Endocrine Journal 2025, 72 (12), 1299-1307. doi:10.1507/endocrj.EJ24-0649

ORIGINAL

Primary aldosteronism increases the risk of urinary stones

Itsuko Asayama, Masakazu Notsu, Miwa Ota, Masahiro Yamamoto and Keizo Kanasaki

Department of Internal Medicine 1, Shimane University Faculty of Medicine, Izumo, Japan

Abstract. Urinary calcium excretion increases in patients with primary aldosteronism (PA) and is associated with higher prevalence of renal stones formations. However, it remains unclear whether the prevalence of urinary stones is higher in patients with PA than in those with nonfunctioning adrenal tumors (NF). We aimed to investigate whether the prevalence of urinary stones is higher in patients with PA than in those without PA. The study was conducted between April 2006 and March 2021. We enrolled 140 PA and 144 NF patients. Urinary stones and renal calcifications were evaluated through patient history or CT findings. Serum and urinary parameters, presence of urinary stones and/or calcifications, were evaluated in both groups. Logistic regression analyses were performed, adjusting for relevant variables. Compared to the NF group, the PA group was younger, and displayed significantly higher blood pressure, aldosterone-rennin ratio, eGFR, serum Na, urinary Ca excretion, and intact PTH levels. In contrast, serum K, Ca and creatinine levels were lower in PA group. PA patients also demonstrated a lower prevalence of diabetes, smaller adrenal tumor size, and a lower percentage of smokers compared to the NF group. Urinary stones and renal calcifications were significantly more frequent in the PA group. Logistic regression confirmed PA as an independent risk factor for urinary stones, regardless of age, sex, BMI, eGFR, serum and urinary calcium, and intact PTH. PA is an independent risk factor for urinary stones and renal calcifications.

Key words: Primary aldosteronism, Urinary stone, Renal calcification, Non-functioning adrenal tumor

Background

Urinary stones and nephrocalcinosis are common problems with an increasing global prevalence [1-3]. A significant challenge in managing urinary stones is their high recurrence rate, with approximately 50% of patients experiencing recurrence within five years [4]. Various genetic and regional factors, as well as metabolic abnormalities, contribute to the development and prevalence of urinary stones. Calcium (Ca) oxalate is the most common urinary stone component in Japan as well as in many other regions [5]. Although disability-adjusted life years and age-standardized death rates decrease annually, urinary stones remain a significant global public health issue [6]. It can cause severe acute colic pain and lead to complications, such as pyelonephritis, acute kidney injury, and chronic kidney disease [7]. Therefore, it is important to prevent the development of urinary stones and nephrocalcinosis. The risk factors associated with urinary stone formation include environmental, lifestyle, and dietary factors. In addition to identifying risk factors, it is necessary to understand the diseases that cause urinary stones and to focus on preventing stone formation.

Primary aldosteronism (PA) is an endocrinological disorders prevalent worldwide. Recent next-generation sequencing analyses identified aldosterone driver somatic mutations that contribute to inappropriate aldosterone production [8, 9]. PA can be diagnosed in at least 5–10% of patients with hypertension; however, many cases remain unrecognized. Moreover, the actual prevalence of PA may be higher than current estimated prevalence [10, 11]. Screening for PA is crucial for simple reasons: to prevent and manage complications such as cardiovascular and renal diseases, which occur more frequently in patients with PA than in those with essential hypertension. A Japanese multicenter cohort study reported that the prevalence of cardiovascular diseases, including ischemic heart disease, heart failure, and stroke, was higher in patients with PA compared to patients with essential hypertension [12].

PA affects Ca and bone metabolism. Patients with PA have a higher urinary Ca excretion than those with essential hypertension [13]. Increased urinary Ca excretion, followed by secondary hyperparathyroidism, affects bone

Submitted Dec. 8, 2024; Accepted Jul. 2, 2025 as EJ24-0649
Released online in J-STAGE as advance publication Aug. 19, 2025
Correspondence to: Masakazu Notsu, Department of Internal Medicine 1, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane, 693-8501, Japan.
E-mail: mnotsu25@med.shimane-u.ac.jp

metabolism in patients with PA. We and others have demonstrated that the prevalence of fractures and osteoporosis is significantly higher in patients with PA than in controls [14]. Increased urinary Ca excretion may contribute to the development of urinary stones. Several case reports have reported that urinary stones are associated with PA pathology. Recently, cohort studies have revealed a link between PA and the development of both renal and bladder stones [15, 16]. However, the underlying mechanisms and risk factors of urinary stones in patients with PA remain unclear. Therefore, we investigated whether the prevalence of urinary stones is higher in patients with PA than in those without PA and aimed to clarify the factors associated with this increased risk.

Subjects and Methods

Subjects

We enrolled 140 patients with PA (mean ± standard deviation (SD) age, 56.9 ± 11.5 years; men, 47.9%) and 144 patients with non-functioning adrenal tumors (NF) (age, 64.7 ± 11.8 years; men, 56.9%), who were diagnosed at our institution between April 2006 and March 2021. Patients taking medications known to influence Ca metabolism, such as vitamin D and glucocorticoids were excluded. Additionally, patients with conditions affecting urinary Ca excretion or parathyroid function, as well as those with severely impaired renal function (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), were excluded. The study was approved by the Research Ethics Committee of Shimane University Faculty of Medicine (No. 20220215-1). Because this study involved the retrospective collection of data from our routine clinical practice, formal written informed consent was not required. Instead, we posted information about the research project on our department's homepage to allow participants to opt out of the study.

Clinical data collection

Height and body weight were measured during hospitalization. The body mass index (BMI) was calculated. Hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥80 mmHg, or the use of antihypertensive medication. Participants were interviewed regarding background characteristics, such as smoking, alcohol consumption, and medical history. Blood and urine samples were collected for further analyses. Hemoglobin A1c (HbA1c) levels, standardized by the National Glycohemoglobin Standardization Program, were determined using high-performance liquid chromatography. Serum concentrations of albumin (Alb), creatinine (Cr), eGFR, uric acid (UA), sodium (Na), potassium (K), magnesium (Mg), Ca, phosphate (P), intact parathyroid hormone (PTH), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), adrenocorticotropic hormone (ACTH), cortisol, urinary Ca (uCa), urinary Ca-to-Cr ratio (uCa/uCr), and percent tubular reabsorption of phosphate (%TRP), were evaluated in both groups using automated techniques in the central laboratory of our hospital. The eGFR was calculated using the equation proposed by the Modification of Diet in Renal Disease Study with modified coefficients for the Japanese population.

Diagnosis of PA and NF

Patients were screened for PA using the plasma aldosterone concentration (PAC) (pg/mL) to plasma renin activity (PRA) (ng/mL/h) ratio, known as the aldosterone-to-renin ratio (ARR), with a cut off value of 200. PAC and PRA were collected from the patients early in the morning after fasting and resting in a recumbent position. PAC and PRA were measured using radio immunoassay (SPAC-S Aldosterone Kit and Renin-RIA Renin kit "FR"; TFB, Inc, Tokyo, Japan). PRA was measured through the generation of angiotensin I. PAC was initially measured by RIA, but from 2020 onwards, the measurement was performed using the CLEIA method (Lumipulse Presto Aldosterone; Fujirebio Inc, Kanagawa Japan). PA was diagnosed according to guidelines of the Japan Endocrine Society [17]. PA was confirmed if one or more of the following confirmatory tests were positive: 1) lack of PAC suppression after intravenous saline loading (2 L of 0.9% saline infused over 4 h); 2) persistence of ARR >200 at 90 min after oral administration of 50 mg captopril; or 3) lack of PRA increase (>2.0 ng/mL/h) after intravenous administration of 40 mg furosemide in a standing position. NF is defined as an adrenal tumor without autonomous hormonal hypersecretion. PA was excluded if screening tests conducted on two different occasions both yielded negative results in the NF group.

Autonomous cortisol secretion was ruled out by assessing diurnal cortisol variation and a 1 mg dexamethasone suppression test. In the PA group, a 1 mg dexamethasone suppression test was performed in 67 of 140 cases. Of these, six cases showed cortisol levels that were not suppressed below 1.8 μg/dL, indicating mild autonomous cortisol secretion (MACS). In the NF group, the 1 mg dexamethasone suppression test was performed in 83 of 144 cases. Out of 83 cases, nine met the criteria for MACS. All 284 patients underwent abdominal computed tomography and adrenal tumor size was measured.

Diagnosis of aldosterone-producing adenomas (APA) and non-APA

The PA, APA and non-APA subtypes, were diagnosed based on lateralized aldosterone hypersecretion as

demonstrated by adrenal venous sampling (AVS). Among the 140 patients in the PA group, AVS was appropriately performed in 38, of which 17 were diagnosed with APA and 21 with bilateral non-APA. In cases in which AVS was not performed, many patients did not exhibit clinical findings strongly suggestive of APA, such as hypokalemia, and were instead suspected to have bilateral disease. Additionally, a substantial proportion of patients declined AVS after being informed of the treatment options and deciding to refuse surgery.

Diagnosis of urinary stone and renal calcification

The presence or absence of urinary stones was determined by interviewing the patients about their history of urinary stones. Renal calcification was diagnosed using abdominal CT scan. The size and location of the renal calcifications were determined.

Statistical analysis

We compared the parameters between the PA and NF subjects and conducted multiple logistic regression analyses after adjusting for the variables. The association between the prevalence of urinary stones and nephrocalcinosis and their related factors, was analyzed using logistic regression analysis. All data are expressed as mean ± SD for each index. Significant differences between groups were determined using the χ^2 test and unpaired *t*-tests. Multiple logistic regression analyses were performed after adjusting for the variables presented in the tables. Statistical analyses were performed using SPSS software (version 19; IBM Corporation, Armonk, NY, USA). Statistical significance was set at $p < 0.05$.

Figure creation

For the creation of the figure in the graphical abstract, we used BioRender.

Results

The PA group (56.9 ± 11.5 years old) was younger than the NF group (64.7 ± 11.8 years old), and displayed significantly higher blood pressure, aldosterone-rennin ratio, eGFR, urinary Ca excretion, levels of serum Na and, intact PTH, and significantly lower levels of serum K, Ca, and Cr (Table 1). The PA group also displayed a lower prevalence of diabetes, smaller adrenal tumors, and a lower percentage of smokers than the NF group. The prevalence of urinary stones (PA group [10.7%], NF group [3.5%]) and renal calcification (PA group [17.2%], NF group [6.3%]) were significantly higher in the PA group.

Logistic regression analysis showed that PA was associated with the presence or history of urinary stones (OR 3.34, 95% CI: 1.18–9.44, $p = 0.023$). This association remained significant after adjusting for age, sex, BMI, eGFR, levels of serum Mg, serum Ca, and intact PTH levels, and urinary Ca excretion (Table 2). In the PA group, patients with urinary stones had a significantly higher proportion of males, higher serum Ca levels, larger adrenal tumors, and lower serum P and Mg levels than those without urinary stones (Table 3).

Logistic regression analysis revealed that PA was also associated with the prevalence of renal calcification (OR 3.13, 95% CI: 1.40–7.00, $p = 0.005$). This association remained significant after adjusting for age, sex, BMI, eGFR, prevalence of diabetes and smoking, serum levels of K, Ca, Mg, and intact PTH, as well as urinary Ca excretion (Table 4). Compared to subjects with PA without renal calcification, those with renal calcification had a significantly higher rate of smoking, higher serum Na levels, and lower serum K levels (Table 5).

The prevalence of urinary stones was 0% and 28.6% in the APA and non-APA groups, respectively, with a significantly higher prevalence observed in the non-APA group. The prevalence of renal calcification was 17.6% in the APA group and 28.6% in the non-APA group, with no significant difference (Table 6).

Discussion

In the current study, we demonstrated that PA was a risk factor for both urinary stones and renal calcification (Graphical Abstract). This association was independent of various physiological and biological parameters, including age, sex, BMI, eGFR, serum levels of Mg, Ca, intact PTH and urinary Ca excretion.

Recent studies have explored the relationship among PA, urolithiasis, and bladder stones. Using the Cox proportional hazards model, a nationwide cohort study from Taiwan showed that PA significantly contributed to the formation of bladder stones [16]. Another study involving 610 patients who tested positive on PA screening reported a higher incidence of renal stones in patients with PA than in the general population. They also found that stone size in patients with PA were larger than that in patients with essential hypertension [15]. More recently, other groups have investigated the association between colic events and urolithiasis in patients with different subtypes of PA [18]. They found that acute colic events and urolithiasis were more prevalent in patients with APA than in those with bilateral aldosterone production. These reports suggest that aldosterone production is associated with renal or bladder stones formation. However, the underlying mechanisms that explain the link between aldosterone production and urinary tract stone formation remain unclear.

Table 1 Baseline characteristics of patients with PA and NF

Parameters (Unit)	PA (n = 140)	NF (n = 144)	p Value
Male/female (No.)	61/79	82/62	0.024
Age (years old)	56.9 ± 11.5	64.7 ± 11.8	<0.001
Height (cm)	160 ± 9.9	161 ± 10.0	0.607
Weight (kg)	63.8 ± 14.1	64.4 ± 15.2	0.753
BMI (kg/m^2)	24.7 ± 4.1	24.7 ± 4.7	0.954
SBP (mmHg)	144 ± 19	132 ± 18	<0.001
DBP (mmHg)	87 ± 13	78 ± 14	<0.001
Alb (g/dL)	4.3 ± 0.4	4.2 ± 0.4	0.155
Cr (mg/dL)	0.70 ± 0.2	0.75 ± 0.2	0.016
eGFR (mL/min/1.73 m^2)	81.3 ± 17.3	76.7 ± 20.2	0.039
UA (mg/dL)	5.21 ± 1.2	5.59 ± 3.5	0.236
Na (mmol/L)	141.4 ± 2.3	140.8 ± 2.2	0.028
K (mmol/L)	3.9 ± 0.4	4.1 ± 0.4	<0.001
Mg (mg/dL)	2.11 ± 0.21	2.08 ± 0.28	0.406
Ca (mg/dL)	9.04 ± 0.31	9.15 ± 0.38	0.007
P (mg/dL)	3.44 ± 0.56	3.47 ± 0.75	0.681
Intact PTH (pg/mL)	56 ± 22	48 ± 19	0.002
HbA1c (%)	6.4 ± 4.7	7.0 ± 1.9	0.236
TG (mg/dL)	125 ± 67	122 ± 71	0.730
HDL-C (mg/dL)	56 ± 15	56 ± 18	0.697
LDL-C (mg/dL)	115 ± 31	113 ± 32	0.438
Urine volume (mL/day)	1,800 ± 660	1,800 ± 700	0.845
Urinary Ca excretion (mg/day)	145 ± 100	106 ± 91	<0.001
uCa/uCr	0.15 ± 0.09	0.12 ± 0.08	0.008
TRP (%)	89 ± 4.2	89 ± 6.0	0.584
PAC (pg/mL)	172 ± 110	105 ± 55	<0.001
PRA (ng/mL/h)	0.4 ± 0.9	2.3 ± 4.0	<0.001
ARR	702 ± 705	109 ± 88	<0.001
ACTH (pg/mL)	25 ± 13	25 ± 14	0.881
Cortisol (μg/dL)	12.2 ± 3.6	12.3 ± 3.7	0.958
Adrenal tumor (%)	72 (51)	144 (100)	—
Adrenal tumor size (mm)	14.5 ± 8.8	17.5 ± 9.9	0.036
Urinary stone (%)	15/140 (11)	5/144 (3)	0.017
Multiple urinary stone (%)	6/140 (4)	0/144 (0)	0.012
Renal calcification (%)	24/140 (17)	9/144 (6)	0.004
Smoking (%)	33/140 (24)	57/144 (40)	0.002
Drinking (%)	45/140 (32)	48/144 (34)	0.735
Hypertension (%)	134/140 (96)	116/144 (81)	<0.001
Anti-hypertensive drug (%)	97/140 (69)	77/144 (54)	0.006
Classes of Anti-hypertensive drugs			
CCB (%)/ARB (%)/ACEi (%)	68.6/8.6/2.9	43.1/21.5/5.6	—
DIU (%)/α-B (%)/β-B (%)	3.6/7.9/2.1	2.1/1.4/2.1	
Diabetes (%)	32/140 (23)	60/144 (42)	<0.001
Myocardial infarction (%)	3/140 (2)	6/144 (4)	0.330
Cerebral infarction (%)	6/140 (4)	8/144 (6)	0.012

Note: Values are expressed as mean ± SD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, urinary acid; Na, serum sodium; K, serum potassium; Mg, serum magnesium; Ca, serum calcium; P, serum phosphate; PTH, parathyroid hormone; HbA1c, Hemoglobin A1c; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; uCa/uCr, urinary calcium-to-creatinine ratio; TRP, tubular reabsorption of phosphate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone renin ratio; ACTH, adrenocorticotropic hormone; CCB, Calcium Channel Blocker; ARB, Angiotensin II Receptor Blocker; ACEi, Angiotensin-Converting Enzyme Inhibitor; DIU, Diuretics; α-B, α-blocker; β-B; β-blocker.

Table 2 Associations between PA and urinary stone

Adjusted Variables	OR (95% CI)	*p* Value
None	3.34 (1.18–9.44)	0.023
Model 1	5.73 (1.70–19.3)	0.005
Model 1 + K	4.99 (1.43–17.4)	0.012
Model 1 + Mg	6.07 (1.69–21.9)	0.006
Model 1 + Ca	6.54 (1.90–22.5)	0.003
Model 1 + intact PTH	5.15 (1.50–17.7)	0.009
Model 1 + uCa	5.53 (1.63–18.8)	0.006

Model 1: adjusted for age, sex, BMI, blood pressure, eGFR, diabetes, smoking.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; K, serum potassium; Mg, serum magnesium; Ca, serum calcium; PTH, parathyroid hormone; uCa, urinary calcium excretion

Table 3 Comparison of clinical parameters between PA patients with and without urinary stones

Parameters (Unit)	Without urinary stones (*n* = 125)	With urinary stones (*n* = 15)	*p* Value
Male/female (No.)	50/75	11/4	0.014
Age (years old)	57.1 ± 11.5	55.0 ± 11.4	0.497
BMI (kg/m^2)	24.6 ± 4.1	25.7 ± 4.2	0.307
SBP (mmHg)	144 ± 20	141 ± 15	0.551
DBP (mmHg)	88 ± 13	82 ± 12	0.146
Alb (g/dL)	4.3 ± 0.3	4.1 ± 0.6	0.065
Cr (mg/dL)	0.70 ± 0.16	0.73 ± 0.21	0.431
eGFR (mL/min/1.73 m^2)	81 ± 17	86 ± 22	0.267
UA (mg/dL)	5.2 ± 1.2	5.3 ± 1.5	0.867
Na (mmol/L)	141.1 ± 2.3	141 ± 2.1	0.979
K (mmol/L)	3.9 ± 0.4	3.8 ± 0.4	0.210
Mg (mg/dL)	2.12 ± 0.20	2.00 ± 0.26	0.049
Ca (mg/dL)	9.02 ± 0.30	9.19 ± 0.30	0.041
P (mg/dL)	3.48 ± 0.54	3.09 ± 0.62	0.009
Intact PTH (pg/mL)	55 ± 21	60 ± 30	0.460
HbA1c (%)	6.4 ± 5.0	6.8 ± 2.2	0.612
TG (mg/dL)	123 ± 66	135 ± 73	0.538
HDL-C (mg/dL)	57 ± 15	54 ± 14	0.441
LDL-C (mg/dL)	115 ± 31	117 ± 34	0.808
Urine volume (mL/day)	1,800 ± 670	1,770 ± 550	0.849
Urinary Ca excretion (mg/day)	143 ± 102	160 ± 83	0.576
uCa/uCr	0.15 ± 0.009	0.14 ± 0.05	0.520
TRP (%)	89 ± 4.2	87 ± 4.4	0.111
PAC (pg/mL)	171 ± 114	181 ± 64	0.727
PRA (ng/mL/h)	0.4 ± 0.9	0.5 ± 0.3	0.698
ARR	728 ± 734	482 ± 349	0.203
ACTH (pg/mL)	25 ± 14	26 ± 8	0.608
Cortisol (μg/dL)	12.2 ± 3.7	13.0 ± 2.6	0.444
Adrenal tumor size (mm)	14 ± 8	23 ± 13	0.012
Smoking (%)	27 (22)	6 (40)	0.113
Drinking (%)	38 (30)	7 (47)	0.202
Diabetes (%)	26 (21)	9 (60)	0.094
Myocardial infarction (%)	2 (2)	1 (7)	0.200
Cerebral infarction (%)	6 (5)	0 (0)	0.386

Note: Values are expressed as mean ± SD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, urinary acid; Na, serum sodium; K, serum potassium; Mg, serum magnesium; Ca, serum calcium; P, serum phosphate; PTH, parathyroid hormone; HbA1c, Hemoglobin A1c; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; uCa/uCr, urinary calcium-to-creatinine ratio; TRP, tubular reabsorption of phosphate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone renin ratio; ACTH, adrenocorticotropic hormone.

Table 4 Associations between PA and renal calcification

Adjusted Variables	OR (95% CI)	*p* Value
None	3.13 (1.40–7.00)	0.005
Model 1	4.43 (1.75–11.2)	0.002
Model 1 + K	3.54 (1.37–9.18)	0.009
Model 1 + Mg	4.31 (1.69–11.0)	0.002
Model 1 + Ca	4.46 (1.75–11.4)	0.002
Model 1 + intact PTH	3.60 (1.38–9.40)	0.009
Model 1 + uCa	4.39 (1.73–11.2)	0.002

Model 1: adjusted for age, sex, body mass index, blood pressure, eGFR, diabetes, smoking.

Table 5 Comparison of clinical parameters between PA patients with and without renal calcification

Parameters (Unit)	Without renal calcification (n = 115)	With renal calcification (n = 25)	*p* Value
Male/female (No.)	51/64	10/15	0.810
Age (years old)	56.4 ± 12.0	58.9 ± 8.6	0.236
BMI (kg/m^2)	24.6 ± 4.3	25.0 ± 3.2	0.703
SBP (mmHg)	144 ± 20	146 ± 18	0.618
DBP (mmHg)	87 ± 13	87 ± 12	0.983
Alb (g/dL)	4.3 ± 0.3	4.2 ± 0.5	0.307
Cr (mg/dL)	0.69 ± 0.15	0.70 ± 0.23	0.813
eGFR (mL/min/1.73 m^2)	81.2 ± 15.5	82.3 ± 24.6	0.846
UA (mg/dL)	5.22 ± 1.22	5.09 ± 1.34	0.650
Na (mmol/L)	141.2 ± 2.26	142.3 ± 2.11	0.043
K (mmol/L)	3.92 ± 0.40	3.72 ± 0.48	0.031
Mg (mg/dL)	2.12 ± 0.21	2.06 ± 0.18	0.164
Ca (mg/dL)	9.03 ± 0.30	9.08 ± 0.33	0.458
P (mg/dL)	3.50 ± 0.54	3.28 ± 0.64	0.135
Intact PTH (pg/mL)	54 ± 21	63 ± 25	0.088
HbA1c (%)	6.5 ± 5.2	6.3 ± 1.9	0.840
TG (mg/dL)	124 ± 68	131 ± 59	0.631
HDL-C (mg/dL)	56 ± 14	59 ± 17	0.283
LDL-C (mg/dL)	117 ± 31	111 ± 30	0.385
Urine volume (mL/day)	1,840 ± 655	1,560 ± 630	0.090
Urinary Ca excretion (mg/day)	147 ± 100	131 ± 101	0.493
uCa/uCr	0.15 ± 0.08	0.15 ± 0.09	0.896
TRP (%)	89 ± 4.0	89 ± 5.5	0.913
PAC (pg/mL)	173 ± 116	168 ± 73	0.843
PRA (ng/mL/h)	0.45 ± 1.00	0.35 ± 0.22	0.603
ARR	710 ± 750	667 ± 455	0.789
ACTH (pg/mL)	25 ± 13	26 ± 13	0.666
Cortisol (μg/dL)	12.5 ± 3.4	11.8 ± 3.5	0.376
Adrenal tumor size (mm)	14 ± 8	16 ± 11	0.471
Smoking (%)	23 (20)	10 (42)	0.023
Drinking (%)	37 (32)	8 (33)	0.912
Diabetes (%)	27 (23)	5 (21)	0.780
Myocardial infarction (%)	1 (1)	2 (8)	0.077
Cerebral infarction (%)	5 (4)	1 (4)	0.724

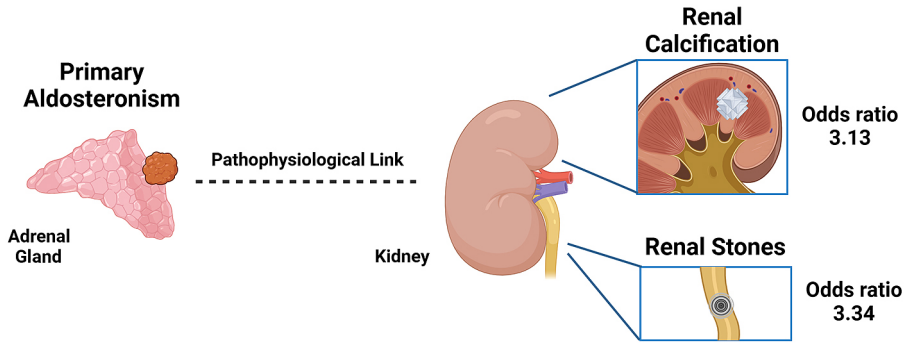
Note: Values are expressed as mean ± SD.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Alb, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, urinary acid; Na, serum sodium; K, serum potassium; Mg, serum magnesium; Ca, serum calcium; P, serum phosphate; PTH, parathyroid hormone; HbA1c, Hemoglobin A1c; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; uCa/uCr, urinary calcium-to-creatinine ratio; TRP, tubular reabsorption of phosphate; PAC, plasma aldosterone concentration; PRA, plasma renin activity; ARR, aldosterone renin ratio; ACTH, adrenocorticotropic hormone.

Table 6 Comparison of the frequency of urolithiasis and renal calcification between APA and non-APA subtypes of PA

Parameters (Unit)	APA (n = 17)	non-APA (n = 21)	p Value
Male/female (No.)	9/8	10/11	0.744
Age (years old)	54.8 ± 10.4	54.1 ± 9.7	0.841
BMI (kg/m^2)	23.5 ± 3.2	25.6 ± 4.5	0.113
BMI ≥25.0 kg/m^2	5/17 (29.4)	12/21 (57.1)	0.087
Urinary stone (%)	0/17 (0)	6/21 (29)	0.016
Multiple urinary stone (%)	0/17 (0)	3/21 (14)	0.104
Renal calcification (%)	3/17 (18)	6/21 (29)	0.431

Abbreviations: APA, aldosterone producing adenoma; BMI, body mass index



Graphical Abstract This study aimed to investigate whether the prevalence of urinary stones is higher in patients with PA than in those without PA and to identify factors contributing to this risk. Compared to the NF group, urinary stones and renal calcifications were significantly more frequent in the PA group. Logistic regression confirmed PA as an independent risk factor for urinary stones, regardless of age, sex, BMI, eGFR, serum and urinary calcium, and intact PTH.

Multiple factors contribute to the pathogenesis of stone formation in the urinary tract [19]. Among these factors, increased urinary Ca excretion is a well-known contributor and has been observed in the pathology of PA. Meta-analyses have indicated that increased urinary Ca levels are a characteristic of patients with PA [13]. In the present study, daily urinary Ca excretion and the urinary Ca/Cr ratio were significantly higher in the PA group than in the NF group. Although this mechanism appears plausible as a factor in urinary stone formation, our study found that PA was associated with a higher risk of urinary stones and renal calcifications, independent of urinary Ca excretion. Hypocitraturia and decreased urine pH are common pathologies of urolithiasis and PA [20]. However, these factors could not be analyzed in our study. Compared to those without a history of urinary stones, patients with PA with urinary stones had a significantly higher proportion of males and lower serum Mg levels. Similarly, among those with renal calcification, patients with PA with renal calcification had a significantly higher smoking rate. Male sex, decreased urine Mg levels, and smoking habits are recognized risk factors for urinary stone formation [21]. However, logistic regression analysis showed that none of these factors emerged as independent risk factors for urinary stones or renal calcification. This suggests that PA and excessive production of aldosterone may be the primary contributors to renal stone and renal calcification.

In the present study, we found no significant differences in aldosterone concentrations or aldosterone-to-renin ratios based on the presence or absence of a history of urinary tract stones or renal calcification. Furthermore, the prevalence of urine stones was significantly lower in the APA group than that in the non-APA group. A recent prospective cohort study from a single center revealed that patients with APA had a higher prevalence of urolithiasis than those without APA. In addition, acute colic pain was more common in the APA group than in the non-APA group [18]. Conversely, another study reported differences in stone size and Hounsfield units between patients with bilateral adrenal hyperplasia (BAH) and those with APA [15]. Patients with BAH tended to be obese despite having a lower PAC than those with APA. Obesity-related factors likely contribute to the pathogenesis of

BAH [22]. Factors associated with obesity, such as increased levels of Ca and Na, oxalic acid excretion, and low urinary pH, are known risk factors for urinary stones, including UA stones [23]. In this regard, metabolic syndrome increases the risk of urinary stones [24]. These previous reports, along with our findings, suggest that various conditions known to increase the risk of urinary stones may coexist in patients with PA. Furthermore, the high prevalence of urinary stones in PA cases without APA implies that classic risk factors for urinary stones—particularly those associated with obesity and metabolic syndrome—are likely to exacerbate stone risk in patients with bilateral PA.

Our study had several limitations, including the retrospective design, single center setting, and small sample size. In addition, the proportion of patients with diabetes was significantly higher in the NF group. As this was a single-center retrospective study conducted in a department specializing in endocrinology and metabolism, some cases of NF may have been incidentally identified during the evaluation of patients with diabetes. This study was based on a consecutive case series over a defined period, and significant differences were observed between the PA and control groups in variables such as sex, age, blood pressure, intact PTH levels, and urinary calcium excretions. Each of these factors, including diabetes mellitus, may influence the development of urolithiasis. In this study, these variables were included as covariates in the analysis to adjust for their potential impact. Since the 1 mg dexamethasone suppression test was not performed in several cases in both the PA and non-PA groups, these groups may include cases in which MACS cannot be excluded. Furthermore, we could not measure several clinical indicators related to the pathology of PA that may contribute to the development of urinary stones, such as urinary oxalic acid and pH. A significant number of patients did not undergo subtype classification into APA or non-APA because AVS was not performed in many cases that lacked the characteristic findings of APA, such as refractory hypertension or hypokalemia, and instead were suggestive of bilateral disease.

Conclusion

In the current study, we demonstrated that PA was a risk factor for both urinary stones and renal calcification. This association was independent of various physiological and biological parameters, including age, sex, BMI, eGFR, serum levels of Mg, Ca, and intact PTH, as well as urinary Ca excretion.

Conflict of Interest (COI)

The authors declare no conflict of interest associated with this manuscript.

Disclosure

Keizo Kanasaki is a member of *Endocrine Journal*'s Editorial Board.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Karagiannis A, Skolarikos A, Alexandrescu E, Basic D, Geavlete P, *et al.* (2017) Epidemiologic study of urolithiasis in seven countries of South-Eastern Europe: S.E.G.U.R. 1 study. *Arch Ital Urol Androl* 89: 173–177.
2. Liu Y, Chen Y, Liao B, Luo D, Wang K, *et al.* (2018) Epidemiology of urolithiasis in Asia. *Asian J Urol* 5: 205–214.
3. Chewcharat A, Curhan G (2021) Trends in the prevalence of kidney stones in the United States from 2007 to 2016. *Urolithiasis* 49: 27–39.
4. Ferraro PM, Curhan GC, D'Addessi A, Gambaro G (2017) Risk of recurrence of idiopathic calcium kidney stones: analysis of data from the literature. *J Nephrol* 30: 227–233.
5. Yasui T, Iguchi M, Suzuki S, Okada A, Itoh Y, *et al.* (2008) Prevalence and epidemiologic characteristics of lower urinary tract stones in Japan. *Urology* 72: 1001–1005.
6. Qian X, Wan J, Xu J, Liu C, Zhong M, *et al.* (2022) Epidemiological trends of urolithiasis at the global, regional, and national levels: a population-based study. *Int J Clin Pract* 2022: 6807203.
7. Moe OW (2006) Kidney stones: pathophysiology and medical management. *Lancet* 367: 333–344.
8. Choi M, Scholl UI, Yue P, Björklund P, Zhao B, *et al.* (2011) K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. *Science* 331: 768–772.
9. Nanba K, Baker JE, Blinder AR, Bick NR, Liu CJ, *et al.* (2022) Histopathology and genetic causes of primary aldosteronism in young adults. *J Clin Endocrinol Metab* 107: 2473–2482.
10. Baudrand R, Guarda FJ, Fardella C, Hundemer G, Brown J, *et al.* (2017) Continuum of renin-independent aldosteronism in normotension. *Hypertension* 69: 950–956.

11. Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, *et al.* (2020) The unrecognized prevalence of primary aldosteronism: a cross-sectional study. *Ann Intern Med* 173: 10–20.
12. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, *et al.* (2018) Prevalence of cardiovascular disease and its risk factors in primary aldosteronism: a multicenter study in Japan. *Hypertension* 71: 530–537.
13. Shi S, Lu C, Tian H, Ren Y, Chen T (2020) Primary aldosteronism and bone metabolism: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)* 11: 574151.
14. Notsu M, Yamauchi M, Yamamoto M, Nawata K, Sugimoto T (2017) Primary aldosteronism as a risk factor for vertebral fracture. *J Clin Endocrinol Metab* 102: 1237–1243.
15. Chang CK, Chang CC, Wu VC, Geng JH, Lee HY (2022) The relationship between renal stones and primary aldosteronism. *Front Endocrinol (Lausanne)* 13: 828839.
16. Chung MC, Lin CL, Wu MJ, Chen CH, Shieh JJ, *et al.* (2021) Primary aldosteronism is associated with risk of urinary bladder stones in a nationwide cohort study. *Sci Rep* 11: 7684.
17. Nishikawa T, Omura M, Satoh F, Shibata H, Takahashi K, *et al.* (2011) Guidelines for the diagnosis and treatment of primary aldosteronism—the Japan Endocrine Society 2009. *Endocr J* 58: 711–721.
18. Kang VJ, Lee BC, Huang JZ, Wu VC, Lin YH, *et al.* (2023) Aldosterone-producing adenoma is associated with urolithiasis in primary aldosteronism. *Endocr Connect* 12: e230056.
19. Alelign T, Petros B (2018) Kidney stone disease: an update on current concepts. *Adv Urol* 2018: 3068365.
20. Shey J, Cameron MA, Sakhaee K, Moe OW (2004) Recurrent calcium nephrolithiasis associated with primary aldosteronism. *Am J Kidney Dis* 44: e7–e12.
21. Abufaraj M, Al Karmi J, Yang L (2022) Prevalence and trends of urolithiasis among adults. *Curr Opin Urol* 32: 425–432.
22. Ohno Y, Sone M, Inagaki N, Yamasaki T, Ogawa O, *et al.* (2018) Obesity as a key factor underlying idiopathic hyperaldosteronism. *J Clin Endocrinol Metab* 103: 4456–4464.
23. Taylor EN, Curhan GC (2006) Body size and 24-hour urine composition. *Am J Kidney Dis* 48: 905–915.
24. Li Z, Fu C, Sun C, Suo Y, Li K, *et al.* (2024) Analysis of metabolic syndrome in bilateral upper urinary tract stones: a retrospective study of 3905 cases. *Heliyon* 10: e31180.