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ORIGINAL RESEARCH

Parathyroid Hormone, Calcium, and Sodium Bridging Between Osteoporosis and Hypertension in Postmenopausal Korean Women

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Abstract The coexistence of osteoporosis and hypertension, which are considered distinct diseases, has been widely reported. In addition, daily intake of calcium and sodium, as well as parathyroid hormone levels (PTH), is known to be associated with osteoporosis and hypertension. This study aimed to determine the association of low calcium intake, high sodium intake, and PTH levels with osteoporosis and hypertension in postmenopausal Korean women. Data for postmenopausal Korean women aged 50 years or older were obtained from the Korea National Health and Nutrition Examination Survey 2008–2011. Osteoporosis was diagnosed using dual energy X-ray absorptiometry, while hypertension was diagnosed using blood pressure data. The odds ratios for osteoporosis and hypertension were calculated using logistic regression analysis for quartiles of the daily calcium intake, daily sodium intake, and PTH levels. Women with hypertension had a high coexistence of osteoporosis (43.6 vs. 36.5 %; $P = 0.022$), and vice versa (21.1 vs. 16.6 %; $P = 0.022$). PTH was significantly associated with osteoporosis and hypertension, and a high intake of calcium was strongly correlated with a low incidence of osteoporosis. This is the first study to report the characteristics of postmenopausal Korean women who have high dietary sodium intake and low dietary calcium intake, in association with the incidence of osteoporosis and hypertension. Osteoporosis and hypertension were strongly associated with each other, and PTH appears to be a key mediator of both diseases, suggesting a possible pathogenic link.

Keywords Osteoporosis · Hypertension · General population studies · Sodium · Calcium

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Introduction

Osteoporosis and hypertension are highly prevalent among aging populations, and are major public health challenges that are significantly associated with levels of morbidity and mortality (e.g., fracture and cardiovascular disease) [1, 2]. Interestingly, clinicians have observed that patients with osteoporosis frequently suffer from cardiovascular diseases [3]. Given their similar pathogeneses, which are related to genetic, environmental, behavioral, and epidemiological factors, there is a high probability that these two diseases coexist [4].

Osteoporosis is a metabolic bone disease that is associated with low bone mass and micro-architectural deterioration of the bone tissue, resulting in increased bone

fragility and the risk of fracture [5]. The incidence of osteoporosis increases with age and is highly associated with menopause among women, due to the related decrease in ovarian estrogen levels [6]. The incidence of osteoporosis has increased dramatically and now affects approximately 25 % of women who are ≥60 years old [7]. In addition, osteoporosis is associated with an approximately 44 % increased risk of fracture among women who are ≥60 years old [8]. Hypertension also presents an important public health challenge, with a worldwide prevalence in adults ranging from 20 to 40 % [2]. Hypertension is associated with 1–4 % of all deaths and is known to cause ischemic heart disease, other cardiovascular diseases, and renal failure [7].

Previous epidemiological and biological studies regarding the pathogenesis of osteoporosis and hypertension support the theory that both diseases share the same etiologies and genetic factors [7]. In addition, several studies have reported common cellular regulating mechanisms in the vascular and bone tissues [9], and Browner et al. have reported the relationship between stroke and increased bone loss or low bone mineral density (BMD) [10, 11]. Furthermore, several other studies have reported that increased bone loss is associated with hypertension, myocardial infarction, and cardiovascular diseases [4].

In addition to the common risk factors for osteoporosis, such as smoking and low levels of physical activity, low dietary intake of calcium may also be a risk factor for osteoporosis [4]. Unfortunately, the mean dietary calcium intake is generally lower in Korea (300–500 mg/day) than that in Western populations (1100–1300 mg/day) [12, 13]. Therefore, it is possible that the relationship between the amount of nutrients that are consumed and their effects on health vary according to the dietary habits of geographic populations. However, few studies have been conducted in Asian populations, which have a lower dietary calcium intake than Western populations [14]. In contrast, the mean sodium intake in Asian populations is known to be higher than that in Western populations [15, 16]. In addition, the mean sodium intake in Korea is twofold to threefold higher than that recommended by the World Health Organization (WHO) (<2000 mg/day) [16, 17]. Unfortunately, excess sodium may induce increased bone remodeling and bone loss by elevating the urinary excretion of calcium [18]. Vitamin D also mediates the interaction between parathyroid hormone (PTH) and calcium levels, and PTH is known to be an important factor in maintaining bone health [14]. Moreover, elevated levels of PTH are associated with high levels of cardiovascular-related morbidity and mortality [19].

Although possible correlations between osteoporosis and hypertension have been widely reported in the literature, some researchers have recently reinvestigated the association of osteoporosis and hypertension in Western populations [4, 7]. However, there are no studies that evaluated these associations in Asian populations. In this study, we verified the association between osteoporosis and hypertension in postmenopausal Korean women (≥50 years old) and investigated whether low calcium intake and high sodium intake might be associated with both diseases in this population. In addition, we identified other independent risk factors (vitamin D and PTH) that might be associated with osteoporosis and hypertension, respectively. Furthermore, we investigated and evaluated the association of the common sources of dietary calcium for postmenopausal Korean women with osteoporosis and hypertension.

Methods

Study Population

This study was conducted using data from the Korea National Health and Nutrition Examination Survey (KNHANES). KNHANES is a nationwide, representative survey of the health and nutritional status of the Korean population. KNHANES has been conducted periodically since 1998, and annually since 2008. The Health and Nutrition Survey division of the Korea Center for Disease Control and Prevention (KCDC) conducts this survey, which uses a stratified, multistage probability sampling design to select household units and include non-institutionalized Korean civilians. A detailed description of the survey has been described elsewhere [20]. KNHANES has been reviewed and approved by the ethics committee of the KCDC (2008-04EXP-01-C, 2009-01CON-03-2C, 2010-02CON-21-C, and 2011-02CON-06-C).

Our analysis evaluated data from three of the four survey components (the Health Interview Survey, the Nutrition Survey, and the Health Examination Survey), which were composed of health interviews, physical examinations, and medical examinations. This study examined data of non-overlapping individuals who participated in the 2008, 2009, 2010, and 2011 KNAHNES (Fig. 1). Among these subjects, postmenopausal women (≥50 years old) were selected for analysis. Subjects without BMD or other missing data were excluded from this study, as well as subjects who had consumed alcohol before the day of the survey. We also excluded subject who were receiving medication that is known to affect calcium metabolism, such as antiresorptive agents (raloxifene, bisphosphonate, or hormone-replacement therapy), and certain drugs for hypertension (diuretics and β-blockers). However, subjects who were taking other anti-hypertensive medications including ACE inhibitors and AT2 blockers were included in this study. Subjects with cancer or abnormal serum

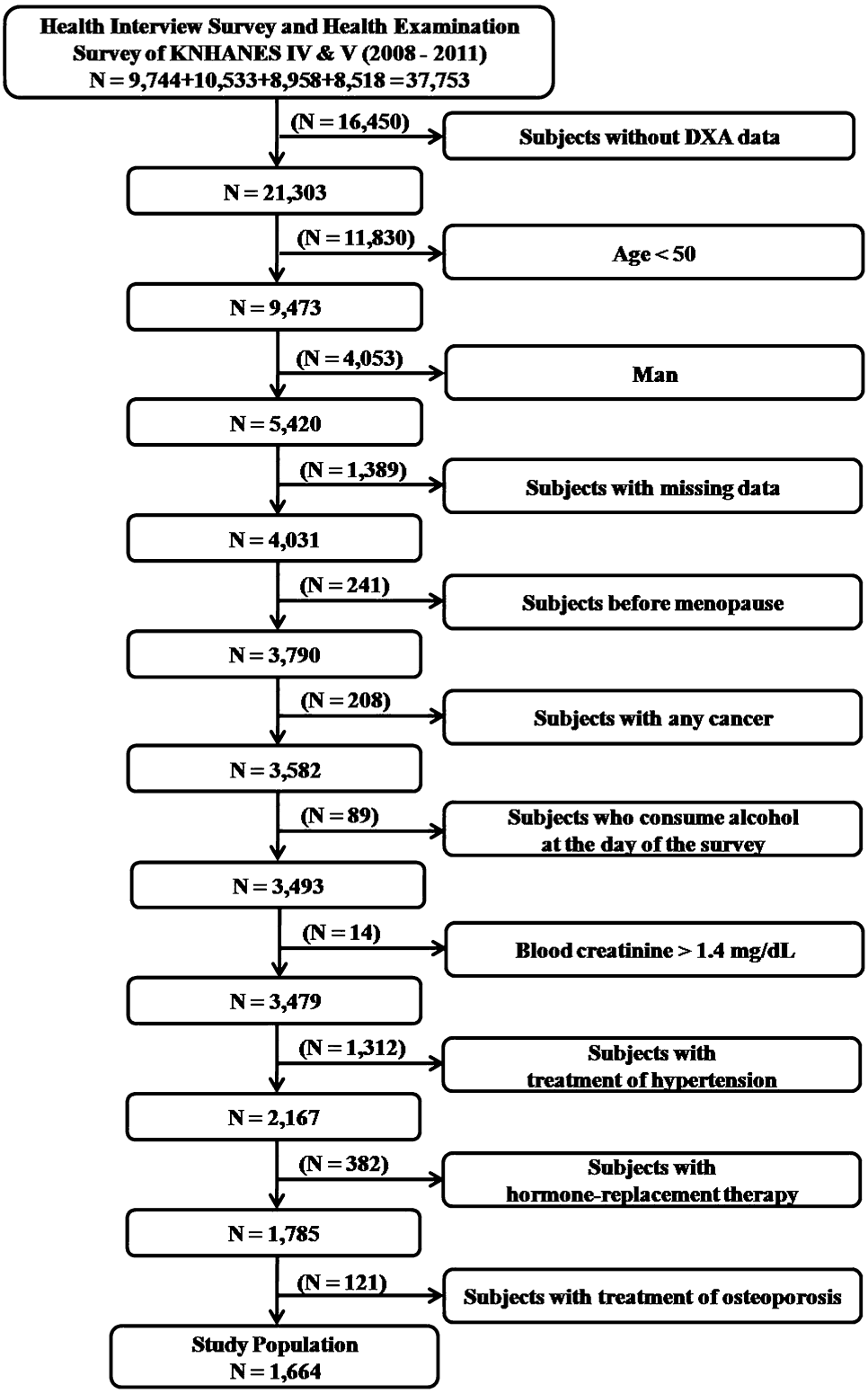

Fig. 1 Flow chart of subject exclusion for the KNHANES datasets

creatinine levels (>1.4 mg/dL) were also excluded, as renal insufficiency is known to affect calcium and bone metabolism [14]. Finally, 1664 individuals were included in this study.

Osteoporosis and Hypertension Assessment

Osteoporosis was defined as a BMD value >2.5 standard deviations (SD) below the T-score, as evaluated using the

WHO criteria [21]. BMD was measured using dual X-ray absorptiometry (DXA) (QDR 4500A; Hologic Inc., Bedford, MA, USA) at the lumbar spine (L1–L4) and femur. The precision of the DXA instrument has been described in previous reports. Results of body composition measurements can vary according to the technology employed and calibration of the instrument used. The DXA instruments used in the NHANES surveys were calibrated according to the methods proposed by Schoeller et al. [22]. The reference values of the NHANES were also obtained using this calibration method [23]. For appropriate comparison between the present and previous data, the NHANES calibrations were applied. DXA calibrations were maintained through an internal referencing system, which periodically measured bone and soft tissue equivalent reference standards during the examination of the patients. The stability of DXA measurements was determined by a daily calibration with phantom supplied from the manufacturer. The within-day coefficients of variation (%) for duplicated measurements in 30 adults ranged from 0.73 to 2.14 among five examiners [24]. DXA calibrations were maintained using an internal referencing system [25]. Hypertension was defined as a diastolic blood pressure (DBP) $\geq$90 mmHg or a systolic blood pressure (SBP) $\geq$140 mmHg. Blood pressure was measured on the right arm using a mercury sphygmomanometer while subjects were in the seated position, after a 5-min rest period. Blood pressure was measured on three occasions, and the average blood pressure was used for our analysis [26].

Biochemical Parameters

Blood samples were collected from each participant after an 8-h fast and were transported to the Central Testing Institute in Seoul, Korea. In this study, we evaluated concentrations of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides, which were assessed using enzymatic assays and an automated analyzer (Hitachi Automatic Analyzer 7600; Hitachi, Tokyo, Japan). The Friedewald equation [27] was used to calculate the concentration of low-density lipoprotein cholesterol (LDL-C). The concentration of 25-hydroxyvitamin D [25(OH)D] was measured using a radioimmunoassay kit (DiaSorin Inc., Stillwater, MN, USA). Serum alkaline phosphatase concentration (ALP) was measured using an auto-analyzer (Hitachi automated analyzer 7600; Hitachi, Tokyo, Japan). Urine sodium was measured using the automated Urisys 2400 system (Roche Diagnostics, Germany). Serum levels of PTH were measured using a chemiluminescence assay (DiaSorin Inc., Stillwater, MN, USA).

Dietary Assessment

Data regarding the subjects' food consumed were collected using a 24-h dietary recall questionnaire that was administered by a trained dietitian. The daily intake of calcium and sodium was calculated using the content of each food source according to the food composition Table (7th revision), which was developed by the National Rural Resources Development Institute in Korea [28]. To compare the frequency with which calcium sources were consumed by the study subjects, a frequency survey was used. This survey used a 10-point scale grade, with responses ranging from 0 (rarely eat) to 9 (eat 3 times per day). In this study, 11 of the most common sources of calcium in Korea [29] were evaluated: bean curd, bean, bean milk, Korean cabbage, radish leaves, bean sprouts, spinach, seaweed, milk, yoghurt, and anchovies.

Data Analyses

Data were reported as mean (SD) for continuous variables and as numbers and percentages for categorical variables. For the univariate analysis, continuous and categorical variables were compared using the t test and the χ^2 test, respectively, among participants with and without osteoporosis, or with and without hypertension. For the multivariate analysis, we used two multivariate models of logistic regression that included all risk factors that were significantly associated with osteoporosis and hypertension in the univariate analysis.

The multiple logistic regression analyses evaluated the relationship between the intake of calcium and sodium and the presence of osteoporosis and hypertension. Multiple models were used to adjust for the presence of potential confounders, such as age, waist circumference (WC), body mass index (BMI), total cholesterol, PTH, and ALP levels, all of which were significant in the multivariate analysis. Moreover, the relative risks for each disease, in association with serum levels of PTH, were estimated using multiple logistic regression analyses, which included age, WC, BMI, total cholesterol, ALP levels, and calcium intake as potential confounders. Crude and adjusted odds ratios (OR) and 95 % confidence intervals (CI) were estimated for the quartiles of calcium and sodium intake, as well as for PTH levels. The highest quartile was set as the reference level for calcium intake, while the lowest quartile was set as the reference level for sodium intake and PTH levels.

The χ^2 test for trend in proportions was used to test for trend in the incidence of osteoporosis and hypertension in the quartiles of calcium intake, sodium intake, and PTH levels. We used Pearson's correlation coefficient (r) to evaluate the association between continuous variables. All statistical tests were two sided and performed using SPSS

20.0 (IBM Corp, Armonk, NY) and the "R" software version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria). *P*-values <0.05 were considered statistically significant.

Results

Baseline Characteristics

Table 1 lists the demographic and clinical characteristics of the study population. The mean age of the 1664 postmenopausal women included in this study was 62.4 (8.4) years. The subjects had a mean daily dietary calcium intake of 418.6 (308.2) mg/day, which is considerably lower than the intake in Western populations (1100–1300 mg/day) [12, 13]. In contrast, female subjects had a mean daily sodium intake of 3845.1 (2720.8) mg/day, which is higher than the 2000 mg/day recommended by WHO [17]. Among the 1664 subjects, 629 (37.8 %) and 305 (18.3 %) had undiagnosed osteoporosis and hypertension, respectively.

Table 1 Demographic and clinical characteristics of the study population

Characteristics	Postmenopausal women ($n = 1664$)
Age (years)	62.4 (8.4)
Height (cm)	153.3 (5.8)
Weight (kg)	55.6 (8.2)
WC (cm)	80.8 (9.0)
BMI (kg/m^2)	23.6 (3.0)
SBP (mmHg)	123.3 (17.4)
DBP (mmHg)	75.6 (9.8)
Pulse Pressure (mmHg)	47.7 (13.1)
TC (mg/dL)	205.4 (35.9)
HDL-C (mg/dL)	48.1 (10.5)
LDL-C (mg/dL)	126.1 (32.2)
TG (mg/dL)	134.0 (81.7)
PTH (pg/mL)	64.5 (23.5)
ALP (IU/L)	258.7 (75.9)
Calcium (mg/day)	418.6 (308.2)
25(OH)D (nmol/L)	47.1 (17.1)
Sodium (mg/day)	3845.1 (2720.8)
Urine sodium (mmol/L)	135.6 (49.7)
Total hip (*T*-score)	−0.67 (1.03)
Lumbar (*T*-score)	−1.90 (1.18)
Femoral neck (*T*-score)	−1.67 (1.01)
Fracture, *n* (%)	95 (5.7)
Osteoporosis, *n* (%)	629 (37.8)
Hypertension, *n* (%)	305 (18.3)

Data are shown as mean (SD) or number of subjects (%)

WC waist circumference, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *PTH* parathyroid hormone, *ALP* alkaline phosphatase, *25(OH)D* 25-hydroxyvitamin D

A Comparison of Women With and Without Osteoporosis and Hypertension

Women with osteoporosis were significantly older and had a significantly lower WC and BMI compared to those without osteoporosis (Table 2). However, women without osteoporosis had significantly lower levels of PTH and ALP and higher daily calcium intake in both the univariate and multivariate analyses. Daily sodium intake was higher in women without osteoporosis, although sodium excretion in the urine was significantly higher in women with osteoporosis. The *T*-scores for the total hip, lumbar, and femoral neck of women with osteoporosis were significantly lower compared to those in women without osteoporosis. Among postmenopausal women, osteoporosis was significantly associated with hypertension in the univariate analysis, although the association was not significant in the multivariate analysis.

Women with hypertension had significantly higher age, WC, BMI, and triglyceride levels in the univariate analysis. In addition, women with hypertension had significantly lower *T*-scores for the total hip and femoral neck, and hypertension was significantly associated with osteoporosis. Increased age, total cholesterol, and levels of PTH and ALP were significantly associated with hypertension in both the univariate and multivariate analyses.

The Prevalence of Osteoporosis and Hypertension by Quartiles of Daily Calcium Intake, Sodium Intake, and Parathyroid Hormone Levels

The proportion of subjects with osteoporosis decreased with increasing daily calcium intake (*P* for trend <0.001) (Table 3), and the lowest quartile of calcium intake was significantly associated with osteoporosis [adjusted OR 1.77 (1.26–2.49)]. The proportion of women with hypertension in the lowest quartile (20.4 %) for calcium intake was similar to that in the highest quartile (20.2 %) of calcium intake. A decreasing trend (*P* for trend <0.001) was observed in the incidence of osteoporosis with increasing daily sodium intake, with a higher incidence of osteoporosis in the lowest quartile (45.2 %) compared to that in the highest quartile (33.4 %). However, sodium intake was not significantly associated with osteoporosis. Similarly, hypertension was not significantly associated with the sodium intake quartiles, based on the P for trend and ORs.

An increasing trend (*P* for trend <0.001) in the incidence of osteoporosis was observed with increasing levels of PTH, with the exception of the second and third

Table 2 Comparison of women with and without osteoporosis or hypertension

	Postmenopausal women ($n = 1664$)							
	Without osteoporosis ($n = 1035$)	With osteoporosis ($n = 629$)	P^a	P^b	Without hypertension ($n = 1359$)	With hypertension ($n = 305$)	P^a	P^b
Age (years)	59.3 (6.8)	67.5 (8.3)	<0.001	**<0.001**	61.9 (8.3)	64.7 (8.7)	<0.001	**<0.001**
Height (cm)	154.8 (5.5)	150.9 (5.5)	<0.001	–	153.6 (5.7)	151.9 (5.9)	<0.001	–
Weight (kg)	57.9 (7.5)	51.7 (7.8)	<0.001	–	55.6 (8.1)	55.6 (8.4)	0.961	–
WC (cm)	82.0 (8.6)	78.8 (9.2)	<0.001	**0.046**	80.5 (8.9)	82.0 (9.2)	0.007	0.749
BMI (kg/m^2)	24.2 (2.9)	22.7 (3.0)	<0.001	**0.001**	23.5 (3.0)	24.0 (3.0)	0.006	0.091
SBP (mmHg)	122.2 (17.2)	125.2 (17.6)	0.001	0.965	117.5 (12.4)	149.4 (11.4)	<0.001	–
DBP (mmHg)	75.9 (9.5)	75.1 (10.3)	0.112	–	73.3 (8.1)	86.0 (10.1)	<0.001	–
Pulse Pressure (mmHg)	46.3 (12.3)	50.1 (14.0)	<0.001	0.366	44.2 (9.8)	63.4 (14.3)	<0.001	–
TC (mg/dL)	207.2 (36.3)	202.4 (35.0)	0.009	0.855	204.2 (35.0)	210.8 (39.3)	0.007	**0.010**
HDL-C (mg/dL)	48.6 (10.6)	47.3 (10.3)	0.009	0.575	48.3 (10.6)	47.4 (10.2)	0.185	–
LDL-C (mg/dL)	127.1 (32.7)	124.5 (31.5)	0.109	–	125.3 (31.4)	129.6 (35.4)	0.052	–
TG (mg/dL)	135.1 (87.1)	132.2 (71.9)	0.460	–	130.9 (80.4)	147.6 (86.0)	0.001	0.054
PTH (pg/mL)	62.6 (22.3)	67.7 (25.1)	<0.001	**0.003**	63.7 (23.4)	68.3 (23.6)	0.002	**0.029**
ALP (IU/L)	251.9 (70.7)	270.0 (82.8)	<0.001	**<0.001**	256.7 (75.7)	267.7 (76.4)	0.023	**0.035**
Calcium (mg/day)	453.9 (317.8)	360.6 (282.5)	<0.001	**0.003**	418.0 (307.2)	421.4 (312.8)	0.862	–
25(OH)D (nmol/L)	47.1 (16.5)	46.9 (18.1)	0.836	–	47.2 (17.0)	46.5 (17.9)	0.530	–
Sodium (mg/day)	3982.2 (2713.3)	3619.3 (2720.3)	0.008	0.283	3818.7 (2731.4)	3962.3 (2674.5)	0.405	–
Urine sodium (mmol/L)	135.5 (51.7)	135.8 (46.3)	0.904	–	134.6 (49.9)	140.0 (48.5)	0.089	–
Total hip (*T*-score)	−0.17 (0.83)	−1.49 (0.77)	<0.001	–	–0.64 (1.02)	–0.80 (1.06)	0.015	0.625
Lumbar (*T*-score)	−1.23 (0.88)	−3.00 (0.72)	<0.001	–	–1.88 (1.18)	–19.7 (1.19)	0.230	–
Femoral neck (*T*-score)	−1.17 (0.82)	−2.50 (0.71)	<0.001	–	–1.64 (1.00)	–1.84 (1.07)	0.002	0.439
Fracture, *n* (%)	51 (4.9)	44 (7.0)	0.082	–	74 (5.4)	21 (6.9)	0.339	–
Osteoporosis, *n* (%)	–	–	–	–	496 (36.5)	133 (43.6)	0.022	0.947
Hypertension, *n* (%)	172 (16.6)	133 (21.1)	0.022	0.447	–	–	–	–

Data are shown as mean (SD) or number of subjects (%)

Boldface indicates significant difference in multivariate analysis

WC waist circumference, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglycerides, *PTH* parathyroid hormone, *ALP* alkaline phosphatase, *25(OH)D* 25-hydroxyvitamin D

[a] *P* value calculated using the *t* test (continuous data) or χ^2test (categorical data)

[b] *P* value calculated using logistic regression for multivariate analysis

quartiles. The highest level of PTH was significantly associated with osteoporosis [adjusted OR 1.66 (1.19–2.32)]. In addition, the incidence of hypertension increased in the higher quartiles of PTH levels (*P* for trend <0.001), and high levels of PTH were significantly associated with hypertension [adjusted OR 1.52 (1.06–2.18)].

A comparison of Calcium Sources for Women With and Without Osteoporosis and Hypertension

Women with osteoporosis had significantly lower calcium intake compared to women without osteoporosis (Table 4). However, the mean dietary calcium intake of women without osteoporosis (453.9 mg/day) was considerably lower compared to that in Western populations [12, 13]. Every source of calcium, except bean milk, was consumed significantly more frequently by women without osteoporosis compared to those with osteoporosis. However, there was no significant difference in the dietary calcium intake between subjects with and without hypertension. However, milk, yoghurt, and anchovies (which are significant sources of calcium) were consumed significantly more frequently by women without hypertension than those with hypertension.

Table 3 The prevalence of osteoporosis and hypertension by quartiles of dietary calcium, dietary sodium, and parathyroid hormone levels

	1st quartile	2nd quartile	3rd quartile	4th quartile	*P* for trend[f]
Daily dietary calcium (mg/day)					
Postmenopausal women	< 209	209–342	342–532	> 532	
Osteoporosis, *n* (%)	213 (51.2)	160 (38.5)	145 (34.9)	111 (26.7)	<0.001
Crude OR (95 % CI)	2.88 (2.16–3.85)	1.72 (1.28–2.30)	1.47 (1.09–1.98)	1 (reference)	
Adjusted OR[e] (95 % CI)[a]	1.77 (1.26–2.49)	1.54 (1.10–2.16)	1.51 (1.08–2.12)	1 (reference)	
Hypertension, *n* (%)	85 (20.4)	74 (17.8)	62 (14.9)	84 (20.2)	0.590
Crude OR (95 % CI)	1.02 (0.72–1.42)	0.86 (0.60–1.21)	0.69 (0.48–0.99)	1 (reference)	
Adjusted OR[e] (95 % CI)[b]	0.81 (0.57–1.15)	0.82 (0.57–1.16)	0.68 (0.47–0.98)	1 (reference)	
Daily dietary sodium intake (mg/day)					
Postmenopausal women	<2123	2123–3185	3185–4824	>4824	
Osteoporosis, *n* (%)	188 (45.2)	155 (37.3)	147 (35.3)	139 (33.4)	<0.001
Crude OR (95 % CI)	1 (Reference)	0.72 (0.55–0.95)	0.66 (0.50–0.88)	0.61 (0.46–0.81)	
Adjusted OR[e] (95 % CI)[a]	1 (Reference)	1.01 (0.73–1.41)	1.04 (0.75–1.45)	1.01 (0.72–1.41)	
Hypertension, *n* (%)	77 (18.5)	71 (17.1)	71 (17.1)	86 (20.7)	0.333
Crude OR (95 % CI)	1 (Reference)	0.91 (0.64–1.29)	0.91 (0.64–1.29)	1.15 (0.81–1.62)	
Adjusted OR[e] (95 % CI)[b]	1 (Reference)	1.04 (0.72–1.49)	1.08 (0.75–1.56)	1.37 (0.96–1.95)	
Parathyroid hormone (pg/mL)					
Postmenopausal women	<48.9	48.9–61.1	61.1–75.2	>75.2	
Osteoporosis, *n* (%)	135 (32.5)	157 (37.6)	144 (34.8)	193 (46.4)	<0.001
Crude OR (95 % CI)	1 (reference)	1.25 (0.94–1.67)	1.11 (0.83–1.48)	1.80 (1.36–2.39)	
Adjusted OR[e] (95 % CI)[c]	1 (Reference)	1.36 (0.98–1.90)	1.15 (0.82–1.61)	1.66 (1.19–2.32)	
Hypertension, n (%)	62 (14.9)	70 (16.7)	79 (19.1)	94 (22.6)	<0.001
Crude OR (95 % CI)	1 (Reference)	1.15 (0.79–1.67)	1.35 (0.94–1.94)	1.67 (1.17–2.38)	
Adjusted OR[e] (95 % CI)[d]	1 (Reference)	1.16 (0.80–1.69)	1.36 (0.94–1.97)	1.52 (1.06–2.18)	

OR odds ratio, *CI* confidence interval, *WC* waist circumference, *BMI* body mass index, *PTH* parathyroid hormone, *ALP* alkaline phosphatase, and *TC* total cholesterol

[a] Adjusted for age, WC, BMI, PTH, and ALP

[b] Adjusted for age, TC, PTH, and ALP

[c] Adjusted for age, WC, BMI, ALP, and calcium intake

[d] Adjusted for age, TC, and ALP

[e] Adjusted OR calculated using multiple logistic regressions

[f] *P* value for trend calculated using the χ^2 test for trend in proportions

Discussion

Our results confirm the previous finding of an association between osteoporosis and hypertension. In addition, we observed that there was a significantly higher incidence of osteoporosis among postmenopausal patients with hypertension (≥50 years old), and that patients with hypertension had a significantly higher incidence of osteoporosis. Moreover, we detected a low dietary intake of calcium and a high dietary intake of sodium among postmenopausal Korean women, using data from a large and representative survey. Kim et al. [14] reported that the mean dietary calcium intake of the Korean population was 490 mg/day and lower than 800 mg/day for most age groups in both men and women older than 20 years. The mean daily dietary calcium intake in our study was 418.6 (308.2) mg/day which was similar to the report of Kim et al. and lower than other ethnic groups. Moreover, the mean fell short of the level recommended in the Korea Dietary Reference Intakes [14]. We attempted to define the association between Korean dietary habits and osteoporosis or hypertension, although we ultimately identified the high levels of PTH as a common risk factor for osteoporosis and hypertension.

Browner et al. were the first to suggest the possible relationship between osteoporosis and hypertension, and they have also reported that a higher risk of stroke and related mortality is associated with low BMD [10, 11]. In our study, a significant association between osteoporosis and hypertension among postmenopausal women was

Table 4 A comparison of calcium sources in women with and without osteoporosis or hypertension

	Postmenopausal women ($n = 1664$)					
	Without osteoporosis ($n = 1035$)	With osteoporosis ($n = 629$)	P^a	Without hypertension ($n = 1359$)	With hypertension ($n = 305$)	P^a
Bean curd (frequency)	3.7 (1.6)	3.0 (1.7)	<0.001	3.4 (1.7)	3.4 (1.6)	0.797
Bean	5.8 (3.1)	5.5 (3.5)	0.031	5.7 (3.2)	5.6 (3.3)	0.111
Bean milk	1.1 (1.8)	1.0 (1.7)	0.335	1.1 (1.8)	1.0 (1.6)	0.063
Korean cabbage	8.1 (1.3)	7.9 (1.9)	0.041	8.0 (1.6)	8.1 (1.6)	0.638
Radish leaves	3.7 (1.9)	3.5 (2.1)	0.029	3.6 (2.0)	3.8 (2.0)	0.262
Bean sprouts	3.4 (1.4)	2.9 (1.6)	<0.001	3.2 (1.5)	3.3 (1.5)	0.384
Spinach	2.5 (1.5)	2.0 (1.6)	<0.001	2.3 (1.6)	2.2 (1.6)	0.235
Seaweed	3.1 (1.3)	2.8 (1.4)	<0.001	3.0 (1.3)	2.9 (1.4)	0.229
Milk	3.3 (2.6)	2.2 (2.6)	<0.001	3.0 (2.7)	2.5 (2.6)	0.004
Yoghurt	1.9 (2.3)	1.2 (1.9)	<0.001	1.7 (2.2)	1.4 (2.1)	0.028
Anchovy	4.1 (2.1)	3.2 (2.3)	<0.001	3.8 (2.2)	3.6 (2.3)	0.038

Data are shown as mean (SD)

Frequency (10-point scale grade): 0 = rarely eat, 1 = eat 6-11 times per year, 2 = eat 1 time per month, 3 = eat 2–3 times per month, 4 = eat 1 time per week, 5 = eat 2–3 times per week, 6 = eat 4-6 times per week, 7 = eat 1 time per day, 8 = eat 2 times per day, 9 = eat 3 times per day

[a] P value calculated using the t test

observed in the univariate analysis, although it was not observed in the multivariate analysis. However, PTH levels were significantly associated with both diseases in the univariate and multivariate analyses, suggesting that PTH is a novel mediator of osteoporosis and hypertension. PTH levels were significantly correlated with SBP and T-scores of the total hip, lumbar, and femoral neck, likely due to the fact that PTH plays an important role in bone resorption and renal calcium reabsorption. In addition, excess levels of PTH are known to cause hypercalcemia and bone loss, and high levels of PTH are a known risk factor for hypertension [19]. Similarly, patients with hyperparathyroidism have a higher risk of cardiovascular mortality and a broad spectrum-related disorders, such as coronary microvascular dysfunction, subclinical aortic valve calcification, increased aortic stiffness, and endothelial dysfunction [30]. Neves et al. reported the contribution of PTH in vascular calcification [31], which leads to increased stiffening; therefore, calcification decreased the compliance of these vessels, causing the important cushioning function of these arteries to be lost, which is known to result in increased pulse pressure [32]. This is consistent with our results that pulse pressure was high in subjects with high levels of PTH with significance. Furthermore, the presence of PTH receptors within the cardiovascular system suggests that the role of PTH in the pathophysiology of cardiovascular diseases extends beyond its role in mineral and bone metabolism [30]. Therefore, our results are consistent with previous studies that have reported that PTH is a principal regulator of bone and calcium homeostasis in the physiological and pathological conditions that are associated with cardiovascular disorders [30]. Moreover, although we do not clearly know the underlying mechanisms, secondary hyperparathyroidism with moderately elevated PTH caused by low vitamin D intake or low calcium intake was found to somehow hinder the elevation of blood pressure by increased sodium intake, resulting in lower blood pressure. However, excess elevation in PTH was found to increase vascular tone, leading to elevation of blood pressure. Therefore, we believe that PTH is a key mediator for osteoporosis and hypertension, although the pathogenesis is not yet known.

In this study, we only included postmenopausal women aged 50 years or older, as many studies have reported the biochemical, cellular, molecular biology effects of estrogen on bone remodeling and concluded that menopause leads to significant bone loss [33]. Moreover, female sex hormones are thought to contribute to the lower incidence of cardiovascular diseases in premenopausal women, although this hypothesis remains controversial [34]. In addition, we excluded patients who had been diagnosed with osteoporosis and hypertension to eliminate the possible effects of medication and changes to habitual behavior (e.g., diet). Therefore, as our study included only subjects with undiagnosed osteoporosis and hypertension, these subjects would likely exhibit fewer characteristics of the diseases, which might explain why a significant association was only detected in the univariate analysis.

The association between calcium intake and osteoporosis has been established by several studies, and most studies have concluded that high calcium intake prevents bone loss and fracture [35]. In our study, a high intake of

Table 5 Relative sodium and calcium intake analysis

	Without osteoporosis ($n = 1035$)	With osteoporosis ($n = 629$)	P^a
Sodium (mg/day)	3982.3 (2713.3)	3619.3 (2720.3)	0.008
Sodium (mg/day)/Weight (kg)	69.6 (47.0)	71.1 (56.0)	0.550
Calcium (mg/day)	418.0 (307.2)	421.4 (312.8)	0.862
Calcium (mg/day)/Weight (kg)	7.6 (5.7)	7.6 (5.6)	0.971

Data are shown as mean (SD)

[a] P value calculated using the t test

calcium was strongly associated with a low incidence of osteoporosis, especially in the lowest quartiles of calcium intake, although the mean daily dietary calcium intake was lower than that in Western populations. Interestingly, Varenna et al. [4] have reported that the risk of osteoporosis is only significantly increased among women in the lowest quartile of calcium intake, although we observed a significant difference in each quartile. In this regard, our results are not consistent with previous studies that have reported that the threshold effect of calcium, that is, the negative effect of low calcium can only be compensated for over a specific intake level [36]. However, it is possible that our subjects did not exhibit the threshold effect of calcium due to their low dietary intake of calcium. The low calcium intake in the Korean population might have caused our subjects to physiologically adapt to levels low calcium, thereby making them more sensitive to calcium intake and removing the threshold effect that is observed in populations who consume greater amounts of calcium [4].

As most previous studies have evaluated calcium intake derived from dairy sources, we evaluated calcium intake from various different food sources including dairy products, and observed that all sources of calcium except bean milk were significantly associated with a low incidence of osteoporosis in postmenopausal women. Interestingly, milk [4], yoghurt [4], and beans [37] are rich sources of calcium and were all significantly associated with a low incidence of osteoporosis. However, although bean curd and bean milk are both derived from beans, only bean curd was significantly associated with a low incidence of osteoporosis. Bean milk was not a significant source of calcium, which may be related to the low consumption of bean milk in both groups. The association between calcium intake and hypertension has also been investigated by many groups. Griffith et al. had suggested that inadequate calcium intake might be associated with hypertension [38], and large observational studies have reported that dairy products reduce blood pressure and the risk of hypertension [4]. However, our results were not consistent with these studies, as we did not observe a consistent trend in the incidence of hypertension (P for trend = 0.590) when it was analyzed according to the quartiles of daily calcium intake; a significant association with hypertension was only observed for the third and fourth quartiles. Interestingly, the North American Menopause Society has reported that a calcium intake of at least 1200 mg/day is associated with improved SBP [6], although the mean daily dietary calcium intake for our subjects was only 418.6 mg/day. Therefore, it is difficult to compare the effects of calcium in our subjects with those in previous studies, given their considerably higher dietary intake of calcium.

Another reason for the lack of association between low calcium intake and hypertension might be the ineffective measurement of calcium intake, as subjects who consume more food will also consume more calcium. In this study, subjects with hypertension had a higher average BMI compared to subjects without hypertension, which indicates that they consumed more food. Therefore, to accurately evaluate the association between the two factors, their normalized consumption of calcium should be used, rather than the total intake of calcium. As food consumption is proportional to the subject's body weight [39], we utilized a relative calcium intake by dividing total calcium intake by weight (Table 5). However, there was no difference in the relative consumption of calcium between the two groups, although the total daily amount calcium was slightly higher in subjects with hypertension. Moreover, the consumption of milk and yoghurt did not proportionally increase with the increasing food consumption. Unfortunately, many foods (e.g., cabbage, radish leaves, and bean sprouts) are preserved with salts and soy sauce, which can interfere with the intake of calcium. Soy is thought to contain isoflavones that are protective against osteoporosis. However, although soy itself may have a protective effect against osteoporosis, soy sauce has a high content of salts, with 7157 mg sodium in 100 g soy sauce [28], which is a high amount of salts compared with soy itself (Table 6). Other major foods such as bean and cabbage have high amounts of salts when preserved in salt or cooked with soy sauce compared with when they are boiled [28] (Table 6).

Interestingly, although women with osteoporosis had significantly lower sodium intake, they have increased

Table 6 Comparison of calcium and sodium content of major food groups [28]

Food and description (100 g)	Calcium (mg)	Sodium (mg)
Soy	245	2
Soy sauce	38	7157
Beans, boiled	75	2
Beans, cooked with soy sauce	97	907
Cabbage, boiled	41	7
Cabbage, preserved with salt	47	1146

sodium excretion in their urine, compared to women without osteoporosis. Moreover, we observed an increasing trend in the incidence of osteoporosis with decreasing sodium intake, although this result contradicts the findings of previous studies. This discrepancy might be related to our use of total sodium intake, rather than relative sodium intake, as subjects with osteoporosis had a slightly higher relative sodium intake, although this increase was not significant (Table 5). Therefore, using relative sodium intake, our results are consistent with a previous study that reported that increased sodium intake elevates calcium excretion in urine, thereby increasing bone remodeling and bone loss [18].

Although no available data exist for plasma sodium, the mean urine sodium level of 135.6 mmol/L was very high even in the presence of high sodium intake, suggesting the possibility of hyponatremia in subjects in this study. There is a high prevalence of chronic hyponatremia in the elderly, frequently owing to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [40]. Considering that subjects in this study were old, with a mean age of 62.4 (8.4) years, SIADH could have been a likely cause of the high urine sodium and low serum sodium. Moreover, there are studies showing that hyponatremia is associated with significantly increased odds of osteoporosis [40]. Therefore, hyponatremia, which is frequently caused by SIADH, might be a cause of the development of osteoporosis.

Daily sodium intake is also known to affect blood pressure, although our analysis revealed no significant association with hypertension (P for trend = 0.333). However, the incidence of hypertension in the first, second, and third quartiles of sodium intake was lower than that in the fourth quartile. This discrepancy may be related to the fact that the daily sodium intake in both groups was already considerably higher than that recommended by WHO.

The incidence of osteoporosis and hypertension increased with the subject age, and both diseases are known to have degenerative characteristics. BMI and WC, which are indices of obesity, were significantly higher in subjects with hypertension, which is consistent with previous studies [41]. However, low BMI has also been reported as a risk factor for osteoporosis and fractures [42], and our subjects with osteoporosis had significantly lower BMI compared to the subjects without osteoporosis. WC is associated with the amount of abdominal visceral adipose tissue, and may also influence bone mass, although the positive association between WC and bone mass remains controversial. Several studies have reported a significant positive association between bone mass and abdominal fat [43], although Jankowska et al. [44] and Huang et al. [45] have reported an inverse relationship between visceral fat and bone mass. Our results indicate that the association between WC and osteoporosis is negative. These conflicting results suggest that the complex effect of visceral fat on bone mass can be affected by sex, sample size, ethnicity, study design, analysis methods, and population structure [43]. Therefore, the exact mechanism for this relationship remains unknown, although it is likely multi-factorial and related to lifestyle, nutrition, and genetic determinants [46].

Vitamin D is an important factor in calcium metabolism and mediates the levels of calcium and PTH [13]. Deficiency in vitamin D has been historically defined and recently recommended by the Institute of Medicine (IOM) as a 25(OH)D of less than 50 nmol/L, while Vitamin D insufficiency has been defined as a 25(OH)D of 52.5–72.5 nmol/L [47]. In accordance with these definitions, postmenopausal Korean women have insufficient 25(OH)D levels with a mean vitamin D concentration of 47.1 (17.1) nmol/L, which failed to compensate for their low dietary calcium intake. Although the mean concentration in this population was 47.1 (17.1) nmol/L and can be considered as surprisingly good, PTH was elevated in this study, which was likely due to low vitamin D intake. This shows that the mean vitamin D concentration of 47.1 (17.1) nmol/L is low in the Korean population, resulting in elevation of PTH. This finding was consistent with the previous studies of the Korean population [12, 14]. Deficiency in vitamin D causes secondary hyperparathyroidism, bone loss, mineralization defects, and hip and other fractures. Moreover, vitamin D deficiency causes high bone turnover indicated by elevated ALP [48]. Our results were consistent with previous findings showing high ALP levels in subjects with high PTH levels.

Our study has several strengths. First, we used data from KNHANES (2008–2011), which provides a large, homogeneous, and representative dataset from the Korean population using a standard nationwide survey. Second, we identified PTH as a novel regulator of both osteoporosis and hypertension. Third, we analyzed the relative calcium and sodium intake of postmenopausal Korean women. There are also several limitations for this study. First, as we used a cross-sectional design, the causality of the relationship of PTH, osteoporosis, and hypertension cannot be evaluated. Second, KNHANES data do not evaluate non-

dietary calcium intake (e.g., supplements), although Korean adults do not typically consume a large amount of calcium supplements [49], and therefore our data likely reflect the total calcium intake of postmenopausal Korean women. Third, it is possible that the 24-h dietary recall questionnaire used by KNHANES might be considered a limitation, although Kim et al. have reported that it is valid and reliable [50]. For more accurate measure in the KNHANES, trained dietary nutritionists visit the subjects' homes and conduct direct face-to-face interviews, using a standard set of measuring guides to help the respondents report the volumes and dimensions of the food items consumed. The amounts of seasonings used during cooking and meals were measured using standardized measuring spoons provided by the KNHANES. The participants were requested to use these spoons, and the nutritionists based their measurements on them. There have been several validation studies measuring 24-h urinary sodium excretion to investigate the accuracy of dietary sodium intake from 24-h recall [51, 52]. However, there can be some inconsistencies in evaluations of dietary sodium, which may be explained by the fact that there was only one measurement of 24-h urinary sodium excretion in the KNHANES. As within-person variability in sodium excretion may be as high as 30 %, [53] a validation study using multiple 24-h measurements could be a more accurate method. Fourth, since we included only subjects with undiagnosed osteoporosis and hypertension, a significant association was only detected in the univariate analysis. Fifth, although we attempted to exclude symptomatic primary hyperparathyroidism by patient history, we could not completely exclude primary hyperparathyroidism by calcium levels, as there were no data for serum calcium, plasma calcium, and phosphate in the KNHANES, leaving the possibility that certain cases of asymptomatic primary hyperparathyroidism were included in this study. However, since primary hyperparathyroidism is not prevalent disease in Korea [54, 55], while it might be a confounding factor, it is not likely to have affected the results substantially.

In conclusion, our results indicate that osteoporosis and hypertension occur more frequently among postmenopausal Korean women who have high sodium and low calcium intake. Osteoporosis and hypertension were significantly associated, and PTH was related to both diseases. In addition, the low calcium intake might have induced the elevated levels of 25(OH)D that we observed in our study population. Although the relationship between osteoporosis and vascular calcification is known as the calcification paradox, the key players in this process remain unclear [27]. Our results also indicate that PTH is a potential mediator of the bone-vascular interaction, although future studies must evaluate the function of PTH in both diseases.

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