Title

Primary aldosteronism as a risk factor for vertebral fracture

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Précis:

We found primary aldosteronism (PA) as a risk factor for prevalent vertebral fracture. Additionally, fracture severity was significantly higher in PA subjects than in age- and sex-matched controls.

Abstract

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.

Design and Patients

We enrolled 56 PA patients and 56 age- and sex-matched healthy individuals. Serum and urinary biological parameters, BMD, and presence of vertebral fractures (VFs) were evaluated in both groups. We compared parameters between PA and control subjects and performed multiple logistic regression analyses after adjustments for variables.

Results

Patients with PA showed higher systolic blood pressure (SBP) and diastolic blood pressure (DBP), higher hemoglobin (Hb)A1c and triglycerides, higher urinary calcium-to-creatinine ratio (uCa/uCr), and lower high-density lipoprotein cholesterol (HDL-C) than controls ($p < 0.05$, each). Prevalence of VFs was significantly higher in PA subjects

(44.6%) than in controls (23.2%, $p < 0.05$). PA patients 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, 1.30-7.51; $p < 0.05$). This association remained significant after further adjustment for SBP and DBP, HbA1c, triglycerides, and HDL-C, but not after adjustment for uCa/uCr 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 PA subjects than in age- and sex-matched controls.

Background

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 about 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) as compared with no VF at baseline was associated with a three-fold 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 (RAAS). Chronic stimulation of the RAAS 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.

Primary aldosteronism (PA) is the most common cause of secondary hypertension and is found in 6.0-9.5% of hypertensive patients (6-8). PA is associated with high mortality

and is known to cause damage to various organs (9). Milliez et al. reported that patients with PA have higher a prevalence of cardiovascular and cerebrovascular diseases (10). 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.

Subjects and methods

Subjects

We enrolled 56 consecutive patients (mean 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 subjects 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 (IV) 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 (IV) saline loading (2 L of 0.9% saline infused over 4 h); (2) persistence of ARR >200 at 90 min after administration of 50 mg captopril orally; (3) lack of PRA (2.0 ng/mL/h) after 40 mg of IV furosemide, in a standing position (15).

Bilateral adrenal venous sampling (AVS) was performed in 34 of the 56 PA patients, 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 (Hb)A1c (National Glycohemoglobin Standardization Program) was determined by high-performance liquid chromatography. Serum concentrations of albumin (Alb), creatinine (Cr), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), intact PTH, urine type I collagen cross-linked N-telopeptide (NTX, as a marker of bone resorption), urinary calcium-to-creatinine ratio (uCa/uCr), and percent tubular reabsorption of phosphate (%TRP) were evaluated in both groups by automated techniques at the central laboratory of our hospital. Urinary examinations were measured in 42 subjects with PA and in 56 healthy control subjects. Estimated glomerular filtration rate (eGFR) 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 RIA (SPAC-S Aldosterone Kit, TFB Inc., Tokyo, Japan; and Renin-RIA Renin kit "FR", TFB Inc, respectively) (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 (CVs) of measurement for BMD at L and FN were 0.9% and 1.7%, respectively. The Z-score is the number of standard deviations (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 normal 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 subjects. Anterior, central, and posterior heights of each of the 13 vertebral bodies from Th4-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 to the height of the nearest uncompressed vertebral body (17). We defined vertebral fractures as grades 1-3 according to the classification by Genant et al. (17). Grade 1 corresponds to a 20-25% reduction in at least one height (anterior, middle, or posterior) along the length of the same vertebra compared to the height of the nearest uncompressed vertebral body. Grade 2 corresponds to a 25-40% 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 subjects had any history of serious trauma.

All data are expressed as mean ± SD for each index. Significant differences between groups were determined using the chi-square 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 (ver. 19. IBM Corporation, Tokyo, Japan). Values of $p < 0.05$ were considered statistically significant.

Results

Baseline characteristics of subjects

Baseline characteristics of subjects are shown in Table 1. Each group contained 56 subjects. PA patients showed higher systolic BP (SBP) and diastolic BP (DBP), higher HbA1c and TG and lower HDL-C than controls ($p < 0.05$, each). Patients with PA showed a higher uCa/uCr than control subjects. Values for Cr, intact PTH, %TRP, u-NTX, L- and FN-BMD did not significantly differ between the groups.

Prevalence of vertebral fracture

VFs were found in 25 subjects with PA and in 13 controls. The prevalence of VF was significantly higher in PA subjects (44.6%) than in controls (23.2%, $p < 0.05$). In the PA group, one patient had a vertebral fracture that had already been diagnosed (clinical VF), and 24 patients had vertebral fractures 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 two, Th7 in five, Th8 in two, Th9 in two, Th10 in two, Th11 in five, Th12 in four, L1 in twelve, L2 in four, and L4 in one patient. In the control group, the site of VF was Th9 in one, Th10 in one, Th11 in two, Th12 in six, L1 in three, L2 in three, L3 in one, and L4 in one patient. Fractures at the thoracolumbar junction were common in both groups. Furthermore, 13 patients with PA and two controls had grade 2 or 3 VFs. PA patients 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%) APA patients had VFs, and five of 12 (42%) of IHA patients had VFs. The VF rate did not significantly differ between these two subgroups.

Prevalence of non-vertebral fracture

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 subjects with and without VF in patients with PA

We compared demographic and biochemical parameters between PA subjects 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, urinary NTX, intact PTH, PAC, PRA, and ARR, were not significantly different between PA subjects 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

(BMI) identified PA as a factor associated with the presence of VF (odds ratio, 3.13; 95% confidence interval, 1.30-7.51; $p < 0.05$). This association remained significant after further adjustment for SBP, DBP, HbA1c, TG, and HDL-C, but not after adjustment for uCa/uCr ($p=0.062$), 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 subjects with PA because the ratio of subjects with grade 2 or 3 VF was significantly higher in PA patients 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 subjects 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). This is the first report to find that the prevalence of VF and fracture severity were

243 significantly higher in PA subjects than in age- and sex-matched controls. Moreover, our
244 study revealed that PAC, PRA, and ARR showed no significant differences between PA
245 subjects with and without VF. Between the PA subtypes of APA and IHA, aldosterone
246 production is higher in APA than in IHA. Although provided only as reference data
247 because of the small number of patients in our study, comparison of the VF rate between
248 the APA and IHA subgroups showed no significant differences. These results suggest that
249 the degree of aldosterone production is not associated with fracture risk.

250 Previous reports about the RAAS and bone metabolism have shown that angiotensin II
251 excess accelerates osteoporosis by activating osteoclasts via the receptor activator of NF-
252 κB (RANK)-RANK Ligand (RANKL) pathway (4,5). However, under conditions where
253 PAC levels are chronically elevated with concomitant suppression of angiotensin II and
254 renin, bone fragility in patients with PA could not be explained by the effect of angiotensin
255 II. Bone fragility in patients with PA may be induced by aldosterone itself. No reports
256 have clarified the direct effects of aldosterone on bone. Several reports have shown that
257 mineralocorticoid receptors (MRs) are observed in human osteoblasts, osteocytes, and
258 osteoclasts (20,21). Treatment with eplerenone, a specific blocker of MR, ameliorated the
259 decreased bone volume and cortical bone thinning caused by prednisolone *in vivo* (21).
260 However, the direct effects of aldosterone on bone are poorly understood.

On the other hand, Chhokar et al. reported that continuous administration of aldosterone to rats induced persistent rises in urinary calcium and elevations in PTH with a concomitant decrease of BMD and bone strength (22). 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, plasma aldosterone concentration correlated positively with uCa/uCr, and the prevalence of VFs was significantly higher in PA subjects than in controls. This association became non-significant 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.

Whether aldosterone affects PTH secretion directly via the parathyroid gland or not remains unclear. An in vitro study found the presence of MR mRNA 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 subjects with a higher ARR than in subjects 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 PA and control subjects. 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 subjects with PA and controls revealed no significant differences in BMD values. Moreover, there were no differences in BMD at any site between PA subjects 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 SBP and DBP. This suggests that patients

297 with PA have a higher risk of VF, independent of BP.

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

308 One of the complications of PA is impaired glucose tolerance. A meta-analysis has
309 shown diabetes mellitus as a risk factor for fracture (28), and we also reported that patients
310 with type 2 diabetes have a higher risk of VF than those without diabetes (29). In the
311 present study, HbA1c was higher in PA subjects than in controls, but PA was still a risk
312 factor for VF after adjustment for HbA1c. Actually, the mean HbA1c in PA subjects was
313 6.4% in this study, which is somewhat lower than that of diabetes patients who had a
314 higher risk of fracture (30).Therefore, it seems unlikely that bone fragility is caused by

dysregulated glucose metabolism.

Some PA patients have renal dysfunction. Chronic kidney disease is also a risk factor for VF (31). In the present study, renal function did not differ between subjects 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 subjects were Japanese. Third, we did not evaluate concentrations of serum 25-hydroxy-vitamin D. PA patients 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 blood pressure. Additionally, fracture severity was significantly higher in PA subjects than in age- and sex-matched controls.

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