Primary Aldosteronism as a Risk Factor for Vertebral Fracture

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Context: Some observational studies have revealed an association between excessive aldosterone levels and reduced bone mineral density (BMD). However, whether patients with primary aldosteronism (PA) are at higher risk of fracture than healthy individuals remains unclear.

Objective: This study aimed to clarify whether PA represents a risk factor for vertebral fracture (VF).

Design and Patients: We enrolled 56 patients with PA and 56 age- and sex-matched healthy individuals. Serum and urinary biological parameters, BMD, and presence of VFs were evaluated in both groups. We compared parameters between PA and control participants and performed multiple logistic regression analyses after adjustments for variables.

Results: Patients with PA showed higher systolic and diastolic blood pressure, higher hemoglobin A1c (HbA1c) and triglycerides, higher urinary calcium-to-creatinine ratio, and lower high-density lipoprotein cholesterol than controls ($P < 0.05$, each). Prevalence of VFs was significantly higher in patients with PA (44.6%) than in controls (23.2%, $P < 0.05$). Patients with PA showed severe fracture more frequently than controls. Multivariate logistic regression analyses adjusted for age, sex, and body mass index identified PA as being associated with the presence of VFs (odds ratio, 3.13; 95% confidence interval, 1.30 to 7.51; $P < 0.05$). This association remained statistically significant after further adjustment for systolic and diastolic blood pressure, HbA1c, triglycerides, and high-density lipoprotein cholesterol but not after adjustment for calcium-to-creatinine ratio and BMD.

Conclusions: We identified PA as a risk factor for VF, independent of blood pressure, HbA1c, and lipid profile. Fracture severity was significantly higher in patients with PA than in age- and sex-matched controls. (***J Clin Endocrinol Metab*** **102: 1237–1243, 2017)**

Osteoporotic fractures are an important problem affecting mortality, quality of life, and the medical economy. In recent years, emerging studies have suggested that these fractures are associated with hypertension and cardiovascular disease (CVD). A population-based case-control study identified hypertension as a risk factor for hip fracture (1). A twin cohort study of around 32,000 patients reported that CVD was a risk factor for hip fracture and that this relationship involved genetic factors (2). Furthermore, the presence of at least one vertebral fracture (VF) compared with no VF at baseline was associated with a threefold increase in the risk of cardiovascular events in postmenopausal women (3). One factor that may explain the relationships among fractures, hypertension, and CVD is activation of the renin-angiotensin-aldosterone system. Chronic stimulation of the renin-angiotensin-aldosterone system is associated with hypertension and CVD and negatively affects bone metabolism due to the effect of angiotensin II (4, 5). However, whether aldosterone excess itself represents a risk factor for fracture remains unknown.

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Abbreviations: APA, aldosterone-producing adenoma; ARR, aldosterone-to-renin ratio; BMD, bone mineral density; BP, blood pressure; CVD, cardiovascular disease; DBP, diastolic blood pressure; FN, femoral neck; HbA1C, hemoglobin A1C; IHA, idiopathic hyperaldosteronism; L, lumbar spine; PA, primary aldosteronism; PAC, plasma aldosterone concentration; PRA, plasma renin activity; PTH, parathyroid hormone; SD, standard deviation; Th, thoracic vertebra; uCa/uCr, urinary calcium-to-creatinine ratio; VF, vertebral fracture.

Primary aldosteronism (PA) is the most common cause of secondary hypertension and is found in 6.0% to 9.5% of hypertensive patients (6–8). PA is associated with high mortality and is known to cause damage to various organs (9). Milliez *et al.* (10) reported that patients with PA have higher a prevalence of cardiovascular and cerebrovascular diseases. Such reports have shown that PA is an important factor associated with atherosclerotic disease, beyond its effects on intravascular volume and blood pressure (BP) (11).

On the other hand, aldosterone increases renal calcium excretion in the renal distal tubules by decreasing tubular reabsorption of sodium and calcium. Previous reports have shown that aldosterone excess induces urinary excretion of calcium, leading to bone mineral density (BMD) loss and high levels of parathyroid hormone (PTH), and patients with PA are at higher risk of osteopenia and osteoporosis than patients with essential hypertension (12, 13). A recent study reported that VF tended to become more prevalent in PA than in non-PA (14). However, whether patients with PA are at higher risk for fracture than healthy individuals remains unclear.

Participants and Methods

Participants

We enrolled 56 consecutive patients [mean ± standard deviation (SD) age, 59 ± 11 years; men, 44.7%] who were diagnosed with PA at our institution between January 2006 and October 2014. The control group comprised a stratified random sampling of 56 age- and sex-matched healthy individuals who underwent health screening for osteoporosis at a community health center. No participants had taken drugs known to influence bone and calcium metabolism such as vitamin D, bisphosphonates, or glucocorticoids. This study was approved by the ethics review board of Shimane University Faculty of Medicine and complied with the Helsinki Declaration. All participants agreed to participate in the study and provided written informed consent prior to enrollment.

Patients were screened for PA using the plasma aldosterone concentration (PAC) (pg/mL) to plasma renin activity (PRA) (ng/mL/h) ratio [aldosterone-to-renin ratio (ARR), pg/mL per ng mL^{-1} h^{-1}], with 200 as the cutoff value after withdrawal of interfering medications, such as angiotensin I–converting enzyme inhibitors and angiotensin II type 1 receptor blockers. Diagnosis of PA was confirmed with intravenous saline loading, captopril challenge test, and furosemide upright test. The diagnosis of PA was confirmed if one of the following conditions was satisfied: 1) lack of PAC suppression (60 pg/mL) after intravenous saline loading (2 L of 0.9% saline infused over 4 h), 2) persistence of ARR >200 at 90 minutes after administration of 50 mg captopril orally, or 3) lack of PRA (2.0 ng/mL/h) after 40 mg intravenous furosemide, in a standing position (15).

Bilateral adrenal venous sampling was performed in 34 of the 56 patients with PA, and 16 of these patients were diagnosed with a unilateral aldosterone-producing adenoma (APA) and underwent surgery. Among these patients, with the exception of two patients thought to have bilateral involvement, antihypertensive drugs could be discontinued or reduced, and the ARR decreased to <200. Twelve patients had idiopathic hyperaldosteronism (IHA), and in six patients, the cause was undetermined. The remaining 22 patients included patients who were elderly, could not tolerate surgery, did not want surgery, or whose blood pressure improved with drug therapy.

Biochemical measurements

After overnight fasting, blood and urine samples were collected. Hemoglobin A1c (HbA1c) (National Glycohemoglobin Standardization Program) was determined by high-performance liquid chromatography. Serum concentrations of albumin, creatinine, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, intact PTH, urine type I collagen cross-linked *N*-telopeptide (as a marker of bone resorption), urinary calcium-to-creatinine ratio (uCa/uCr), and percent tubular reabsorption of phosphate were evaluated in both groups by automated techniques at the central laboratory of our hospital. Urinary examinations were measured in 42 patients with PA and in 56 healthy controls. Estimated glomerular filtration rate was calculated using the equation proposed by the Modification of Diet in Renal Disease Study with modified coefficients for the Japanese population. Samples for PAC and PRA were collected from patients early in the morning after fasting and while resting in a recumbent position. PAC and PRA were measured with radio immunoassay (SPAC-S Aldosterone Kit and Renin-RIA Renin kit "FR"; TFB, Inc, Tokyo, Japan) (16). PRA was measured through the generation of angiotensin I.

BMD measurements

BMD at the lumbar spine (L) and femoral neck (FN) were measured by dual-energy X-ray absorptiometry using the QDR-4500 system (Hologic, Waltham, MA). BMD was automatically calculated from the bone mineral content (in grams) and bone area (in square centimeters) and expressed as an absolute value in grams per square centimeter. Coefficients of variation of measurement for BMD at L and FN were 0.9% and 1.7%, respectively. The *z* score is the number of SDs by which a given measurement differs from the mean for a sex-, age-, and race-matched reference population. The T score is the number of SDs by which a given measurement differs from the mean for a healthy young adult reference population.

Radiography

Lateral X-rays of the thoracic and lumbar spine were taken in the same week as serum collection in all participants. Anterior, central, and posterior heights of each of the 13 vertebral bodies from thoracic vertebra (Th) 4 to L4 were measured. VF was diagnosed if at least one of the three height measurements along the length of the same vertebra was decreased by >20% compared with the height of the nearest uncompressed vertebral body (17). We defined VFs as grades 1 to 3 according to the classification by Genant *et al.* (17). Grade 1 corresponds to a 20% to 25% reduction in at least one height (anterior, middle, or posterior) along the length of the same vertebra compared with the height of the nearest uncompressed vertebral body. Grade 2 corresponds to a 25% to 40% reduction in any height, and grade 3 corresponds to a more than 40% reduction in any height. We defined severe fracture as grade 2 or 3 VF. VFs were diagnosed by two investigators who were blinded to each

other's readings and also blinded to PA group and control group status. Fractures were assessed at the same time, and if there was disagreement between the two investigators, the findings were assessed by three investigators. No participants had any history of serious trauma.

All data are expressed as mean ± SD for each index. Significant differences between groups were determined using the χ^2 and unpaired t tests. Multiple logistic regression analyses were performed after adjustments for the variables shown in the tables. Statistical analyses were performed using SPSS software (version 19; IBM Corporation, Tokyo, Japan). Values of $P < 0.05$ were considered statistically significant.

Results

Baseline characteristics of participants

Baseline characteristics of participants are shown in Table 1. Each group contained 56 participants. Patients with PA showed higher systolic BP and diastolic BP (DBP), higher HbA1c and triglycerides, and lower high-density lipoprotein cholesterol than controls ($P < 0.05$, each). Patients with PA showed a higher uCa/uCr than controls. Values for creatinine, intact PTH, percent tubular reabsorption of phosphate, urine type I collagen cross-linked *N*-telopeptide, and L- and FN-BMD did not significantly differ between the groups.

Prevalence of VF

VFs were found in 25 patients with PA and in 13 controls. The prevalence of VF was significantly higher in patients with PA (44.6%) than in controls (23.2%, $P < 0.05$). In the PA group, one patient had a VF that had already been diagnosed (clinical VF), and 24 patients had VFs not previously diagnosed (morphometric fractures). All fractures in the control group were morphometric fractures that had not previously been diagnosed. In the PA group, the site of VF was Th4 in 2, Th7 in 5, Th8 in 2, Th9 in 2, Th10 in 2, Th11 in 5, Th12 in 4, L1 in 12, L2 in 4, and L4 in 1 patient. In the control group, the site of VF was Th9 in 1, Th10 in 1, Th11 in 2, Th12 in 6, L1 in 3, L2 in 3, L3 in 1, and L4 in 1 patient. Fractures at the thoracolumbar junction were common in both groups.

Table 1. Baseline Characteristics of Patients With PA and Controls

Parameter	PA	Controls Participants	*P* Value
Male/female, No.	25/31	25/31	
Age, y	58.7 ± 11.1	59.4 ± 11.5	0.729
Height, cm	159.2 ± 10.5	159.2 ± 8.7	0.981
Weight, kg	62.9 ± 14.0	60.0 ± 19.9	0.387
BMI, kg/m^2	24.7 ± 4.0	23.5 ± 6.3	0.241
SBP, mm Hg	144 ± 21	131 ± 18	<0.001
DBP, mm Hg	85 ± 14	75 ± 13	<0.001
Creatinine, mg/dL	0.76 ± 0.36	0.71 ± 0.36	0.447
eGFR, mL/min/1.73 m^2	79 ± 22	82 ± 19	0.411
HbA1c, %	6.4 ± 1.6	5.5 ± 1.2	0.002
TC, mg/dL	189 ± 29	207 ± 37	0.006
TG, mg/dL	129 ± 71	95 ± 43	0.003
HDL-C, mg/dL	56 ± 14	64 ± 17	0.007
LDL-C, mg/dL	115 ± 28	125 ± 31	0.098
Ca, mg/dL	9.1 ± 0.4	9.2 ± 0.4	0.193
P, mg/dL	3.4 ± 0.6	3.3 ± 0.5	0.388
Intact PTH, pg/mL	56 ± 37	47 ± 26	0.171
uCa/uCr	0.16 ± 0.10	0.07 ± 0.05	<0.001
TRP, %	89 ± 8	89 ± 5	0.695
u-NTX, nMBCE/mM	50.8 ± 42.4	50.5 ± 95.1	0.982
PAC, pg/mL	199.4 ± 139.6	—	—
PRA, ng/mL/h	0.31 ± 0.22	—	—
ARR, pg/mL per ng mL^{-1} h^{-1}	1086 ± 1444	—	—
L-BMD, g/cm^2	0.926 ± 0.200	0.971 ± 0.183	0.251
T score	−0.52 ± 1.48	−1.00 ± 1.75	0.143
z score	0.22 ± 1.32	0.50 ± 1.19	0.267
FN-BMD, g/cm^2	0.681 ± 0.165	0.684 ± 0.130	0.907
T score	−1.19 ± 1.02	−1.24 ± 1.25	0.798
z score	−0.10 ± 1.14	0.03 ± 1.07	0.596
No. (%) of participants with VF	25 (45)	13 (23)	0.018
No. (%) of participants with multiple VFs	8 (14)	5 (9)	0.557
No. (%) of participants with severe VFs	13 (23)	2 (4)	0.004

Values are expressed as mean ± SD unless otherwise indicated.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Ca, serum calcium; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, serum phosphate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TRP, tubular reabsorption of phosphate; u-NTX, urine type I collagen cross-linked *N*-telopeptide.

Furthermore, 13 patients with PA and two controls had grade 2 or 3 VFs. Patients with PA showed severe fracture more frequently than controls (23.2% vs 3.6%, $P < 0.01$).

The VF rate was examined according to PA subtype (APA and IHA) in a small number of patients. Eight of 14 (57%) patients with APA had VFs, and five of 12 (42%) of patients with IHA had VFs. The VF rate did not significantly differ between these two subgroups.

Prevalence of non-VF

Non-VFs were present at the following sites in the PA group and control group. In the PA group, these included one patient each with a forearm, humerus, and wrist fracture and two patients with ankle fractures (total of five). In the control group, these included one patient each with a femoral neck, wrist, and rib fracture and two patients with ankle fractures (total of five). The non-VF rate did not differ between the two groups.

Associations of PAC, PRA, and ARR with various parameters

We analyzed simple correlations between PAC and various parameters, including BMD and bone turnover markers, in patients with PA. PAC showed significant positive correlations with DBP and uCa/uCr, and significant negative correlations with lumbar *z* and T scores. On the other hand, PRA and ARR did not correlate with any of the parameters examined (data not shown).

Comparison of various parameters between participants with and without VF in patients with PA

We compared demographic and biochemical parameters between PA patients with and without VF (Table 2). Patients with VF tended to be older than patients without VF. Other parameters, such as duration of hypertension, BMD, urine type I collagen cross-linked *N*-telopeptide, intact PTH, PAC, PRA, and ARR, were not significantly different between PA patients with and without VF. Femoral neck T and *z* scores of patients with grade 2 or 3 VFs were significantly lower than in patients without VF.

Association between PA and presence of VF

Multivariate logistic regression analyses adjusted for age, sex, and body mass index identified PA as a factor associated with the presence of VF (odds ratio, 3.13; 95% confidence interval, 1.30 to 7.51; $P < 0.05$). This association remained significant after further adjustment for systolic BP, DBP, HbA1c, triglycerides, and high-density lipoprotein cholesterol but not after adjustment for uCa/uCr ($P = 0.062$) and L- and FN-BMD ($P = 0.173$ and $P = 0.103$, respectively) (Table 3).

Discussion

This study revealed that fracture risk was increased in patients with PA. Furthermore, severity of fractures seemed higher in patients with PA because the ratio of patients with grade 2 or 3 VF was significantly higher in patients with PA than in controls. The VF rate in the control group in our study was high. Ethnic differences in the incidence of VF exist—namely, compared with Western populations, Japanese people have a higher incidence of VF (18). The VF rate in our control group, however, was slightly higher than fracture rates previously reported in Japanese people (19). One possible reason for this higher VF rate is that our control group included participants being screened for osteoporosis. However, the VF rate in the PA group was still significantly higher than in the control group. Our results are consistent with previous studies reporting that VFs tended to be more prevalent, and the prevalence of osteoporosis was higher in patients with PA than in those without PA (14). To our knowledge, this is the first report to find that the prevalence of VF and fracture severity was significantly higher in patients with PA than in age- and sex-matched controls. Moreover, our study revealed that PAC, PRA, and ARR showed no significant differences between PA patients with and without VF. Between the PA subtypes of APA and IHA, aldosterone production is higher in APA than in IHA. Although provided only as reference data because of the small number of patients in our study, comparison of the VF rate between the APA and IHA subgroups showed no significant differences. These results suggest that the degree of aldosterone production is not associated with fracture risk.

Previous reports about the renin-angiotensin-aldosterone system and bone metabolism have shown that angiotensin II excess accelerates osteoporosis by activating osteoclasts via the receptor activator of nuclear factor–κB ligand pathway (4, 5). However, under conditions where PAC levels are chronically elevated with concomitant suppression of angiotensin II and renin, bone fragility in patients with PA could not be explained by the effect of angiotensin II. Bone fragility in patients with PA may be induced by aldosterone itself. To our knowledge, no reports have clarified the direct effects of aldosterone on bone. Several reports have shown that mineralocorticoid receptors are observed in human osteoblasts, osteocytes, and osteoclasts (20, 21). Treatment with eplerenone, a specific blocker of mineralocorticoid receptors, ameliorated the decreased bone volume and cortical bone thinning caused by prednisolone *in vivo* (21). However, the direct effects of aldosterone on bone are poorly understood.

On the other hand, Chhokar *et al.* (22) reported that continuous administration of aldosterone to rats induced persistent rises in urinary calcium and elevations in PTH

Table 2. Comparison of Demographic and Biochemical Parameters, Bone Turnover Markers, and Bone Mineral Density Between Participants With and Without VF in Patients With PA

Characteristic	Without VF	With VF	*P* Value	With Severe VF (G2 or G3)	*P* Value
Number of participants	31	25		13	
Male/female, No. (%)	14 (45)/17 (55)	11 (44)/14 (56)	0.931	6 (46)/7 (54)	0.952
Age, y	56.2 ± 10.7	61.7 ± 10.9	0.068	62.2 ± 12.7	0.119
Duration of hypertension, y	10.7 ± 11.0	9.7 ± 8.3	0.729	9.8 ± 8.9	0.801
BMI, kg/m^2	24.6 ± 3.2	24.8 ± 4.9	0.795	25.8 ± 5.0	0.315
SBP, mm Hg	146 ± 17	142 ± 25	0.445	139 ± 18	0.246
DBP, mm Hg	86 ± 14	83 ± 15	0.476	82 ± 11	0.453
Creatinine, mg/dL	0.76 ± 0.31	0.77 ± 0.43	0.902	0.68 ± 0.09	0.221
eGFR, mL/min/1.73 m^2	79.3 ± 23.2	77.7 ± 20.0	0.784	79.1 ± 11.9	0.966
HbA1c, %	6.3 ± 1.5	6.4 ± 1.6	0.943	6.3 ± 1.0	0.963
TC, mg/dL	192 ± 34	185 ± 24	0.426	180 ± 17	0.244
TG, mg/dL	140 ± 67	116 ± 74	0.210	130 ± 98	0.687
HDL-C, mg/dL	54 ± 14	57 ± 14	0.416	53 ± 15	0.742
LDL-C, mg/dL	117 ± 32	113 ± 23	0.603	112 ± 22	0.602
Ca, mg/dL	9.1 ± 0.4	9.0 ± 0.3	0.415	9.0 ± 0.3	0.479
P, mg/dL	3.5 ± 0.6	3.3 ± 0.5	0.345	3.4 ± 0.5	0.670
Intact PTH, pg/mL	48.5 ± 22.4	64.3 ± 46.5	0.127	53.2 ± 15.1	0.517
uCa/uCr	0.16 ± 0.11	0.16 ± 0.08	0.977	0.19 ± 0.07	0.963
TRP, %	89.9 ± 5.9	88.2 ± 9.7	0.473	89.9 ± 4.7	0.994
u-NTX, nMBCE/mM	46.0 ± 20.6	56.3 ± 58.0	0.387	75.5 ± 77.1	0.216
PAC, pg/mL	194.6 ± 101.9	205.4 ± 177.8	0.775	239 ± 239	0.391
PRA, ng/mL/h	0.31 ± 0.19	0.31 ± 0.25	0.982	0.29 ± 0.25	0.686
ARR, pg/mL per ng mL^{-1} h^{-1}	1035 ± 929	1147 ± 1908	0.777	1541 ± 2572	0.345
L BMD, g/cm^2	0.949 ± 0.210	0.897 ± 0.187	0.406	0.874 ± 0.105	0.277
T score	−0.88 ± 1.90	−1.17 ± 1.57	0.589	−0.134 ± 0.92	0.335
z score	0.27 ± 1.50	0.14 ± 1.08	0.751	0.11 ± 0.95	0.744
FN-BMD, g/cm^2	0.712 ± 0.177	0.641 ± 0.143	0.167	0.598 ± 0.114	0.061
T score	−0.96 ± 1.34	−1.60 ± 1.05	0.096	−0.96 ± 0.82	0.030
z score	0.10 ± 1.35	−0.3 ± 0.78	0.215	−0.60 ± 0.21	0.024

Values are expressed as mean ± SD. *P* value was compared to without VF.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; Ca, serum calcium; G2, grade 2; G3, grade 3; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; P, serum phosphate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; TRP, tubular reabsorption of phosphate; u-NTX, urine type I collagen cross-linked *N*-telopeptide.

with a concomitant decrease of BMD and bone strength. An aldosterone infusion study in humans showed that aldosterone affects the parathyroid glands indirectly by reducing serum calcium levels (23). Actually, patients with PA showed higher levels of urinary calcium as well as lower serum calcium and BMD than patients with essential hypertension (12, 13). These results indicate that aldosterone excess increases fracture risk via urinary calcium excess through the effects of aldosterone on the distal tubule. In our study, PAC correlated positively with uCa/uCr, and the prevalence of VFs was significantly higher in patients with PA than in controls. This association became nonsignificant after additional adjustment for uCa/uCr. These findings suggest that aldosterone excess markedly affects calcium excretion, and this effect is partly associated with an increased risk of VF.

Table 3. Associations Between PA and Presence of VF

OR (95% CI)	*P* Value	Adjusted Variables
2.67 (1.18–6.02)	0.018	None
3.13 (1.30–7.51)	0.011	Model 1
3.17 (1.28–7.84)	0.013	Model 1 + SBP
2.94 (1.19–7.26)	0.020	Model 1 + DBP
3.40 (1.34–8.61)	0.010	Model 1 + HbA1c
3.55 (1.43–8.84)	0.006	Model 1 + TG
3.13 (1.27–7.73)	0.013	Model 1 + HDL-C
2.84 (0.95–8.46)	0.062	Model 1 + uCa/uCr
2.09 (0.73–6.03)	0.173	Model 1 + L-BMD
2.40 (0.84–6.90)	0.103	Model1 + FN-BMD

Model 1: adjusted for age, sex, and body mass index.

Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; TG, triglyceride.

Whether aldosterone affects PTH secretion directly via the parathyroid gland remains unclear. An *in vitro* study found the presence of MR messenger RNA and protein in normal and adenomatous human parathyroid tissues (23, 24). A recent study of 3105 individuals from the general population revealed higher serum PTH concentrations in individuals with a higher ARR than in those with a lower ARR (25). These findings suggest that aldosterone excess is associated with PTH elevation. Previous reports have presumed that higher urinary calcium excretion and

secondary increases in PTH induce bone loss (12, 13). However, in this study, there were no significant differences in PTH levels between patients with PA and controls. Moreover, PTH was not identified as a factor associated with VF (data not shown). Our results suggest that secondary elevations of PTH are unrelated to vertebral fragility in patients with PA. PTH excess mainly causes fragility of cortical bone. The absence of a difference in PTH is probably because our study focused on the vertebra, which are predominantly cancellous bone.

This study showed that comparison of patients with PA and controls revealed no significant differences in BMD values. Moreover, there were no differences in BMD at any site between PA patients with and without VFs. Our results suggest that PA may cause bone fragility attributed to the deterioration of bone quality. The rate of non-VFs in predominantly cortical bone sites did not differ between the PA group and control group in our study. The deterioration of bone quality in PA may involve deterioration in the microstructure of cancellous bone.

Hypertension is reportedly associated with bone loss (26). In this study, logistic regression analyses showed an association between PA and VF, and this association was still significant after additional adjustment for systolic BP and DBP. This suggests that patients with PA have a higher risk of VF, independent of BP.

PACs do not always reflect the severity of PA. On the other hand, longer disease duration is more likely associated with organ damage. Therefore, the duration of hypertension, which probably reflects the duration of PA, was compared with regard to VFs. However, hypertension duration did not differ between patients with and without VFs in our study. The possible reason for the absence of a difference may be because the history of hypertension duration given by patients did not reflect the true duration of their hypertension. Alternatively, a genome-wide association study searching for new genes involved in osteoporosis reported genes associated with the aldosterone signaling pathway (27). Therefore, the influence of excessive aldosterone may vary genetically in individuals and may play a role in this process.

One of the complications of PA is impaired glucose tolerance. A meta-analysis has shown diabetes mellitus as a risk factor for fracture (28), and we also reported that patients with type 2 diabetes have a higher risk of VF than those without diabetes (29). In the current study, HbA1c was higher in patients with PA than in controls, but PA was still a risk factor for VF after adjustment for HbA1c. Actually, the mean HbA1c in patients with PA was 6.4% in this study, which is somewhat lower than that of patients with diabetes, who had a higher risk of fracture (30). Therefore, it seems unlikely that bone fragility is caused by dysregulated glucose metabolism.

Some patients with PA have renal dysfunction. Chronic kidney disease is also a risk factor for VF (31). In the current study, renal function did not differ between those with and without PA, and PA represented a risk factor for VF after adjustment for renal function.

Several limitations of this study must be clarified. First, we diagnosed PA by suppression or stimulation tests without histopathological diagnoses after surgery. The diagnosis of PA in this study was based on biochemical studies. Currently available histopathological methods are insufficient to conclusively establish a diagnosis of PA. Second, the sample size in this study was small, and all participants were Japanese. Third, we did not evaluate concentrations of serum 25-hydroxyvitamin D. Patients with PA have been reported to have a higher prevalence of vitamin D deficiency (13). Finally, the conclusions of this study are weakened by the cross-sectional design. A longitudinal study is necessary to clarify the causal direction of these.

In conclusion, we identified PA as a risk factor for prevalent VF independent of BP. In addition, fracture severity was significantly higher in patients with PA than in age- and sex-matched controls.

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