Lower Bone Mass and Higher Bone Resorption in Pheochromocytoma: Importance of Sympathetic Activity on Human Bone

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Context: Despite the apparent biological importance of sympathetic activity on bone metabolism in rodents, its role in humans remains questionable.

Objective: To clarify the link between the sympathetic nervous system and the skeleton in humans.

Design, Setting, and Patients: Among 620 consecutive subjects with newly diagnosed adrenal incidentaloma, 31 patients with histologically confirmed pheochromocytoma (a catecholamine-secreting neuroendocrine tumor) and 280 patients with nonfunctional adrenal incidentaloma were defined as cases and controls, respectively.

Results: After adjustment for confounders, subjects with pheochromocytoma had 7.2% lower bone mass at the lumbar spine and 33.5% higher serum C-terminal telopeptide of type 1 collagen (CTX) than those without pheochromocytoma ($P = 0.016$ and 0.001, respectively), whereas there were no statistical differences between groups in bone mineral density (BMD) at the femur neck and total hip and in serum bone-specific alkaline phosphatase (BSALP) level. The odds ratio (OR) for lower BMD at the lumbar spine in the presence of pheochromocytoma was 3.31 (95% confidence interval, 1.23 to 8.56). However, the ORs for lower BMD at the femur neck and total hip did not differ according to the presence of pheochromocytoma. Serum CTX level decreased by 35.2% after adrenalectomy in patients with pheochromocytoma, whereas serum BSALP level did not change significantly.

Conclusions: This study provides clinical evidence showing that sympathetic overstimulation in pheochromocytoma can contribute to adverse effects on human bone through the increase of bone loss (especially in trabecular bone), as well as bone resorption. (***J Clin Endocrinol Metab*** **102: 2711–2718, 2017)**

The bone remodeling process, a result of the concerted actions of osteoclasts and osteoblasts, is essential for maintaining bone mass and considered to be regulated by many factors, including nutritional status, humoral factors, and biomechanical stress (1–5). Many lines of evidence in animal studies now indicate that the sympathetic nervous system (SNS) plays a pivotal role in bone metabolism as well, especially through targeting

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Abbreviations: AI, adrenal incidentaloma; ANCOVA, analysis of covariance; BMD, bone mineral density; BMI, body mass index; BSALP, bone-specific alkaline phosphatase; BTM, bone turnover marker; CI, confidence interval; CTX, C-terminal telopeptide of type 1 collagen; CV, coefficient of variation; OR, odds ratio; SD, standard deviation; SNS, sympathetic nervous system; β2AR, β2-adrenergic receptor.

β2-adrenergic receptors (β2ARs). Knockout of the β2AR in osteoblasts has been shown to increase bone formation and decrease bone resorption, resulting in a high bone mass phenotype (6). Likewise, pharmacological interventions with β-blockers and β-agonists in rodents have been shown to increase and decrease bone mass, respectively (7, 8). In addition, the lack of dopamine β-hydroxylase, an enzyme required for the synthesis of catecholamines, was shown to result in high bone mass in mice (9).

Despite its apparent biological importance in rodents, the role of sympathetic activity in bone metabolism in humans remains questionable. Several epidemiological studies on the association between β-blocker use and bone health have yielded conflicting results showing positive, negative, or no effects (10–14), whereas a recent meta-analysis indicated that β-blockers were associated with a reduced risk of fracture with a relatively small effect size (15). For β-agonists, three cross-sectional studies failed to demonstrate an effect on fracture risk in chronic obstructive pulmonary disease (16–18), and a prospective study reported that selective β2 adrenergic agonists did not affect human bone turnover (14). These inconsistent results may be attributable to the highly heterogeneous characteristics of the included populations in terms of the selectivity, dose, duration, and delivery route of β-adrenergic receptor modulators. Therefore, to overcome these methodological limitations and to adequately assess the role of the SNS on human bone metabolism, a human disease model implicating the SNS is necessary.

Pheochromocytoma is a catecholamine-secreting neuroendocrine tumor that arises from chromaffin cells of the adrenal medulla (19). Because catecholamines are the main neurotransmitters of the SNS, Veldhuis-Vlug *et al.* (20) hypothesized and demonstrated that increased sympathetic stimulation in patients with pheochromocytoma could contribute to increased bone resorption. Although the authors did not present the effects on bone mass, this case-control study has an important implication in that it provided evidence supporting the concept of regulation of bone remodeling by the SNS in humans. By the extension of this background, to further clarify the role of sympathetic activity in human bone health, we investigated the association of catecholamine excess with osteoporosis-related phenotypes, especially focusing on bone mineral density (BMD), in a Korean cohort consisting of patients with pheochromocytoma and controls.

Materials and Methods

Study participants and protocol

The study population was based on the Asan Medical Center cohort, which is a subset of the "Co-work of Adrenal Research" study (clinicaltrial.gov no. NCT01382420), a randomized, parallel-group, multicenter, open-label trial conducted at three medical centers in Korea. From July 2011 to June 2014, we recruited 620 consecutive patients with newly diagnosed adrenal incidentaloma (AI). The diagnosis of AI was based on the detection of an adrenal mass (size ≥1 cm) on computed tomography performed for an unrelated disease. Among these, 536 subjects had BMD information and thus were eligible for inclusion in this study. After excluding 225 subjects who were suspected to have hypercortisolism, primary aldosteronism, congenital adrenal hyperplasia, adrenal carcinoma, adrenal metastasis, or adrenal tuberculosis, we identified 31 patients with histologically confirmed pheochromocytoma after adrenalectomy, and these were defined as the case group. The remaining 280 subjects with nonfunctional AI were defined as the control group.

The following patient information was obtained by using an interviewer-assisted questionnaire: smoking habits (current smoker), alcohol intake (≥3 units/d), regular outdoor exercise (≥30 min/d), history of medication use, previous medical or surgical procedures, and reproductive status including menstruation.

This study was approved by the institutional review board of Asan Medical Center. Written informed consent was provided by all enrolled participants.

BMD measurement

Areal BMD (g/cm^2) was measured at the lumbar spine (L1–L4) and proximal femur by using dual-energy x-ray absorptiometry with Lunar equipment (running software version 9.30.044; Prodigy, Madison, WI). The precision values of the equipment, in terms of the coefficients of variations (CVs), were 0.67% and 1.25% for the lumbar spine and femur neck, respectively, which were determined with measurements in 17 volunteers who were not enrolled in this study. Each volunteer underwent five scans on the same day and were required to get on and off the table between examinations.

To categorize the subjects, we adopted the recommendations by the International Society for Clinical Densitometry (21). For premenopausal women and men aged <50 years, BMD "below the expected range for age" was defined by a z score of ≤−2.0 standard deviation (SD) and BMD "within the expected range for age" was defined by a z score of >−2.0 SD. For postmenopausal women and men aged ≥50 years, osteoporosis was defined by a T score of ≤−2.5 SD, osteopenia by $-1.0 > T > -2.5$ SD, and normal as ≥−1 SD. From this background, in the analyses of this study, "lower BMD" was defined by z score ≤–2.0 for premenopausal women and men aged <50 years, or T score ≤–1.0 for postmenopausal women and men aged ≥50 years.

Hormonal and biochemical measurements

Urine fractionated metanephrine levels were measured with a high-performance liquid chromatography assay by using a commercially available kit (Chromsystems, Munich, Germany) on an Agilent 1100 high-performance liquid chromatography system (Agilent Technologies, Santa Clara, CA). The lower limit of detection of the kit was 5 to 11 μg/L, and the intra- and interassay CVs were less than 3% and 4.4%, respectively.

To measure biochemical bone turnover markers (BTMs), fasting blood samples were obtained in the morning. Serum

C-terminal telopeptide of type 1 collagen (CTX) levels were measured by means of an electrochemical luminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), with intra- and interassay CVs of 1.0% to 4.6% and 1.6% to 4.7%, respectively. The reference mean ± SD values were 0.299 ± 0.137 ng/mL for premenopausal women, 0.556 ± 0.226 ng/mL for postmenopausal women, 0.300 ± 0.142 ng/mL for men aged 30 to 49 years, 0.304 ± 0.200 for men aged 50 to 69 years, and 0.394 ± 0.149 ng/mL for men aged 70 years or older. Serum bone-specific alkaline phosphatase (BSALP) levels were determined by using the Metra BAP immunoassay kit (Quidel Corp., San Diego, CA), with inter- and intraassay CVs of 4.4% and 3.6%, respectively. The reference ranges were 11.6 to 29.6 U/L for women aged 22 to 44 years, 14.2 to 42.7 U/L for women aged 45 years or older, and 15.0 to 41.3 U/L for men aged 25 years or older.

Statistical analysis

Continuous variables are reported as the mean and SD or the median and interquartile range, and categorical variables as the number and percentage, unless otherwise specified. The baseline characteristics of the cases and controls were compared by using Student *t* tests for continuous variables and χ^2 tests for categorical variables. The association of urinary fractionated metanephrines with BMD and BTM was investigated through multiple linear regression analyses after adjustment for potential confounding factors including age; sex; menopause status; body mass index (BMI); current smoking; alcohol intake; regular outdoor exercise; diabetes; and medication use including corticosteroids, antihypertensive agents, bisphosphonates, and replacement hormones. In these analyses, the levels of urinary fractionated metanephrines and BTMs were log transformed because of the skewed distribution. To generate the odds ratios (ORs) [95% confidence intervals (CIs)] per log-unit increase of urinary fractionated metanephrines or according to the presence of pheochromocytoma for "lower BMD," multiple logistic regression analyses were performed after adjustment for confounders. The multivariable-adjusted least-square mean levels (95% CIs) of BMD and BTM in terms of the presence of pheochromocytoma were estimated and compared by using analysis of covariance (ANCOVA). Differences in BTM before and after adrenalectomy were assessed with the Wilcoxon signed-rank test. All statistical analyses were performed by using SPSS statistical software (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the 311 study subjects are listed in Table 1. Of the 280 controls without pheochromocytoma, 168 (60.0%), 34 (12.1%), and 78 (27.9%) were men, premenopausal women, and postmenopausal women, respectively. Of the 31 cases, 12 (38.7%), 12 (38.7%), and 7 (22.6%) were men, premenopausal women, and postmenopausal women, respectively. The mean ages of controls and cases were 54.5 ± 10.0 years (range, 22 to 78 years) and 50.2 ± 11.5 years (range, 31 to 76 years), respectively (P = 0.029). The BMI values were significantly lower in subjects with pheochromocytoma, whereas the levels of urinary metanephrine and normetanephrine were markedly higher in subjects with pheochromocytoma than in those without. There were no significant differences in current smoking, alcohol intake, regular outdoor exercise, diabetes, and medication use (including corticosteroids, antihypertensive agents, bisphosphonates, and replacement hormones) between groups.

When we tested whether any association between urinary fractionated metanephrines and BMD values might be modified by sex and menopause status, we found no interactions between the levels of urinary metanephrine or normetanephrine (expressed as a continuous

Table 1. Baseline Characteristics of the Study Participants According to the Presence of Pheochromocytoma

Variables	Subjects Without Pheochromocytoma (n = 280)	Subjects With Pheochromocytoma (n = 31)	*P*
Sex and menopause status, no. (%)			**<0.001**
Male	168 (60.0)	12 (38.7)	
Female			
Premenopause	34 (12.1)	12 (38.7)	
Postmenopause	78 (27.9)	7 (22.6)	
Age (y), mean ± SD	54.5 ± 10.0	50.2 ± 11.5	**0.029**
BMI (kg/m^2), mean ± SD	25.6 ± 3.6	23.3 ± 3.8	**0.001**
Current smoker, no. (%)	82 (29.3)	6 (19.4)	0.244
Alcohol intake ≥3 U/d, no. (%)	72 (25.7)	5 (16.1)	0.241
Regular exercise ≥30 min/d, no. (%)	141 (50.4)	12 (38.7)	0.218
Diabetes, no. (%)	50 (17.9)	5 (16.1)	0.811
Medication use, no. (%)			
Corticosteroid	1 (0.4)	1 (3.2)	0.190
Antihypertensive agent	105 (37.5)	11 (35.5)	0.826
Bisphosphonate	7 (2.5)	0 (0.0)	0.999
Replacement hormone	5 (1.8)	0 (0.0)	0.999
Urine MN (μg/d), median (IQR)	103.3 (71.6–134.2)	325.1 (123.7–999.6)	**0.003**
Urine NM (μg/d), median (IQR)	231.4 (178.1–298.5)	825.8 (365.4–2291.8)	**<0.001**

Bold numbers indicate statistically significant values. IQR, interquartile range; MN, metanephrine; NM, normetanephrine.

variable) and sex and menopause status (coded as 0, 1, and 2 for premenopausal women, postmenopausal women, and men, respectively, and expressed as a categorical variable) for the association with BMD values at the lumbar spine, femur neck, or total hip (P for tests of interaction = 0.601 to 0.944). Therefore, instead of separating premenopausal women, postmenopausal women, and men, we performed further analyses together after adjustment for sex and menopause status.

Multiple linear regression analyses were performed to examine the independent association of urinary fractionated metanephrines with BMD and BTM (Supplemental Table 1). After adjustment for all potential confounders, including age, sex, menopause status, BMI, current smoking, alcohol intake, regular outdoor exercise, diabetes, and medication use, a higher urinary metanephrine level was significantly associated with lower BMD at the lumbar spine, whereas this association was not observed at the femur neck and total hip. Similarly, the urinary normetanephrine level was inversely associated with BMD at the lumbar spine, but not at the femur neck and total hip. Interestingly, both urinary metanephrine and normetanephrine levels were positively associated with serum CTX, a bone resorption marker. However, both urinary metanephrine and normetanephrine had no correlation with serum BSALP, a bone formation marker.

The ORs per log-unit increase in urinary metanephrine and normetanephrine for lower BMD at either the lumbar spine, femur neck, or total hip were 1.35 and 1.89, respectively, after considering potential confounders (Supplemental Table 2). However, the statistical significance in the case of urinary metanephrine was only marginal (P = 0.091). When the risk for lower BMD was separately analyzed at various skeletal sites, each log-unit increase in urinary metanephrine and normetanephrine was significantly associated with a 1.60-fold and 2.08-fold higher OR for lower BMD at the lumbar spine, whereas this association was not observed at the femur neck and total hip.

The subjects were then categorized into four groups according to each level of urinary fractionated metanephrines. Multiple logistic regression analyses revealed that the ORs for lower BMD at either the lumbar spine, femur neck, or total hip had an increased tendency with increasing urinary metanephrine quartiles with a marginal significance (P for trend = 0.056), and the odds for lower BMD at the lumbar spine were 2.42-fold higher in subjects in the highest metanephrine quartile in comparison with those in the lowest metanephrine quartile [Fig. 1(a)]. However, the odds for lower BMD at the femur neck and total hip did not differ among urinary metanephrine quartiles (P for trend = 0.457 and 0.858, respectively). Similarly, the odds for lower BMD at any site and the lumbar spine were 4.19- and 3.94-fold higher, respectively, in subject in the highest urinary normetanephrine quartile than in those in the lowest normetanephrine quartile [Fig. 1(b)], whereas there was no statistical difference among urinary normetanephrine quartiles in terms of the odds for lower BMD at the femur neck and total hip (P for trend = 0.721 and 0.991, respectively).

Differences in BMD and BTM between subjects without and with pheochromocytoma were assessed by using ANCOVA. After adjustment for confounding factors, subjects with pheochromocytoma had 7.2% lower bone mass at the lumbar spine than those without pheochromocytoma (Fig. 2). However, there were no statistical differences between the groups in terms of BMD values at the femur neck and total hip. Importantly, the serum CTX level was 33.5% higher in subjects with pheochromocytoma than in controls, whereas serum BSALP level was not significantly different between the groups.

In multiple logistic regression analyses, the odds for lower BMD at either the lumbar spine, femur neck, or total hip was 2.54-fold higher with marginal significance (P = 0.056) in subjects with pheochromocytoma than in those without (Table 2). When the risk for lower BMD was separately analyzed at various skeletal sites, the OR for lower BMD at the lumbar spine in the presence of pheochromocytoma was 3.31. However, the ORs for lower BMD at the femur neck and total hip did not differ according to the presence of pheochromocytoma.

Among 31 patients with pheochromocytoma, information about BTM after adrenalectomy was available in 14 patients. The serum CTX levels were decreased by 35.2% after adrenalectomy (from 0.495 to 0.321 ng/mL), whereas the serum BSALP levels were not significantly different before and after adrenalectomy (Fig. 3).

Finally, although the major strength of this study is that we enrolled consecutive patients with newly diagnosed AI to minimize selection bias, we investigated whether the association of pheochromocytoma with osteoporosis-related parameters could be changeable or not after matching characteristics. The 31 controls including 12 men and 19 women were randomly selected among 280 subjects without pheochromocytoma and matched 1:1 to cases in terms of sex, age, and menopause status in women. As shown in Supplemental Figure 1, both men and women with pheochromocytoma had significantly lower bone mass at the lumbar spine and higher serum CTX level than those without pheochromocytoma, whereas there were no statistical differences between groups in BMD at the femur neck and total hip and in serum BSALP level, indicating that the results are the exactly same direction with our original analyses.

Meanwhile, as expected, the partial correlation analyses after adjustment for confounders showed that

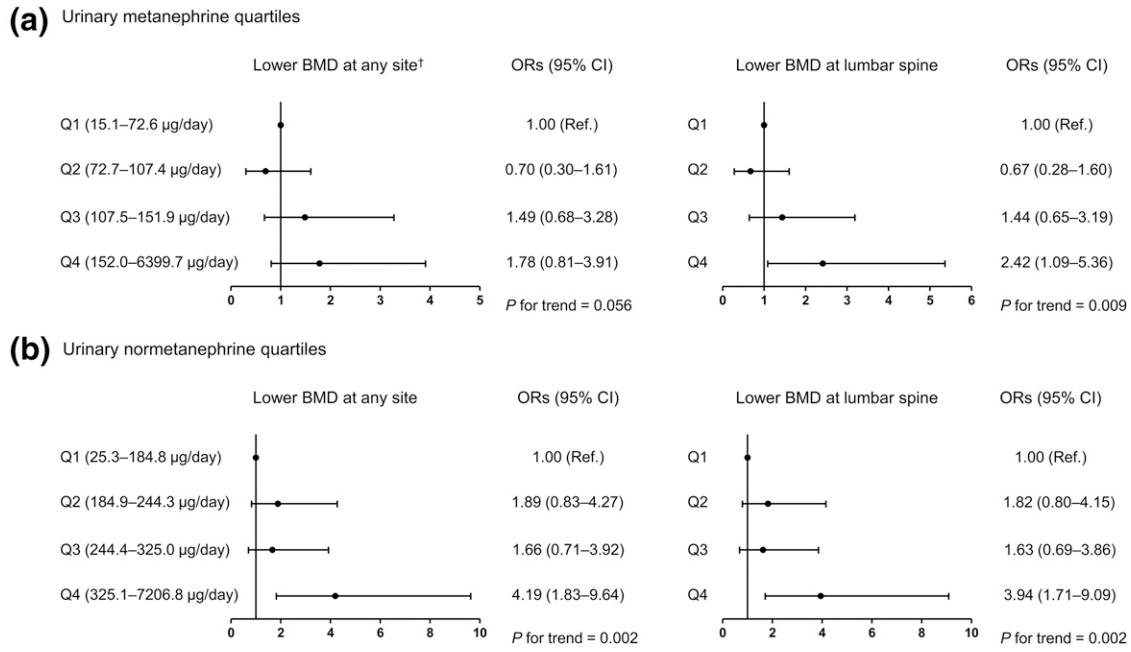

Figure 1. Multiple logistic regression analyses for determining the ORs for lower BMD* according to the quartile categories of urinary fractionated metanephrines. (a) Urinary metanephrine quartiles. (b) Urinary normetanephrine quartiles. *Lower BMD was defined by *z* score ≤ –2.0 for premenopausal women and men aged <50 years, or *T* score ≤ –1.0 for postmenopausal women and men aged ≥50 years. †"Any site" includes the lumbar spine, femur neck, and/or total hip. The multivariable adjustment factors in these analyses were age; sex; menopause status; BMI; current smoking; alcohol intake; regular outdoor exercise; diabetes; and medication use including corticosteroids, antihypertensive agents, bisphosphonates, and replacement hormones.

higher serum CTX level was consistently associated with lower BMD values at the lumbar spine ($\gamma = -0.334$, $P < 0.001$), femur neck ($\gamma = -0.231$, $P < 0.001$), and total hip ($\gamma = -0.249$, $P < 0.001$).

Discussion

This case-control study showed that subjects with pheochromocytoma had slightly but significant lower bone mass at the lumbar spine and markedly higher bone resorption rate, which decreased after adrenalectomy. Consistently, both urinary metanephrine and normetanephrine were inversely correlated with the lumbar spine BMD and positively correlated with serum CTX level after adjustment for potential confounders. These findings provide clinical evidence showing that catecholamine excess and the resultant sympathetic overstimulation in pheochromocytoma could be associated with a higher probability of lower bone mass, as well as increased bone resorption.

Because of the fundamental difficulty of controlling for diverse confounding factors in human studies with β-adrenergic receptor modulators, the question of whether sympathetic activity can really affect human bone metabolism, as observed in rodents, has remained. In this viewpoint, pheochromocytoma, characterized by excess secretion of catecholamines, could be an ideal human model for elucidating the role of the SNS on the pathogenesis of diverse diseases including osteoporosis. In fact, a recent cohort study demonstrated the importance of the sympathetic control of human bone remodeling by showing increased bone resorption in patients with pheochromocytoma, which normalized after adrenalectomy (20), and these findings were perfectly replicated in the current study. Furthermore, this study reports significant lower bone mass in subjects with pheochromocytoma than in those without this condition. Because both lower BMD as a static marker and higher bone resorption rate as a dynamic indicator are well established predictors for osteoporotic fractures (22, 23), and the risk of fracture is higher when these conditions occur concurrently (24), all these results support the detrimental effects of sympathetic overstimulation on human bone metabolism. Further, they suggest that pheochromocytoma could be a potential risk factor for osteoporosis and related fractures, and thus should be effectively treated to maintain bone health.

A particularly important observation in the current study was that urinary fractionated metanephrines were inversely associated with BMD only at the lumbar spine (primarily composed of spongy, cancellous bone) but not at the proximal femur (mainly composed of cortical bone). Although we cannot determine the exact reason for this finding in the current study, experts in this field have speculated that the SNS may have dual actions on different skeletal compartments owing to the differential innervation of these skeletal regions by sympathetic

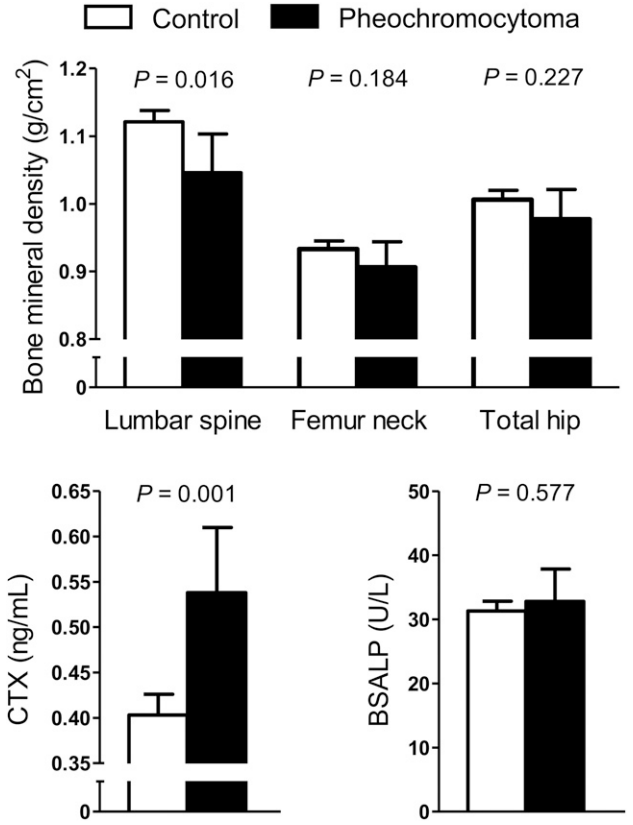

Figure 2. Differences in BMD and BTMs between subjects without and with pheochromocytoma. Values are presented as the estimated means with 95% CI, from ANCOVA after adjustment for age; sex; menopause status; BMI; current smoking; alcohol intake; regular outdoor exercise; diabetes; and medication use including corticosteroids, antihypertensive agents, bisphosphonates, and replacement hormones.

Table 2. Multiple Logistic Regression Analyses for Determining the ORs for Lower BMD According to the Presence of Pheochromocytoma

	Subjects With Pheochromocytoma OR (95% CIs)	*P*
Lower BMD[a] at any site[b]	2.54 (0.98–6.60)	0.056
Lower BMD at the lumbar spine	**3.31 (1.23–8.56)**	**0.014**
Lower BMD at the femur neck	1.18 (0.31–4.45)	0.806
Lower BMD at the total hip	0.80 (0.17–3.75)	0.772

Bold numbers indicate statistically significant values. The multivariable adjustment factors in these analyses were age; sex; menopause status; BMI; current smoking; alcohol intake; regular outdoor exercise; diabetes; and medication use including corticosteroids, antihypertensive agents, bisphosphonates, and replacement hormones.

[a] Lower BMD was defined by *z* score ≤ –2.0 for premenopausal women and men aged <50 years, or *T* score ≤ –1.0 for postmenopausal women and men aged ≥50 years.

[b] "Any site" includes the lumbar spine, femur neck, and/or total hip.

nerve fibers (25–27). This hypothesis was further supported by the human study of Farr *et al.* (25), which showed that sympathetic activity, as measured with microneurography, was inversely associated with trabecular microstructure but not with cortical bone parameters. Taken altogether, these findings indicate the disparate responses to excessive sympathetic activity between trabecular and cortical bones, and additional investigations are necessary to clarify specific mechanism.

Under steady-state conditions, the balance between bone resorption and bone formation is normally tightly controlled in a local, coordinated, and sequential manner, which is referred to as the "coupling phenomenon" (28), and imbalance between these two processes leads to metabolic bone disorders such as osteoporosis and osteopetrosis (29, 30). In both a recent human study (20) and our study, subjects with pheochromocytoma showed a markedly higher bone resorption rate without affecting the bone formation rate. This uncoupling in pheochromocytoma can be adequately explained by an animal study with β2AR-deficient mice showing that the SNS favors bone resorption by increasing the expression of the osteoclast differentiation factor RANKL in osteoblast progenitor cells (31). In addition, chronic stimulation of the β-adrenergic receptor in mice induces bone loss mainly through enhanced bone resorption without suppressing bone formation (8). All these data indicate that low bone mass associated with sympathetic overstimulation could be attributable to an uncoupling between excessive bone degradation and inadequately balanced bone formation, and subsequent ongoing bone loss.

To appropriately investigate the pathophysiological links of the SNS with bone health, we considered as many confounding factors as possible. Despite this strength, several potential limitations should be considered when interpreting our results. First, although our study is meaningful in that there have been no clinical studies reporting the possible lower bone mass in pheochromocytoma, serial bone mass changes, which need relatively long periods to achieve the least significant change, before and after adrenalectomy could not be assessed. We expect that this study can be an important beginning and background for future prospective studies. Second, central dual-energy x-ray absorptiometry including lumbar spine and proximal femur may not be enough to dissect the different effects of SNS on trabecular and cortical bones. Further researches using forearm BMD and/or computed tomography can be necessary. Third, whereas control group consisted of 280 subjects, only 31 patients with pheochromocytoma were identified, half of which had serum CTX measurements after adrenalectomy. This limitation reflects the rare nature of the disease, as discussed in other study (20). However, 31 cases are the largest number in clinical studies relating pheochromocytoma to bone health, and can yield enough statistical power to generate the conclusion. Fourth, although a recent expert

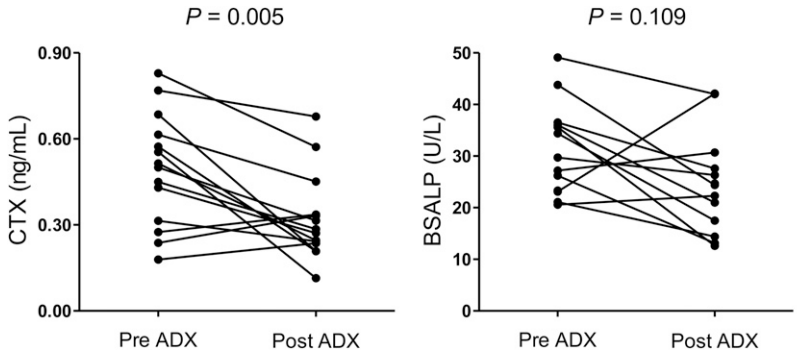

Figure 3. Serum BSALP and CTX levels in subjects with pheochromocytoma before and after adrenalectomy. Wilcoxon signed-rank test was performed for analysis. ADX, adrenalectomy.

panel proposed that amino terminal propeptide of type 1 procollagen becomes the reference marker of bone formation (32), we used BSALP, which is also known to be useful bone formation marker, as the best alternative due to unavailability of propeptide of type 1 procollagen in clinical practice in Korea. Finally, despite our efforts, we cannot exclude the possibility that the observed association could be the result of uncontrolled factors that affect the SNS and/or bone, such as 25-hydroxyvitamin D levels.

In summary, subjects with pheochromocytoma had lower bone mass in the lumbar spine mainly consisting of trabecular bone, and higher bone resorption that was suppressed after adrenalectomy. The data presented here provide important evidence that sympathetic overstimulation can contribute to adverse effects on human bone through the increase of bone loss, as well as bone resorption, and may have clinical implications justifying aggressive treatment of pheochromocytoma in terms of bone health in addition to cardiovascular risks. Additional experimental studies are necessary to unravel the complex mechanisms linking the SNS and bone metabolism in humans.

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