline levels of serum bone turnover markers in postmenopausal women (verification group) stratified by urinary sodium excretion amount (low, moderate and high).

The major finding of our study was that serum bone turnover markers were significantly higher in the excessive urinary sodium excretion group (⩾2 g/day) than in the low urinary sodium excretion group (< 2 g/day) (Figure 2). High bone turnover markers in postmenopausal women might indicate rapid bone loss. A previous study shows that serum bone ALP levels were 28% higher and serum OC was 21% higher in postmenopausal women with rapid bone loss than in those with slow bone loss.[28] The study also shows that odds of rapid bone loss are 1.8–2.0 times higher for each s.d. that the bone ALP and OC are away from the mean. Gerdhem *et al.*[29] report that bone resorption markers, including serum CTX-I, are consistently higher in women who have sustained at least one fracture than in those without any history of fracture, and individuals with high serum CTX-I were 2.15 times more likely to sustain at least one fracture (95% confidence interval, 1.41–3.28). As demonstrated in these recent studies, biochemical markers of bone formation and resorption are strongly associated with rapid bone loss and higher levels increase the probability of rapid bone loss. In particular, serum CTX-I, which was significantly higher in both the moderate and high urinary sodium excretion group (⩾2 g/day) in our study, is considered one of the most accurate predictors of fracture risk.[30,31] Biochemical markers may provide a representative indication of overall skeletal bone loss and may predict fracture risk earlier and more accurately than measured rates of change in BMD at a single skeletal site.[28,32–34] Moreover, evaluation of rapid bone loss through serial estimations of BMD is time-consuming in clinical settings, whereas increased bone turnover markers may indicate increasing fracture risk in a more timely manner independent of current BMD.[28,32,35–40] We demonstrated that excessive urinary sodium excretion (⩾2 g/day) increased bone turnover markers; hence, we could suggest that excessive dietary sodium intake may accelerate bone turnover rate and can predict rapid bone loss.

The correlation between bone turnover markers and sodium intake in previous studies is inconsistent so far. Although low sodium intake has been thought to decrease bone turnover markers, no published data have shown that high sodium intake increases them. In addition, no studies have investigated the effects of excessive sodium intake on bone turnover markers in patients with low bone mass. Teucher *et al.*[9] report that the bone resorption markers, serum pyridinoline and deoxypyridinoline, are significantly increased only with low-calcium diets ($P < 0.05$) and

Table 3. Serum biochemical markers of bone formation (OC, bone ALP) and bone resorption (CTX-I) according to sodium excretion amount

	Low excretion (< 2 g/day) (n = *77*)	*Moderate excretion (2–4.4 g/day)* (n = *354*)	*High excretion (⩾4.4 g/day)* (n = *106*)	P-*value*[a]	P-*value*[b]
CTX-I (ng/ml)	0.516 ± 0.233	0.631 ± 0.272	0.607 ± 0.229	**0.003**	**0.002**
OC (ng/ml)	22.3 ± 8.3	26.1 ± 7.9	24.8 ± 8.8	**0.001**	**0.006**
Bone ALP (μg/l)	22.0 ± 13.8	24.0 ± 10.2	24.4 ± 9.4	**0.025**	0.296

Abbreviations: ALP, alkaline phosphatase; CTX-I, C-telopeptides of type I collagen; OC, osteocalcin. Data are presented as mean ± s.d. Bold entries are significant values of $P < 0.05$. [a]*P*-values for differences in serum biochemical markers across the three sodium excretion groups, calculated by analysis of variance analysis. [b]*P*-values for differences in serum biochemical markers across the three sodium excretion groups adjusted by years since menopause, calculated by analysis of covariance.

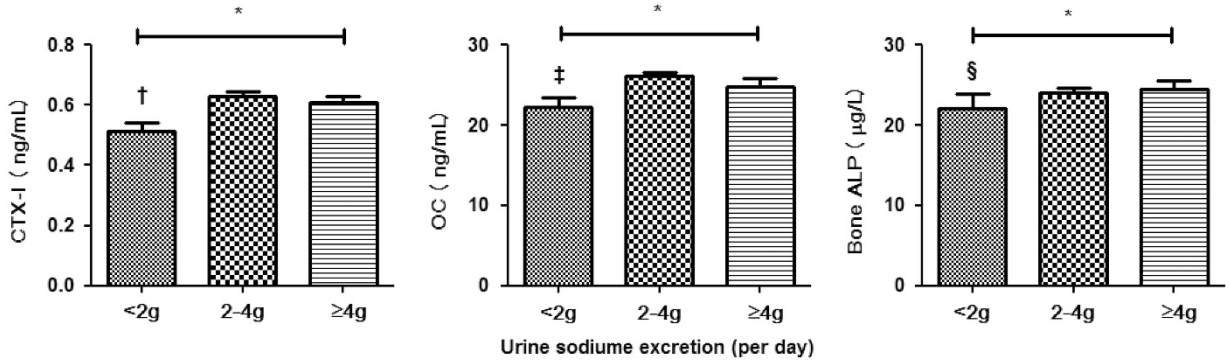

Figure 1. Baseline bone turnover markers according to urinary sodium excretion amount. Bars represent the means and SE. *Differences across the three urinary sodium excretion groups, $P < 0.05$; by analysis of variance test. †Low vs moderate, $P = 0.001$; low vs high, $P = 0.01$; moderate vs high, $P = 0.526$; ‡low vs moderate, $P = 0.001$; low vs high, $P = 0.043$; moderate vs high, $P = 0.086$. §low vs moderate, $P = 0.015$; low vs high, $P = 0.009$; moderate vs high, $P = 0.601$. (By Mann–Whitney test, significant differences $P < 0.017$ applied by Bonferroni's correction.)

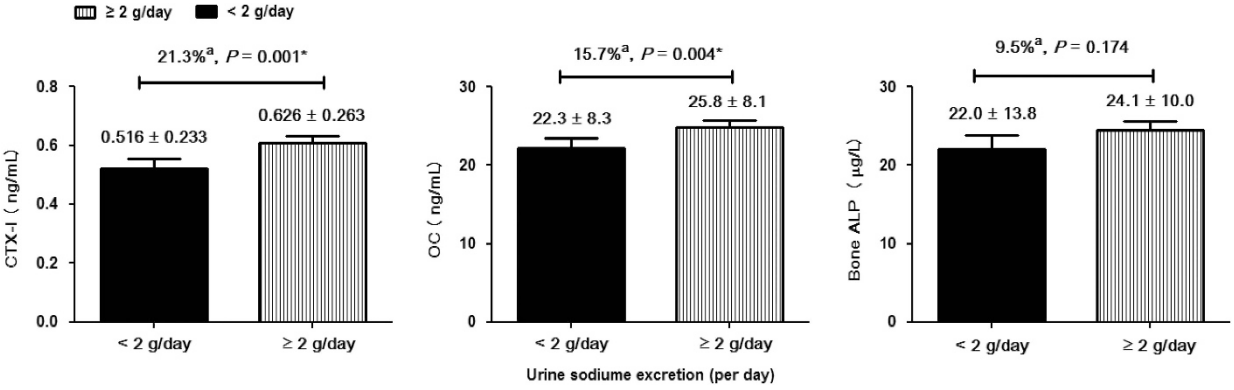

Figure 2. Bone turnover markers in the low (< 2 g/day) ($n = 77$) and both the moderate and high (⩾2 g/day) ($n = 460$) urinary sodium excretion groups. [a]Differences of levels. *t*-Test, significant differences $^*P < 0.05$.

Table 4. Baseline bone mineral density stratified by sodium excretion

T-score	*Low excretion (< 2 g/day)* (n = *77*)	*Moderate excretion (2–4.4 g/day)* (n = *354*)	*High excretion (⩾4.4 g/day)* (n = *106*)	P-*value*[a]
LS	−2.7 ± 0.7	−2.7 ± 0.6	−2.6 ± 0.5	0.296
FN	−2.1 ± 0.6	−2.1 ± 0.5	−2.1 ± 0.6	0.969
TH	−1.9 ± 0.6	−1.8 ± 0.5	−1.9 ±0.5	0.419

Abbreviations: FN, femoral neck; LS, lumbar spine; TH, total hip. [a]*P*-values for differences in BMD across the three sodium excretion groups.

are not significantly changed with a low-sodium intervention diet. Conversely, Laura *et al.* report that serum propeptide of type I collagen is significantly lower with a low-sodium diet.[15] Another study shows that high sodium intake does not affect serum OC and CTX-I, although reducing sodium intake decreases the serum OC by about 3% ($P < 0.01$).[14]

Biochemical markers were not significantly different between the moderate (2–4.4 g/day) and high urinary sodium excretion

groups (⩾4.4 g/day), suggesting that dietary sodium intake above the current WHO recommendation level has negative effects on bone metabolism by accelerating the rate of bone turnover. However, there might be no further increase in bone turnover markers as urinary sodium excretion increased above the 2 g/day.

In our study, calciotropic hormones, including intact PTH and 25-hydroxyvitamin D, were not different across the three urinary sodium excretion groups. Some studies suggest that PTH and calcitriol increase with higher urinary sodium excretion to compensate for urinary calcium losses,[14,41,42] although the relationship between PTH and urinary sodium excretion is controversial, especially in postmenopausal women. The increase in PTH and calcitriol with salt loading is observed in young adults but not in postmenopausal women, indicating a lack of adaptation to high salt intake in older women.[43,44] Furthermore, postmenopausal women do not increase calcium absorption, which may be due to impairments in calcitriol synthesis,[45] intestinal resistance to 1,25-dihydroxycholecalciferol[46] or loss of estrogen.[47] These findings from previous studies may explain the lack of differences in calciotropic hormones across the urinary sodium excretion groups in our study.

BMD was not different across the urinary sodium excretion groups in our study. A single 24-h urinary sodium excretion measurement likely does not reflect the long-term dietary habits and may not be accurate for analyzing the association between dietary sodium intake and BMD. In addition, we could not analyze serial BMD measurements to assess the response according to urinary sodium excretion amount, which may be a more accurate assessment of bone status in response to dietary sodium intake compared with the single BMD measurement.

Our study had some limitations. We collected only one 24-h urine sample to estimate sodium and calcium excretion. Multiple 24-h urine samples give a more accurate estimate of sodium intake because they better reflect their usual diet over a long period of time.[48] We analyzed the correlation between sodium intake and the 24-h urinary sodium excretion in the confirmation group to compensate for this limitation and directly confirm the association between intake and excretion. The subjects in the verification group who had either osteopenia or osteoporosis were started on calcium and vitamin D supplements or bisphosphonate agents after the first visit to our clinic. Because the subjects needed prompt treatment, we were unable to follow-up the changes of bone turnover markers and BMDs. Finally, this is a single-center-designed study, and thus the results could not be generalized to the overall population.

In conclusion, high urinary sodium excretion (⩾2 g/day) was associated with increased bone turnover markers in Korean postmenopausal women, suggesting that excessive sodium intake might accelerate bone turnover rate. Additional long-term trials, including assessment of serial BMDs and fracture incidences, are needed to confirm the effect of high-sodium diet on bone health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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