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Original Research

Non-suppression of renin by renal cysts in a subset of patients with primary aldosteronism—a prospective observational single center study

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Abstract

Background: Screening for primary aldosteronism is based on measuring aldosterone-to-renin ratio. Non-suppressed renin may cause false negative screening results, and such patients may miss focused, potentially curable treatment. We investigated the association between renal cysts and non-suppressed plasma renin.

Methods: Altogether, 114 consecutive patients with confirmed primary aldosteronism undergoing adrenal vein sampling were prospectively recruited between October 7, 2020 and December 30, 2021. During the procedure, plasma samples for renin analyses were collected from the right and left renal veins and the inferior vena cava. Renal cysts were identified using contrast-enhanced computed tomography.

Results: Renal cysts were found in 58.2% of the 114 patients. Neither screening nor renal vein renin concentrations were significantly different in patients with and without cysts, or when the kidneys with and without cysts were evaluated. However, cysts were significantly more prevalent in the "high-normal renin" group (cut point 23.0 mU/L) than in the "low to low-normal renin" group (90.9%, $n = 11$ vs. 56.0%, $n = 102$, $P = .027$, respectively). All patients ≤50 years of age in the "high-normal renin" group had renal cysts. Strong correlations were found between renin concentrations in the right and left renal veins ($r = .984$), and between renin concentration and renin activity in the inferior vena cava ($r = .817$).

Conclusion: Renal cysts are found in the majority of patients with primary aldosteronism, and they may interfere with diagnostics, especially in patients aged 50 years or less. In patients with non-suppressed renin due to renal cysts, aldosterone-to-renin ratio below the diagnostic threshold does not always exclude the diagnosis of primary aldosteronism.

Keywords: aldosterone-to-renin ratio, hypertension, primary aldosteronism, renal cysts, renin

Significance

Renal cysts are present in most patients with primary aldosteronism, a condition generally characterized by suppressed plasma renin. Factors that increase circulating renin concentration may influence the diagnostics of primary aldosteronism due to the subsequent decrease in aldosterone-to-renin ratio. We found that patients with renal cysts may present with non-suppressed plasma renin especially when aged 50 years or less. Therefore, at least in a subset of patients, renal cysts are a previously unrecognized factor interfering with the diagnostic flow of primary aldosteronism. This may prevent such patients from receiving the correct and targeted treatment of the disease.

Introduction

Primary aldosteronism (PA) is the most common cause of treatable secondary hypertension,[1–3] the screening of which is based on the determination of aldosterone-to-renin ratio (ARR). In PA, renin secretion is suppressed due to aldosterone hypersecretion that is considered as a key diagnostic requirement.[4] However, salt intake, medication, and more rarely concomitant renal artery stenosis can influence ARR especially by changing renin secretion.[5] Unknown factors may also increase renin secretion.[5–7] An association between renal cysts and prehypertension and hypertension has been suggested.[7] Several papers have reported an association between essential hypertension and renal cysts and discussed that the

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pressure effect of cysts on renal arterioles or renin-producing cells may be the underlying mechanism.[8–15] Chin et al.[8] described that number, size, and location of cysts were important characteristics that related them to the presence of hypertension, however, the study did not address whether the cyst effects were caused by the activation of the renin-angiotensin system. Of note, in polycystic kidney disease, renin is produced by some but not all cyst-lining cells that originate from the distal tubules.[16]

All measures should be taken to detect patients with unilateral surgically treatable PA, or those eligible for mineralocorticoid receptor antagonist treatment.[1–3] Any mechanism increasing the denominator of the equation, renin, decreases ARR and may cause a false negative result that excludes such patients from confirmatory testing of PA. The awareness of renin-increasing factors requires vigilance from clinicians.[1–3,5]

We hypothesized that the presence of renal cysts might be associated with elevated plasma renin concentration (PRC) and potentially cause false negative screening results of ARR in patients with PA. We examined the influence of renal cysts, detected in computed tomography (CT), on PRC and ARR in samples obtained during PA screening, and in samples taken from renal veins and the inferior vena cava (IVC) during adrenal vein sampling (AVS). Additionally, plasma renin activity (PRA) and PRC were compared from samples taken from the IVC.

Methods

Study subjects

We prospectively included all subjects with confirmed PA referred to Tampere University Hospital for AVS between October 7, 2020 and December 30, 2021. Inclusion criteria were age between 18 and 80 years, AVS performed in Tampere University Hospital, written informed consent, and secondary hypertension due to confirmed PA according to the Endocrine Society guideline.[1] The ARR cutoff for aldosteronism screening was 30 pmol/mU,[7,17,18,19,20] and confirmatory testing for PA was performed to all but 3 participants (see below).[1] Of the referred 130 consecutive patients, 115 patients signed written informed consent. One patient with chronic kidney disease was excluded due to lack of reliable CT data, as the procedure was carried out without contrast media. The screening concentrations of renin and aldosterone were missing, but ARR was available, in 1 included patient. Five patients presented with minor elevations in the screening tests for hypercortisolism, and these were interpreted as adrenal cortisol co-secretion, were not a criterion for exclusion.

Our approach to patient grouping was 2-fold. First, patients with renal cysts (cyst group) were compared with those without cysts (no-cyst group) (Table 1). Second, mean screening PRC (23.0 mU/L) between complete suppression and the upper limit of normal was used to form 2 groups: "low to low-normal renin" and "high-normal renin" (Table 2). The PRC reference range was from 4.4 to 46.0 mU/L. An additional analysis of PRCs measured from the left adrenal vein and the right adrenal vein was done by grouping the 228 kidneys to those containing cysts and those without cysts.

Clinical data were obtained from the patient records. Supine blood pressures were measured from the right and left arms in the morning of AVS before cosyntropin infusion.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Pirkanmaa Hospital District (R20023) and was registered in ClinicalTrials.gov (NCT05435703).

Laboratory methods

The Endocrine Society guideline was applied in PA diagnostics,[1] except for the use of a lower ARR cutoff.[17,20] The present ARR threshold of 30 pmol/mU was based on several previous studies,[7,17–19] and corresponds closely to the cutoffs validated by the German Conn Registry.[20] The screening and confirmatory testing for PA were performed by the referring hospitals originating from 14 out of 20 Finnish hospital districts. The values of PRC and serum aldosterone concentration (SAC) were obtained from the referrals. The ARR results were available once for 45, twice for 43, thrice for 16, 4 times for 7, 5 times for 2, and 6 times for 1 patient. The mean, minimum, and maximum screening PRCs and SACs were recorded.

The confirmatory tests included 24-h urine aldosterone excretion during oral sodium loading (cutoff ≥33 nmol) or the seated saline suppression test (SSST) (cutoff ≥170 pmol/L).[1] The 24-h urine aldosterone excretion was determined once for 84, twice for 17, thrice for 4, and 4 times for 3 patients. The SSST was done to 16 patients. In 3 patients, PA diagnosis was derived from high SAC, hypokalemia, and suppressed renin without the need for confirmatory testing.[1] In 1 participant, the 24-h urine aldosterone was in the gray zone (30 mmol).

We also assessed whether the findings were applicable to PRA-based analyses. Thus, in addition to PRC, PRA was analyzed from samples taken from the IVC during AVS.

We calculated daily defined doses (DDDs) for all antihypertensive medications and grouped them to renin-increasing and renin-decreasing compounds (Tables S1 and S2).

Renal and peripheral vein PRC samples during the AVS were immediately frozen and determined using chemiluminescence immunoassay (CLIA) analyzer Liaison XL (DiaSorin, Saluggia, Italy). Plasma renin activity was determined from the IVC samples using a competitive enzyme immunoassay technique (Demeditec Diagnostics GmbH, Kiel, Germany). Aldosterone concentrations were analyzed using liquid chromatography-tandem mass spectrometry (LC-MS/MS) with a Triple Quad 5500 MS-system (AB Sciex, Framingham, MA, USA) linked with an HP 1200 HPLC system (Agilent Technologies, Santa Clara, CA, USA) using SunFire C18 columns (Waters, Milford, MA, USA). Plasma cortisol was determined using an electrochemical luminescence immunoassay (ECLIA) in the Cobas e801 module (Roche Diagnostics, Mannheim, Germany). Plasma potassium and creatinine levels were measured using routine laboratory techniques, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.[21]

Computed tomography

Computed tomography imaging with contrast media was done in the referring hospitals to determine adrenal vein structure and exclude adrenal carcinoma. Imaging data were electrically transferred to the study center. Most CT scans included thin axial slices from 0.5 to 1.0 mm to maximize resolution of adrenal veins (Table S3). The right kidney was completely visible in CT scans of 104 patients and the left kidney in CT scans of 102 patients. Computed tomography scans of 11 right kidneys and 13 left kidneys showed more than 50%

Table 1. Characteristics of the patients in the no-cyst and cyst groups.

	No-cyst group	Cyst group	*P* value
Number	47 (41.2%)	67 (58.8%)	
Age, years	47.1 (±9.9)	54.5 (±9.8)	<.001
Age ≤50	29 (61.7%)	24 (35.8%)	.007
Duration of hypertension, years	10 [2-13]	14 [5-20]	.083
Female	22 (46.8%)	22 (32.8%)	.131
BMI, kg/m^2	30.4 (±6.3)	29.9 (±5.3)	.952
Systolic BP, mmHg	143 (±15)	154 (±21)	.003
Diastolic BP, mmHg	91 (±9)	94 (±12)	.123
Smoker or ex-smoker	12 (25.5%)	9 (13.4%)	.101
Dyslipidemia[a]	11 (23.4%)	18 (26.9%)	.676
Diabetes or prediabetes[b]	5 (10.6%)	21 (31.3%)	.010
Sleep apnea	12 (25.5%)	26 (38.8%)	.139
Cancer	3 (6.4%)	6 (9.0%)	.734
Stroke[c]	2 (4.3%)	5 (7.5%)	.698
Atrial fibrillation	1 (2.1%)	5 (7.5%)	.398
Heart failure	1 (2.1%)	3 (4.5%)	.642
Coronary artery disease	1 (2.1%)	2 (3.0%)	1.000
Renal disease[d]	1 (2.1%)	6 (9.0%)	.237
Number of antihypertensive medications	2 [2-3]	3 [2-4]	.009
DDD of antihypertensive medications	3.2 [2.0-5.3]	4.0 [2.4-5.5]	.124
Hypokalemia	35 (74.5%)	57 (85.1%)	.228
Lowest plasma potassium, mmol/L	3.0 (±0.3)	2.9 (±0.3)	.272
eGFR, mL/min/1.73 m^2	91.6 (±27.5)	80.5 (±23.0)	.036
Adenoma in CT	23 (48.9%)	35 (52.2%)	.730
Unilateral hyperaldosteronism	21 (44.7%)	30 (44.8%)	.992
Mean screening PRC[e], mU/L	4.6 [1.9-10.0]	5.2 [2.6-11.2]	.435
Right renal vein PRC, mU/L	4.0 [1.4-9.0]	4.3 [2.2-12.0]	.292
Left renal vein PRC, mU/L	4.0 [1.7-10.0]	4.3 [2.4-11.0]	.371
Inferior vena cava PRC, mU/L	3.7 [1.2-8.1]	3.6 [2.0-9.0]	.447
Inferior vena cava PRA, ng/mL/h	0.24 [0.07-0.68]	0.28 [0.13-0.63]	.271

Data are expressed as *n* (%), mean (±SD) or median [IQR].
ARR, aldosterone-to-renin ratio; BMI, body mass index (weight in kilograms divided by height in meters squared); BP, blood pressure; CT, computed tomography; DDD, daily defined dose; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation was used); LI, lateralization index; PRA, plasma renin activity; PRC, plasma renin concentration.
[a]Dyslipidemia includes hypercholesterolemia, combined dyslipidemia, and hypertriglyceridemia.
[b]Diabetes includes type I and type II diabetes, and prediabetes includes patients with impaired glucose tolerance.
[c]Stroke includes transient ischemic attacks, cerebral bleeding, or cerebral infarction.
[d]Renal disease includes nephrocalcinosis due to surgically treated primary hyperparathyroidism ($n = 2$), hypertensive nephrosclerosis ($n = 2$), contracted kidney on one side ($n = 1$), and diabetic chronic kidney disease stage 1 ($n = 1$) and stage 3 ($n = 1$).
[e]Average PRC in the screening tests.

of the organs but not the whole kidneys, as the indication for the CT was visualization of the adrenals, not the kidneys. In the subtotally visualized kidneys, right-sided cysts were seen in 4 and left-sided cysts in 7 patients. None of the patients had a polycystic kidney disease or a sponge kidney. One patient had right-sided contracted kidney.

One blinded, abdominal radiologist analyzed all CT scans retrospectively. Cysts adjacent to the renal pelvis were classified as peripelvic and other cysts as parenchymal.[22] The following variables were recorded: The volumes of the kidneys; the presence of scars, hydronephrosis, calcification, and angiomyolipomas; highest Bosniak class;[23,24] number of all cysts (total, parenchymal, or peripelvic); total volume of all cysts (excluding cysts <5 mm); and the number of cysts sized <5 mm, 5-20 mm, and >20 mm. Kidney and cyst volumes were calculated using the ellipsoid volume formula $4/3 \times \pi \times A \times B \times C$.[25]

Adrenal vein sampling

Mineralocorticoid receptor antagonists were discontinued 6 weeks prior to AVS. If needed, alpha-blockers and verapamil were used to control blood pressure, and potassium supplementation to maintain normokalemia.

Adrenal vein sampling procedures were carried out in Tampere University Hospital by 3 interventional radiologists, and each of them performed 12 (10.5%), 26 (22.8%), or 76 (66.7%) of the AVS procedures. The AVS protocol was done according to the Endocrine Society guideline[1] and included cosyntropin infusion.[26] After sampling, the right adrenal vein (cortisol and aldosterone), the right main renal vein, and the left main renal vein thereafter were sampled for renin with the same catheter before switching to the catheterization of the left adrenal vein (cortisol and aldosterone). The IVC was sampled at the end of the AVS (cortisol, aldosterone, and renin). The AVS was successful in 111 patients (97%) after the first sampling, and success rate was 100% after resampling the 3 patients.

Statistical analysis

Because of scarce previous data, exact sample size calculation was not possible. We planned to include 200 patients but to perform an interim analysis after recruiting 100 patients with sufficient data for analyses. Chi-square or Fisher's exact test was used for the comparison of proportions of the categorical variables between the groups. Mann-Whitney U test was used as the nonparametric test for skewed variables, and the results presented as median and interquartile range (IQR). *t*-Test was used in case of normally distributed variables, and mean with standard deviation (SD) is presented

Table 2. Patient characteristics in the "low to low-normal renin" and "high-normal renin" groups.

	Low to low-normal renin PRC < 23.0 mU/L	High-normal renin PRC ≥ 23.0 mU/L	*P* value
n	102 (90.3%)	11 (9.7%)	
Age, years	51.5 (±10.5)	51.5 (±10.8)	.950
Age ≤ 50	46 (45.1%)	6 (54.5%)	.752
Duration of hypertension, years	10 [3-17]	13 [4-19]	.588
Female	39 (38.2%)	5 (45.5%)	.748
Systolic BP, mmHg	149.2 (±20.4)	150.8 (±10.8)	.482
Diastolic BP, mmHg	92.1 (±11.1)	97.7 (±11.2)	.154
BMI, kg/m^2	30.3 (±5.8)	29.1 (±4.5)	.677
Smoker or ex-smoker	17 (16.7%)	4 (36.4%)	.120
Dyslipidemia[a]	28 (27.5%)	0 (0%)	.063
Diabetes or prediabetes[b]	26 (25.5%)	0 (0%)	.066
Sleep apnea	35 (34.3%)	3 (27.3%)	.748
Cancer	8 (7.8%)	1 (9.1%)	1.000
Stroke[c]	7 (6.9%)	0 (0%)	1.000
Atrial fibrillation	5 (4.9%)	1 (9.1%)	.467
Heart failure	4 (3.9%)	0 (0%)	1.000
Coronary artery disease	2 (2.0%)	0 (0%)	1.000
Renal disease[d]	5 (4.9%)	2 (18.2%)	.138
Number of antihypertensive medications	3 [2-4]	2 [2-3]	.181
DDD of antihypertensive medications	3.7 [2.0-5.7]	2.0 [1.2-5.2]	.167
Hypokalemia	83 (81.4%)	9 (81.8%)	1.000
Lowest plasma potassium, mmol/L	3.0 (±0.3)	3.0 (±0.3)	.672
eGFR, mL/min/1.73 m^2	85.7 (±25.5)	78.3 (±26.1)	.318
Adenoma in CT	54 (52.9%)	4 (36.4%)	.353
Unilateral hyperaldosteronism	47 (46.1%)	4 (36.4%)	.752
LI in unilateral PA	12.1 [7.2-34.1]	9.1 [5.9-11.8]	.314
LI in bilateral PA	1.7 [1.2-2.3]	1.2 [1.1-1.5]	.032
Number of renal cysts	1 [0-2]	2 [1-6]	.013
Number of small parenchymal cysts[e]	1 [1-2]	6 [2-]	.053
Volume of cysts, cm^3	18.5 [4.7-69.5]	9.9 [3.0-20.4]	.309
Maximum PRC, mU/L	5.8 [2.4-9.2]	46.0 [33.0-61.0]	<.001
Minimum PRC, mU/L	3.2 [1.4-6.5]	16.0 [13.9-27.0]	<.001
Maximum SAC, pmol/L	651 [489-937]	871 [685-1150]	.030
Minimum SAC, pmol/L	499 [362-734]	426 [309-724]	.309
Maximum ARR, pmol/mU	229 [84-448]	41 [32-67]	<.001
Minimum ARR, pmol/mU	110 [55-271]	12 [10-22]	<.001
Maximum 24-h urine aldosterone, nmol	66.0 [50.3-91.8]	94.0 [82.0-108.0]	.012
Minimum 24-h urine aldosterone, nmol	62.0 [44.2-89.8]	51.0 [46.0-67.0]	.457
Right renal vein PRC, mU/L	4.0 [1.8-8.8]	37.0 [17.0-59.0]	<.001
Left renal vein PRC, mU/L	3.8 [1.9-8.1]	34.0 [16.0-60.0]	<.001
Inferior vena cava PRC, mU/L	3.4 [1.4-6.2]	31.0 [13.0-46.0]	<.001
Inferior vena cava PRA, ng/mL/h	0.23 [0.09-0.51]	3.86 [1.45-6.32]	<.001

Data are expressed as *n* (%), mean (±SD) or median [IQR].
ARR, aldosterone-to-renin ratio; BMI, body mass index (weight in kilograms divided by height in meters squared); BP, blood pressure; CT, computed tomography; DDD, daily defined dose; eGFR, estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation was used); LI, lateralization index; PRA, plasma renin activity; PRC, plasma renin concentration; SAC, serum aldosterone concentration.
[a]Dyslipidemia includes hypercholesterolemia, combined dyslipidemia, and hypertriglyceridemia.
[b]Diabetes includes type I and type II diabetes, and prediabetes includes patients with impaired glucose tolerance.
[c]Stroke includes transient ischemic attacks, cerebral bleeding, or cerebral infarction.
[d]Renal disease includes nephrocalcinosis due to surgically treated primary hyperparathyroidism ($n = 2$), hypertensive nephrosclerosis ($n = 2$), contracted 1-sided kidney ($n = 1$), and diabetic chronic kidney disease stage 1 ($n = 1$) and stage 3 ($n = 1$).
[e]Cyst ≤5 mm and not adjacent to the renal pelvis.

when appropriate. Spearman's correlations with 95% confidence intervals (CI) were calculated for non-normally distributed variables. All tests were 2-sided. Data analysis was conducted using SSPS software version 27 (IBM Corp., Armonk, NY, USA), and $P < 0.05$ was considered statistically significant.

Results

Patients with renal cysts compared with patients without cysts

Renal cysts were found in 58.2% of the patients. The patients in the cyst group were older, had higher systolic blood pressure and prevalence of prediabetes or diabetes, used more antihypertensive medications, and had about 11 mL/min/1.73 m^2 lower eGFR than patients in the no-cyst group (Table 1). The Spearman correlation between age and cyst number was 0.358 ($P < .001$). However, neither mean screening PRC nor renal vein and IVC PRC during AVS was different between the groups (Table 1). Additionally, renal vein PRC was not different when kidneys with and kidneys without cysts were compared (4.1 [2.4-8.0] vs. 4.2 [2.1-12.0] mU/L, $P = .967$). Renal cysts and other abnormalities found in the CT scans are presented in Table S4. The number or volume of renal cysts did not correlate with PRC or ARR (Table S5).

"Low to low-normal renin" group compared to "high-normal renin" group

The mean screening PRC was below the lower limit of normal in 48 patients (42.4%) and non-suppressed in 65 patients (57.5%) (PRC normal range 4.4-46 mU/L). The number but not the volume of renal cysts was higher in the "high-normal renin" group ($n = 11$) than in the "low to low-normal renin" group ($n = 102$, cut point PRC 23.0 mU/L, Table 2). In analyses based on mean screening PRC, renal cysts were more prevalent in the "high-normal renin" group than in the "low to low-normal renin" group (90.9% vs. 55.9%, $P = .027$) (Figure 1). When patients ≤50 years were analyzed separately, all had cysts in the "high-normal renin" group (100% of 6 subjects) while 39.1% of 46 subjects had cysts in the "low to low-normal renin" group ($P = .007$). In patients >50 years, cyst prevalence was not different between the groups (80.0% vs. 69.6%) (Figure 1).

When maximum available screening PRC was used to group patients, renal cysts were more prevalent in the "high-normal renin" group than in the "low to low-normal renin" group (85.7% vs. 55.6%, $P = .041$). Corresponding to the above results, when patients ≤50 years were analyzed separately, renal cysts were more prevalent in the "high-normal renin" group than in the "low to low-normal renin" group (87.5% vs. 38.6%, $P = .018$). In patients >50 years, no differences were found between groups (83.3% vs. 69.1%, $P = .660$).

When minimum available screening PRC was used for grouping, no differences were found between the groups in cyst prevalence (100% vs. 58.2%, $P = .269$). The results remained the same when patients ≤50 years were analyzed separately (100.0% vs. 44.0%, $P = .208$), and patients >50 years were analyzed separately (100.0% vs. 70.0%, $P = 1.000$).

Minimum (Figure 2A), mean, and maximum PRCs were higher, and maximum (Figure 2B) but not minimum screening SAC and 24-h urine aldosterone were higher in the "high-normal renin" group than the "low to low-normal renin" group (Table 2). Both maximum (Figure 2C) and minimum screening ARR were higher in the "low to low-normal renin" group when compared with the "high-normal renin" group. Despite considerable differences in screening results, the proportion of patients with unilateral disease was not different (Figure 2D). The renin-influencing medications were not

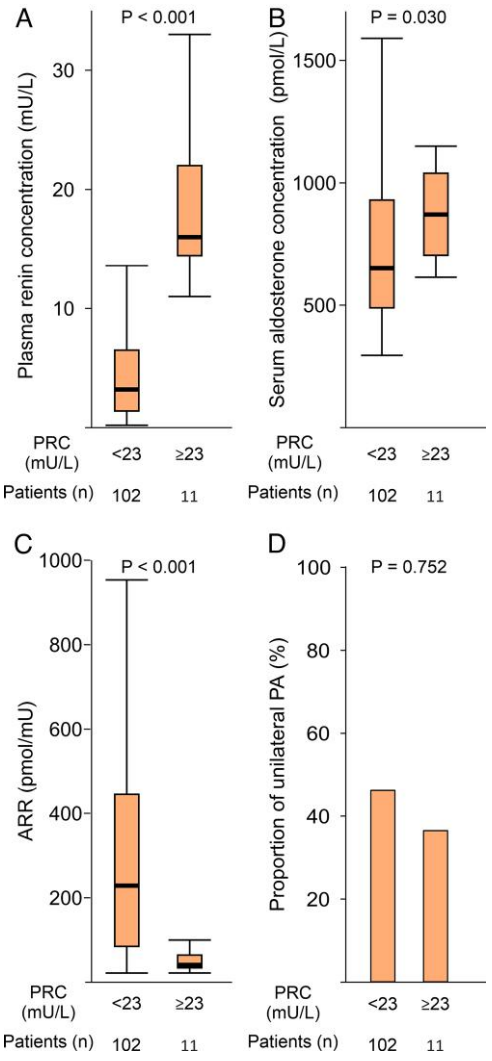

Figure 2. Box plots of minimum plasma renin concentration (PRC) (A), maximum serum aldosterone concentration (SAC) (B), maximum aldosterone-to-renin ratio (ARR) (C), and bar graphs showing proportions of unilateral primary aldosteronism (PA) (D) in groups of "low to low-normal" and "high-normal" PRC (cut point 23.0 mU/L); median (thick line inside box), interquartile range (box), and range (whiskers); mean PRC during screening was used to define the groups.

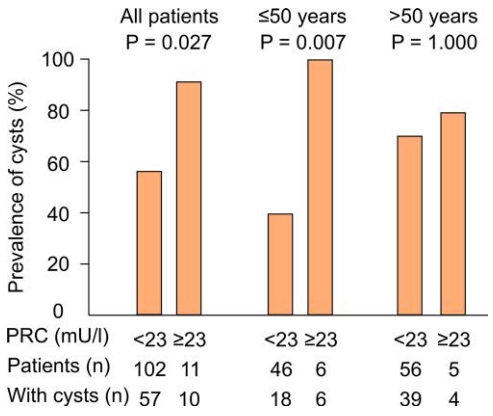

Figure 1. Renal cysts were more prevalent in the "high-normal renin" group than in the "low to low-normal renin" group (divided according to the mean renin concentration of the reference range). The same result was seen when patients aged ≤50 years were analyzed separately but not in patients aged >50 years. PRC, plasma renin concentration.

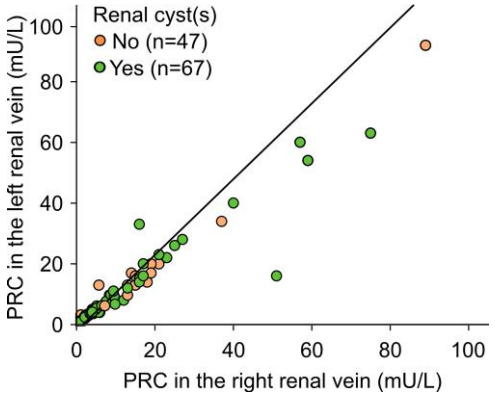

Figure 3. High correlation ($r_S = 0.984$) between plasma renin concentrations (PRCs) in the right and left renal vein samples. One outlier was omitted from the figure (PRC in the right renal vein 125 mU/L and in the left renal vein 224 mU/L).

discontinued in this study, but there were no significant differences in the DDD of the antihypertensive medications between the groups in analyses focused on renin-increasing, renin-decreasing, or individual medication groups (Tables S1 and S2). Whether compared in all participants (Table S1), or in participants ≤50 years of age (Table S2), 95.7%-97.1% of the subjects in the "low to low-normal renin" group used renin-increasing medications versus 66.7%-81.2% in the "high-normal renin" group.

Renin-to-renin correlations

Correlation of PRC between the right renal vein and the left renal vein was strong ($r = .984$, [95% CI, 0.976-0.989]) (Figure 3). The correlation persisted when the patients were divided to subgroups: No-cyst subgroup ($r = .967$ [0.940-0.982]) and cysts subgroup ($r = .989$ [0.982-0.993]).

Both right ($r = .978$ [0.968-0.985]) and left renal vein PRCs ($r = .982$ [0.973-0.988]) highly correlated with inferior vena cava PRC. Also, the mean ($r = .613$ [0.478-0.719]), maximum ($r = .582$ [0.440-0.695]), and minimum screening PRCs ($r = .531$ [0.379-0.655]) correlated with PRC sampled from the IVC during AVS despite subjects being seated during screening and supine during AVS.

A strong correlation ($r_S = .817$ [0.743-0.872]) was also found between PRA and PRC measured from samples taken from the IVC during cosyntropin stimulation (Figure S1).

Discussion

To our knowledge, this is the first prospective study to examine the association between non-suppressed PRC and renal cysts as a potential source of false negative screening test in PA patients. Our results are of importance because renal cysts were present in more than half of the patients with confirmed PA. Plasma renin concentration analysis is widely used in Europe as the screening test because it is less laborious and less costly than PRA determination.[27] All previous renal cyst–related studies in PA patients were based on analyses of PRA.[28,29,30,31]

Patients with PA present with renal cysts more often than patients with essential hypertension or subjects in the general population.[13,14,29,31–33] In addition, the amount and extent of renal cysts have been reported to associate with low plasma potassium, aging, impaired renal function, high systolic blood pressure, high serum aldosterone, and high PRA.[28–31] Despite the common assumption of suppressed renin in PA, a recent study presented 7 patients with non-suppressed renin who were cured by unilateral adrenalectomy.[5] In the present study, we first compared patients with and without renal cysts. Our results are in line with previous studies as patients with cysts were older, and had higher systolic blood pressure and lower eGFR.[28–31] We also found that diabetes was more frequent in patients with renal cysts. Pretreatment cysts are also an independent risk factor for persistence of post-treatment hypertension in PA, while renal cysts do not progress after surgical or medical treatment of PA.[29] The authors concluded that hypokalemia and its severity are probably the main contributors to cyst formation in PA patients.[29]

In analyses where all present patients with cysts were compared to those without cysts, the PRC concentrations were not significantly different, and the number or volume of renal cysts did not correlate with PRC or ARR. Thus, most of the patients with renal cysts did not present with increased renin. This finding is in line with the report that even in polycystic kidney disease, renin synthesis is detected only in some but not all of the cyst-lining cells.[16] However, we found that renal cysts are highly prevalent in subjects with renin exceeding the mean concentration of the reference range ("high-normal renin" group) when compared with the "low to low-normal renin" group (Figure 1 and Table 2). Previously, Lee et al.[32] found a significant association between the presence of renal cysts and serum renin concentration in patients with essential hypertension, and Torres et al.[31] reported a similar finding between renal cysts and PRA in patients with PA. Our results strengthen the previous studies and suggest a role for renal cysts causing increases of PRC to high-normal values. The association between renal cysts and high-normal renin was especially clear in patients ≤50 years old but was absent in older patients. The increasing prevalence of cysts associated with aging may explain the diluted association between renal cysts and PRC in patients older than 50 years.[33,34] Lee et al.[32] reported higher serum renin levels when the size of cysts exceeded 2 cm in patients with essential hypertension, but this finding was not reproduced in our study. A putative explanation is that smaller cysts may also affect renin concentrations.

Renal cysts may reflect end-organ damage caused by a severe hypertension. Previously, renin suppression has been associated with hypertensive complications.[35] The presentation of PA at a younger age might increase the likelihood of kidney damage,[36] renal cyst formation, and non-suppression of PRC. Renal cysts are highly frequent in patients with PA, and one of the mechanisms for cyst generation may be the hypokalemia and its severity in these patients.[29]

In previous reports, the prevalence of renal cysts in PA patients has varied between 23% and 44%,[28,29,30,31] but we found a higher prevalence of cysts (58%). These differences may be explained by the methods applied. Torres et al.[31] used contrast-enhanced CT in only 34 of 55 patients (62%), whereas contrast media was used in all 114 patients in our study. The use of contrast media improves the visibility of renal cysts in CT. Current CT scans with thin slices (Table S1) have also better resolution than those during earlier decades.[28,30,31] Novello et al.[29] used ultrasound to evaluate renal cysts, but CT is a more sensitive method for cysts detection than ultrasound.[9,28] Of note, simple renal cysts, which have no clear relevance to the prevailing clinical problem, go often unreported by the radiologists during their routine work.

In the present study, young PA patients (≤50 years) had numerically higher prevalence of renal cysts (45%, Table 1) than the prevalence (38%) reported by Torres et al.[31] in patients <60 years. However, cyst prevalence in PA in both of the above studies was higher than in young patients (<50 years) with essential hypertension (3%-15%).[8,9] Excessive prevalence of cysts in young PA patients may reflect increased risk of end-organ complications when compared with essential hypertension.[36,37]

We emphasize that to yield a diagnostic ARR value for PA screening, the maximum SAC was significantly higher in the "high-normal renin" group ($n = 11$) than in the "low to low-normal renin" group ($n = 102$) (871 pmol/L vs. 651 pmol/L, respectively, Figure 2). In the much smaller former group, the maximum ARR value remained at a lower level (41 vs. 229 pmol/mU, respectively) despite similar proportion of patients having a unilateral, surgically curable disease (Figure 2). Primary aldosteronism patients with renal cysts and non-suppressed renin may be excluded from further

diagnostic measures when ARR is solely used as the screening test. The recently presented simplified algorithm for PA screening based on SAC ≥277 pmol and PRC below the lower limit of the reference range[38] would easily miss such patients. Therefore, high suspicion of PA in a young hypertensive patient with non-suppressed renin and renal cysts may warrant confirmatory testing despite non-diagnostic ARR. Alternatively, a lower threshold of ARR could be applied. Renal imaging such as ultrasound should be used in young hypertensive patients with non-suppressed renin to rule out potential confounding caused by renal cysts when secondary hypertension is suspected.

Recently, 7 surgically treated patients with proven aldosterone-producing adenoma and non-suppressed renin were described.[5] We applied the ARR cutoff 30 pmol/mU[7,17–19] and found a false-negative, minimum ARR below 30 pmol/mU in 16.7% of patients. As the denominator of ARR, PRC between 11.5 and 61.0 mU/L caused the low ARR, while repeated measurements showed ARR above 30 pmol/mU in all but one of these patients. Jansen et al.[7] have criticized the use of ARR cutoff 91 pmol/mU, which would have resulted in a sensitivity of only 22% and a specificity of 99% in their study. However, high sensitivity is the most important feature of a screening test. By using the Endocrine Society guideline, we would have missed 38 (33.3%) patients among whom 14 (12.3%) were unilateral, operable cases.

We did not detect differences between renal vein PRCs from kidneys expressing cysts and those without cysts (data not shown). The detection of differences might have been possible if we had sampled renal veins segmentally.[39,40] The subtle lateralization of PRC may only become apparent with the administration of intravenous angiotensin-converting-enzyme inhibitors (ACE), an approach that has been applied in the diagnostics of juxtaglomerular tumors.[40] However, segmental renal vein sampling and ACE inhibitor administration were not feasible during the AVS. Giant cysts may cause a pressure effect that increases renin secretion and blood pressure. Aspiration or surgical operation may cure hypertension in these cases.[15,41] Our patient population did not contain cases with giant cysts.

Although PA screening was done in referring hospitals, we found a good correlation between PRC during screening and PRC taken during AVS from the IVC, and between PRC and PRA measured from the IVC. We also found a strong correlation between PRC in the right and left renal veins and IVC during AVS. A significant part of blood flows through the renal arteries and veins, which quickly equalizes the renin concentration in the circulatory system. The reported half-life of renin, based on analyses of PRA, ranges from 10 to 280 min.[42,43] The long half-life of renin is the probable cause for the lack of lateralization in PRC between the renal veins.

In our work, all patients had confirmed PA, and there were no healthy subjects or patients with primary hypertension. The size of the study group was relatively small when compared with earlier imaging-based renal cyst population studies or studies in primary hypertension. However, for an invasive study, our approach included more patients than many earlier studies with PA patients.[29–31] The diagnostic PRCs and SACs were analyzed by the laboratories of the referring hospitals.

One limitation of this study was that renin-influencing medications were not discontinued. This policy is in accordance with the Endocrine Society guideline.[1] Importantly, the use of renin-increasing medications was not more prevalent in the "high-normal renin" group when compared with the "low to low-normal renin" group. However, future studies with discontinuation of all renin-affecting medications should confirm our results. To control possible bias, PRC was also sampled from the IVC during the AVS, and the correlation between screening PRC and samples taken during AVS was good. Contrast-enhanced CT scans were primarily focused to find the adrenal veins and pathologic changes in the adrenal glands, and only secondarily to evaluate the presence of kidney pathology. Therefore, some renal cysts might have been undetected. Nevertheless, 9 out of 12 incompletely visible kidneys had renal cysts. A strength is that all CTs were evaluated centrally in a blinded fashion.

Conclusions

Renal cysts are highly prevalent in PA already at relatively young age, which may reflect disease severity and end-organ complications.[29] According to our results, PRC at screening has a wide range in surgically curable PA, which questions the dogma of PA always being a disease of suppressed renin. Our results suggest that in addition to the known renin-increasing factors such as antihypertensive medications (angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, thiazides, furosemide, and potassium sparing diuretics), salt restriction, and renal artery stenosis, also renal cysts may increase plasma renin. Therefore, in patients with clinical suspicion of PA but non-suppressed PRC, the presence of cysts should be assessed when imaging the kidneys.

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Supplementary material

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Author contributions

A.Y. and P.I.N. reviewed the literature and wrote the original version of the manuscript. A.Y., I.P., and H.H. performed the statistical analyses. P.I.N. carried out the clinical examinations of patients and was responsible for conducting the study. T.H. performed most of the AVS sampling. R.N. analyzed the data of computed tomography. O.N. contributed to the laboratory analyses. P.I.N., N.M., A.Y., E.H., T.H., R.N., and I.P. participated in the design of the technical details and methodology of the study. All authors contributed to the discussion

and editing the manuscript. All authors take the responsibility for the contents of the manuscript.

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