

Lower Trabecular Bone Score in Patients With Primary Aldosteronism: Human Skeletal Deterioration by Aldosterone Excess

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Context: Despite the potential detrimental effects of aldosterone excess on bone metabolism, discrepancies exist between fracture risk and bone mass in patients with and without primary aldosteronism (PA).

Objective: To clarify the possibility that aldosterone excess might mainly affect bone properties not explained by the bone mineral density (BMD).

Design, Setting, and Patients: Among 625 consecutive patients with newly diagnosed adrenal incidentaloma (AI), 72 with biochemically confirmed PA and 335 with nonfunctional AI were defined as cases and controls, respectively.

Results: In women, although no statistically significant differences in lumbar spine BMD were found between groups, the lumbar spine trabecular bone score (TBS) was significantly lower in patients with PA than in controls after adjustment for confounders ($P = 0.007$). Consistently, the plasma aldosterone concentration (PAC) correlated inversely with the lumbar spine TBS ($P = 0.028$) but not with bone mass in women. Compared with women in the lowest PAC quartile, those in the highest PAC quartile had significantly lower lumbar spine TBSs ($P = 0.004$). Importantly, all these observations in women remained statistically significant after additional adjustment for the lumbar spine BMD in the multivariable model. However, BMD and TBS at the lumbar spine did not differ according to the presence of PA and the level of PAC in men.

Conclusion: These findings provide clinical evidence that aldosterone excess in PA might contribute to deteriorated bone quality through weak microarchitecture, regardless of bone mass, especially in women. (*J Clin Endocrinol Metab* 103: 615–621, 2018)

Osteoporotic fractures are a worldwide epidemic, and the predicted aging of the population will further increase the burden of these minimal trauma fractures on health care systems. Although bone mineral density (BMD) is one of the best available tools for assessing future fracture risk, only 50% to 70% of total bone strength is attributable to BMD, and approximately two-

thirds of individuals who sustain fractures do not have BMD-defined osteoporosis (1). These findings suggest that the BMD test alone is not sufficient to adequately assess bone strength and predict future fracture risk. The trabecular bone score (TBS), which is determined by quantifying pixel gray-level variations on lumbar spine dual-energy X-ray absorptiometry (DXA) scans, has

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Abbreviations: AI, adrenal incidentaloma; AMC, Asan Medical Center; ANCOVA, analysis of covariance; ARR, aldosterone/renin ratio; BMD, bone mineral density; BMI, body mass index; BP, blood pressure; CV, coefficient of variation; DXA, dual-energy X-ray absorptiometry; GFR, glomerular filtration rate; ISE, ion selective electrode; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; TBS, trabecular bone score.

been introduced as a parameter representing the bone microarchitecture (2, 3). Low TBSs reflect deteriorated microarchitecture and predict for osteoporotic fractures independent of BMD (4–6). Therefore, the TBS is regarded as a valuable noninvasive clinical tool in fracture risk assessment, because it provides skeletal information that is not captured during the standard BMD measurement (2, 7).

Primary aldosteronism (PA) is a disorder of the adrenal gland characterized by the autonomous hypersecretion of aldosterone and is the most common cause of secondary hypertension, accounting for 5% to 10% of all patients with hypertension (8, 9). PA has been associated with end-organ damage, affecting the heart, carotid arteries, and kidneys, in particular, independently of the blood pressure (BP) (10). Increasing evidence has shown that aldosterone excess might play an important role in human bone metabolism as well. Clinical studies have shown that PA is associated with an increased risk of bone fracture, especially of the vertebrae (11–13). However, despite these consistently adverse outcomes of PA in terms of fracture, studies assessing the association between aldosterone excess and BMD have yielded conflicting results, with some showing a negative association and others, no association (11, 12). These data suggest that the poor bone health observed in PA might be mediated by the deterioration of bone quality, another important component of bone strength, other than the bone mass. To clarify the potential effects of aldosterone excess on human bone, we investigated the association of PA with the TBS as a skeletal fragility index in a Korean cohort consisting of patients with PA and controls.

Materials and Methods

Study participants and protocol

We recruited 919 consecutive patients with newly diagnosed adrenal incidentaloma (AI) in the adrenal clinic of the Asan Medical Center (AMC; Seoul, Korea) between July 2011 and December 2015. The diagnosis of AI was determined by the detection of an adrenal mass (size ≥ 1 cm) on computed tomography performed for an unrelated disease. All patients with AI underwent a biochemical evaluation to determine the presence of hormonal abnormalities. Among these patients, 625 agreed to undergo an assessment of bone properties using DXA and were included in the present study. The BMD and TBS were obtained and interpreted without knowledge of the functional status of the patients. Using the appropriate hormonal evaluation results and computed tomography scan findings, we excluded 206 patients suspected to have hypercortisolism, pheochromocytoma, congenital adrenal hyperplasia, adrenal carcinoma, adrenal metastasis, or adrenal tuberculosis. In addition, 12 patients who had taken drugs that could affect the bone metabolism, such as bisphosphonates, systemic glucocorticoids, or hormonal replacement therapy, were excluded. After applying these criteria, 407 participants were deemed eligible for inclusion.

Before screening for PA by measuring the aldosterone/renin ratio (ARR), all interfering antihypertensive medications, such as angiotensin I converting enzyme inhibitors and angiotensin II receptor blockers, were withdrawn for ≥ 4 weeks for all patients (9). If necessary, the patients took an α -blocker (*e.g.*, doxazosin) and a slow-releasing calcium channel blocker (*e.g.*, verapamil), according to the guidelines of the Endocrine Society (9). All patients were encouraged to consume unrestricted dietary salt intake before testing and to continue with oral potassium supplementation in the case of hypokalemia.

The screening test result was considered positive if the ARR was ≥ 30 (ng/dL)/(ng/mL/h). The diagnosis of PA was confirmed by a nonsuppressed plasma aldosterone concentration (PAC; >10 ng/dL) after an intravenous saline infusion test (2 L of 0.9% saline infused over 4 hours) (9). If the postinfusion PAC was <5 ng/dL, PA was excluded. If the postinfusion PAC was 5 to 10 ng/dL, the intravenous saline infusion test was repeated. However, in the setting of spontaneous hypokalemia, a plasma renin level less than the detection level, and a PAC >20 ng/dL, PA was diagnosed without a confirmatory test (9). Consequently, we identified 72 patients with PA. These patients were defined as the case group. The remaining 335 patients with nonfunctional AI were defined as the control group. The institutional review board of AMC approved the present study, and all enrolled participants provided written informed consent.

Lifestyle factors and anthropometric measurements

The following patient information was obtained using an interviewer-assisted questionnaire: smoking habits (current smoker), alcohol intake (≥ 3 U/d), regular outdoor exercise (≥ 30 min/d), history of medication use, previous medical or surgical procedures, and reproductive status, including menstruation. Height (cm) and weight (kg) were measured using a standardized protocol with the participants wearing light clothing without shoes. The body mass index (BMI; kg/m^2) was calculated from their height and weight. BP (mm Hg) was recorded twice using a mercury manometer after the patient had rested for >15 minutes, and the average value was calculated.

Assessment of BMD and TBS

Areal BMD (g/cm^2) was measured at the lumbar spine (L1–L4) and proximal femur using DXA with Lunar equipment (running software version, 9.30.044; Prodigy, Madison, WI). The precision values of the equipment, in terms of the coefficient of variation (CV), were 0.67% and 1.25% for the lumbar spine and femur neck, respectively. TBS was retrospectively analyzed from the lumbar spine DXA scans using iNsite software, version 3.0.2.0 (Med-Imaps, Pessac, France), on the same regions of interest as those used for the lumbar spine BMD determination. Pre-existing lumbar spine DXA files were anonymized to ensure blinding of the investigators to all clinical parameters and outcomes. The region of interest was automatically generated by the DXA system and adjusted by the technologist as necessary. The instruments were calibrated using TBS phantoms in accordance with the manufacturer's instructions. The CV of the lumbar spine TBS was 1.1%.

Although a normal range for the TBS in men has not yet been established, a working group of TBS users from different countries proposed the following ranges for TBSs in postmenopausal women, by analogy with the three BMD categories (*i.e.*, normal bone mass, osteopenia, and osteoporosis) (2, 14):

a TBS ≥ 1.350 is considered normal; a TBS between 1.200 and 1.350 is considered consistent with partially degraded bone microarchitecture; and a TBS ≤ 1.200 represents degraded microarchitecture. Because the number of postmenopausal women with TBS ≤ 1.200 in our cohort was too small for separate analysis ($n = 2$), postmenopausal women who met the criteria for at least partially degraded microarchitecture (TBS < 1.350) were classified as having “abnormal microarchitecture” by combining the TBS values from 1.200 to 1.350 and ≤ 1.200 .

Hormonal and biochemical measurements

Morning blood samples were obtained after overnight fasting and subsequently analyzed at the certified laboratory at AMC. The PAC and plasma renin activity (PRA) were measured using a radioimmunoassay using SPAC-S aldosterone and PRA kit (TFB Inc., Tokyo, Japan), respectively, on a Cobra II Gamma Counter (Packard Instrument Co., Meriden, CT). The lower limit of PAC for detection by the kit was > 1.53 ng/dL, and the intra-assay and interassay CVs were $< 3.2\%$ and $< 6.7\%$, respectively. The lower limit of PRA for detection by the kit was > 0.09 ng/mL/h, and the intra-assay and interassay CVs were $< 8.3\%$ and $< 9.7\%$, respectively.

The serum potassium level was measured by an ion selective electrode (ISE) using a Roche ISE Standard Low/High (Roche Diagnostics, Mannheim, Germany) on a Cobas 8000 ISE analyzer (Roche Diagnostics). The intra-assay and interassay CVs for serum potassium were $< 0.5\%$ and $< 1.6\%$, respectively. The serum creatinine level was measured by the kinetic colorimetric assay using the Roche CREA J2 kit (Roche Diagnostics) on a Cobas c 702 module (Roche Diagnostics). The intra-assay and interassay CVs were $< 2.3\%$ and $< 2.7\%$, respectively. The glomerular filtration rate (GFR) was estimated using the Cockcroft–Gault equation (15).

Statistical analysis

Continuous variables are reported as the mean \pm standard deviation or median and interquartile range and categorical variables as the frequency and percentage, unless otherwise

specified. The baseline characteristics of the cases and controls were compared using Student *t* tests for continuous variables and χ^2 tests for categorical variables. The multivariable-adjusted least squares mean levels (95% confidence intervals) of the BMD and TBS in terms of the presence of PA were estimated and compared using analysis of covariance (ANCOVA) after adjustment for potentially confounding factors, including age, menopause status in women, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR. The associations of PAC with BMD and TBS were investigated using multiple linear regression analyses. After categorizing women into four groups according to the PAC, the differences in the TBS among the PAC quartiles were estimated using ANCOVA after adjusting for confounders. Finally, to generate the odds ratios for abnormal microarchitecture according to the presence of PA in postmenopausal women, multiple logistic regression analyses were performed. All statistical analyses were performed using SPSS, version 18.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered to indicate statistical significance.

Results

The 407 study participants were divided according to PA status, and their baseline characteristics are listed in Table 1. In the 174 women, the mean age of the controls ($n = 136$) and cases ($n = 38$) was 54.4 ± 10.2 years (range, 22 to 79) and 56.4 ± 9.4 years (range, 33 to 75), respectively ($P = 0.291$). The difference in menopausal status between the two groups was not substantial. In the 233 men, the mean age of the controls ($n = 199$) and cases ($n = 34$) was 54.8 ± 9.8 years (range, 27 to 80) and 57.1 ± 7.5 years (range, 41 to 73), respectively ($P = 0.187$). In both sexes, the patients with PA had markedly higher systolic and diastolic BP values, PACs, and ARRs and significantly lower frequencies of regular exercise and lower K^+ and PRA than those without PA. However, for both women and men, the

Table 1. Baseline Characteristics of Study Participants Stratified by Presence of PA

Variable	Women Without PA (n = 136)	Women With PA (n = 38)	P Value	Men Without PA (n = 199)	Men With PA (n = 34)	P value
Age, y	54.4 \pm 10.2	56.4 \pm 9.4	0.291	54.8 \pm 9.8	57.1 \pm 7.5	0.187
Postmenopausal, n (%)	93 (68.4)	31 (81.6)	0.112	NA	NA	NA
BMI, kg/m ²	25.0 \pm 6.0	24.9 \pm 3.8	0.924	25.8 \pm 3.2	25.7 \pm 2.7	0.891
Systolic BP, mm Hg	122.2 \pm 15.5	131.9 \pm 15.4	0.001 ^a	127.6 \pm 12.4	139.5 \pm 15.3	$< 0.001^a$
Diastolic BP, mm Hg	75.3 \pm 9.5	79.0 \pm 10.1	0.036 ^a	79.1 \pm 9.6	85.0 \pm 11.1	0.001 ^a
Current smoker, n (%)	8 (5.9)	2 (5.3)	0.885	89 (44.7)	10 (29.4)	0.095
Alcohol intake ≥ 3 U/d, n (%)	24 (17.6)	6 (15.8)	0.789	66 (33.2)	10 (29.4)	0.666
Regular exercise ≥ 30 min/d, n (%)	53 (39.0)	6 (15.8)	0.008 ^a	110 (55.3)	8 (23.5)	0.001 ^a
GFR, mL/min	95.0 \pm 38.4	92.8 \pm 25.0	0.748	96.4 \pm 25.0	92.2 \pm 20.4	0.360
K^+ , mEq/L	4.00 \pm 0.38	3.77 \pm 0.52	0.023 ^a	4.15 \pm 0.29	3.84 \pm 0.49	0.001 ^a
PAC, ng/dL	16.3 (12.4–21.2)	24.9 (18.8–30.2)	$< 0.001^a$	14.7 (11.3–18.8)	23.9 (20.7–29.0)	$< 0.001^a$
PRA, ng/mL/h	0.84 (0.34–1.78)	0.24 (0.20–0.45)	$< 0.001^a$	1.10 (0.46–2.60)	0.23 (0.20–0.45)	$< 0.001^a$
ARR, (ng/dL)/(ng/mL/h)	16.7 (9.75–42.2)	87.8 (53.2–152.0)	0.002 ^a	13.0 (5.66–29.5)	100.0 (46.0–148.9)	$< 0.001^a$

Data presented as mean \pm standard deviation or median (interquartile range), unless otherwise indicated.

Abbreviation: NA, not applicable.

^aStatistically significant.

two subgroups did not differ in terms of BMI, current smoking, alcohol intake, or GFR.

Differences in BMD and TBS between participants without and with PA were assessed using ANCOVA, after adjusting for all potential confounders, including age, menopausal status in women, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR. In women, although no statistically significant difference in BMD values at the lumbar spine was found between groups, the lumbar spine TBS was 3.4% lower in patients with PA than in the controls (Fig. 1A). When the lumbar spine BMD value was additionally adjusted in this multivariable model, the statistically significant difference in the lumbar spine TBS between women without and with PA persisted. In men, patients with PA showed a trend toward a lower TBS, although it did not reach statistical significance (Fig. 1B). In contrast, men without and with PA did not differ in terms of lumbar spine BMD. In addition, no statistically significant differences were found in BMD values at the femur neck and total hip between groups in both sexes (data not shown).

Multiple linear regression analyses were performed to examine the independent association of PAC with BMD and TBS (Table 2). In women, after adjustment for confounders, higher PAC was significantly associated with lower lumbar spine TBS, with no correlation between PAC and BMD values at any site of measurement. The inverse association between PAC and lumbar spine TBS in women remained statistically significant after additional adjustment for lumbar spine BMD in the multivariable model. However, the association of PAC with BMD and TBS was not found in men, regardless of the adjustment model. In addition, PRA and ARR, two other important parameters related to PA, were associated with neither BMD values at any site of measurement nor lumbar spine TBS in both sexes (data not shown).

To better understand the clinical implications of these results and determine whether a threshold effect exists in the association between PAC and lumbar spine TBS in

women, we categorized the women into four groups according to the PAC (Fig. 2). When multivariable-adjusted least squares mean TBSs according to PAC quartile was estimated after considering potential confounders, women in the highest PAC quartile (quartile 4) had a significantly lower lumbar spine TBS than those in the lowest PAC quartile (quartile 1), and the statistical significance persisted after additional adjustment for the lumbar spine BMD.

Because a normal range for TBS values has been proposed only for postmenopausal women (2, 14), we performed multiple logistic regression analyses to determine the risk of abnormal bone microarchitecture according to the presence of PA in the subgroup of postmenopausal women ($n = 124$; Table 3). The odds for abnormal microarchitecture after adjustment for potential confounders and additional adjustment for lumbar spine BMD were 2.52-fold greater with marginal significance and 4.41-fold greater, respectively, in patients with PA compared with those without PA.

Discussion

The present case-control study showed that women with PA had significantly lower lumbar spine TBSs and that PAC correlated inversely with the lumbar spine TBS in women, after adjustment for potential confounders. These associations in women remained statistically significant after additional adjustment for lumbar spine BMD in the multivariable model. However, the BMD and TBS at the lumbar spine did not differ according to the presence of PA and the degree of PAC in men. To the best of our knowledge, these findings provide the first clinical evidence that aldosterone excess in PA might contribute to the deterioration of bone quality through weak microarchitecture, regardless of bone mass, especially in women.

The ultimate goal of bone biology research is to prevent osteoporotic fractures, and continuous efforts to find secondary causes of skeletal fragility are necessary to achieve this. We identified two clinical studies that assessed

Table 2. Multiple Linear Regression Analysis Results Assessing Association of PAC With BMD and TBS

Multivariable Adjustment	Women				Men			
	$\beta 1$	SE	$\beta 2$	P Value	$\beta 1$	SE	$\beta 2$	P Value
Lumbar spine BMD	−0.001	0.001	−0.060	0.447	0.000	0.001	−0.021	0.758
Femur neck BMD	−0.001	0.001	−0.113	0.156	0.000	0.001	0.008	0.901
Total hip BMD	−0.001	0.001	−0.126	0.117	0.000	0.001	−0.012	0.845
TBS	−0.001 ^a	0.000 ^a	−0.184 ^a	0.028 ^a	−0.001	0.001	−0.116	0.097
TBS with additional adjustment for LS BMD	−0.001 ^a	0.000 ^a	−0.159 ^a	0.040 ^a	−0.001	0.001	−0.111	0.103

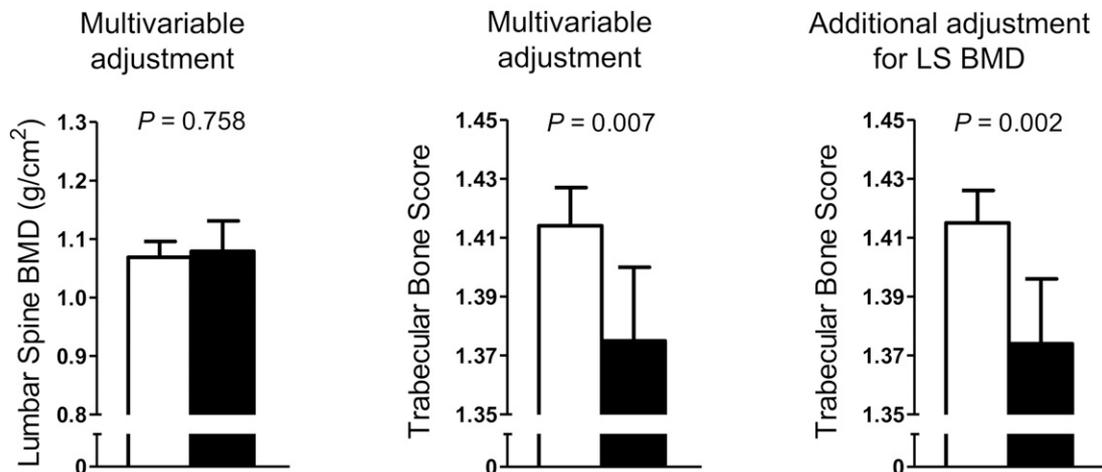
Multivariable adjustment factors in these analyses were age, menopausal status in women, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR.

Abbreviations: $\beta 1$, unstandardized regression coefficient; $\beta 2$, standardized regression coefficient; LS BMD, lumbar spine BMD; SE, standard error.

^aStatistically significant.

A) Women

□ Control ■ Primary aldosteronism



B) Men

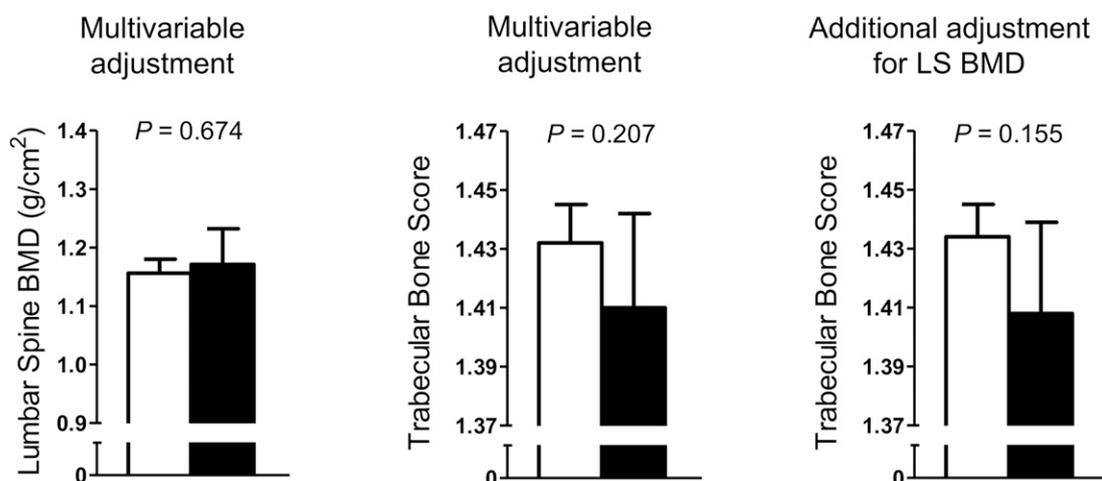


Figure 1. Differences in BMD and TBS between participants without and with PA. Data presented as the estimated mean with 95% confidence intervals from ANCOVA after multivariable adjustment, including age, menopausal status in women, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR. LS BMD, lumbar spine BMD.

the relationship between biochemically confirmed PA and fracture. Salcuni *et al.* (11) showed that vertebral fracture and osteoporosis tended to be more prevalent in 11 patients with PA than in 15 patients in the non-PA group. A more recent study also reported a greater prevalence of vertebral fractures in 56 patients with PA than in 56 age- and sex-matched controls (12). However, consistent with our results, no difference was found between PAC and BMD in that study (12). Collectively, despite the possible detrimental effects of aldosterone excess on human bone metabolism, discrepancies exist between fracture risk and bone mass in patients with and without PA, raising the possibility that aldosterone excess might mainly affect bone properties not explained by the BMD.

The TBS is a textural parameter that evaluates pixel gray-level variations in the lumbar spine DXA image, providing an indirect index of trabecular micro-architecture (2, 3, 7). The TBS can be particularly useful in the case of a paradox between fracture risk and BMD. For example, the increased fracture risk in individuals with diabetes, despite their normal or even higher BMD (16), is consistent with the lower lumbar spine TBS seen in those with diabetes relative to those without diabetes (17, 18). When we used this method in our study, we found that greater PACs correlated with statistical significance with lower TBSs in women, regardless of the BMD. This suggests that the previously observed greater risk of fracture in patients with PA (11–13) might be, at least

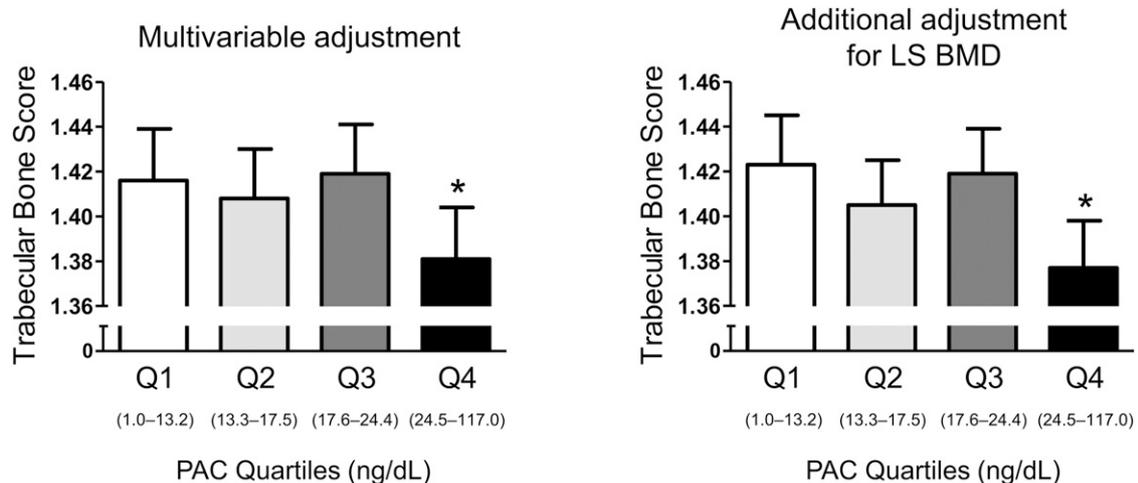


Figure 2. TBSs according to PAC quartiles in women. Data presented as the estimated mean with 95% confidence intervals from ANCOVA after multivariable adjustment, including age, menopausal status, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR. *Differences statistically significant from the lowest quartile [quartile (Q)1] by ANCOVA. LS BMD, lumbar spine BMD.

in part, attributable to the poor bone quality in these patients.

Although the activation of the renin-angiotensin system could induce osteoporosis via increased bone resorption (19, 20), PA is a condition with suppression of renin and angiotensin II through a negative feedback due to elevated PACs. Furthermore, no correlation was found with PRA and bone parameters in our study. Taken together, these indicate that the skeletal deterioration in patients with PA might result from the aldosterone excess *per se*, possibly through direct effects on bone cells (21), increased urinary calcium excretion and consequent secondary hyperparathyroidism (22–24), or chronic inflammation (25).

A particularly interesting observation in the present study was that the PAC was inversely associated with the lumbar spine TBS only in women but not in men. Although we could not determine the exact reason for the difference according to sex at present, we speculate that women with relatively large sex hormonal variations

could be more vulnerable to the deleterious effects of aldosterone excess than are men. Further studies focusing on how male and female hormones interact with aldosterone in relation to bone could help to explain the sex difference found in the association between PA and the lumbar spine TBS.

The major strength of the present study was that we enrolled consecutive patients with newly diagnosed AI to minimize selection bias. Also, cases and controls were available for comparative analysis. Furthermore, to appropriately determine the pathophysiological links of aldosterone excess with bone health, we considered as many confounding factors as possible, including systolic and diastolic BP and GFR. Despite these strengths, several potential limitations should be considered when interpreting our results. First, because this was a cross-sectional study, we could not determine whether a causal relationship exists between aldosterone excess and poor bone quality in patients with PA. Second, several parameters linking aldosterone to bone metabolism, such as parathyroid hormone and urinary calcium, were not tested in our cohort; thus, specific mechanisms inducing low bone quality by aldosterone excess could not be determined. Finally, despite our efforts, we could not exclude the possibility that the observed association could have resulted from uncontrolled factors that affect the renin-angiotensin-aldosterone system and/or bone, such as 25-hydroxyvitamin D levels.

In conclusion, women with PA had a markedly lower lumbar spine TBS than did those without PA, although the BMD measured using DXA was not significantly different statistically between cases and controls in both sexes. These results suggest that aldosterone excess can contribute to poor bone health outcomes mainly through the detrimental effects on bone quality. Therefore, to

Table 3. Multiple Logistic Regression Analysis Results to Determine Odds Ratio for Abnormal Microarchitecture^a in the Presence of PA in Postmenopausal Women

Adjustment	OR (95% CI)	P Value
Multivariable	2.52 (0.89–7.11)	0.082
Additional for LS BMD	4.41 (1.36–14.29)	0.013 ^b

Multivariable adjustment factors in these analyses included age, BMI, current smoking, alcohol intake, regular outdoor exercise, systolic and diastolic BP, and GFR.

Abbreviation: LS BMD, lumbar spine BMD; OR, odds ratio.

^aAbnormal microarchitecture was defined by TBS <1.350.

^bStatistically significant.

explain the high risk of fracture in patients with PA, determination of the lumbar spine TBS could be useful in determining skeletal fragility in patients with PA when a discrepancy is found with bone mass, especially in women.

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