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Risk factors for renal impairment revealed after unilateral adrenalectomy in patients with primary aldosteronism

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Abstract

Primary aldosteronism (PA) may induce significant decline of renal function and structural damage of kidney. However, it is difficult to evaluate accurate renal function in patients with PA, because glomerular hyperfiltration and aldosterone escape can conceal renal impairment. In this retrospective cohort study, we compared changes in renal function after unilateral adrenalectomy between patients with PA and patients with other adrenal diseases. Risk factors associated with postoperative renal impairment in patients with PA were analyzed.

A total of 558 patients who received unilateral adrenalectomy between January 2002 and June 2013 were included: 136 patients with PA and 422 patients with other adrenal diseases (control). Postoperative serial changes in estimated glomerular filtration rate (eGFR) were analyzed in both groups. Multivariate analyses were performed to identify risk factors of renal impairment after adrenalectomy in all patients and the PA group. Postoperative renal impairment was defined as postoperative eGFR decline of >25% from preoperative eGFR. Chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2.

There were no differences in preoperative eGFR between groups. The PA group showed a significant decrease in eGFR 3 days, 2 weeks, and 6 months after surgery compared to the control group. The PA group showed significant improvement of hypertension after surgery. In the PA group, 53 (39.0%) patients showed postoperative renal impairment. Multivariate regression analysis identified long-standing hypertension, low body mass index, low serum potassium, and high preoperative eGFR as risk factors for postoperative renal impairment. Among the 89 patients with preoperative eGFR ≥60 mL/min/1.73 m^2, 29 (32.6%) patients developed CKD postoperatively. Age, low serum potassium, low preoperative eGFR, and high serum cholesterol or uric acid were associated with the postoperative CKD development.

Our study demonstrates that patients with PA with old age, low serum potassium, long-standing hypertension, and high serum uric acid or cholesterol are at risk of renal impairment after surgical treatment. High preoperative eGFR was also a risk factor for postoperative renal impairment, whereas low preoperative eGFR was a risk factor for postoperative CKD. Close monitoring of renal function and adequate management are required for patients with these risk factors.

Abbreviations: AKI = acute kidney injury, ANOVA = analysis of variance, ARR = aldosterone to renin ratio, BMI = body mass index, BP = blood pressure, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, PA = primary aldosteronism, PO = postoperative, SD = standard deviation.

Keywords: adrenalectomy, chronic kidney disease, primary aldosteronism, renal impairment

1. Introduction

Primary aldosteronism (PA) is a disease characterized by autonomous aldosterone secretion from an adrenocortical lesion.[1] Patients with PA show low plasma renin activity, high aldosterone levels, and consequent endocrine hypertension and hypokalemia due to increased potassium excretion.[2] Inappropriate aldosterone secretion stimulates sodium reabsorption and subsequent extracellular volume expansion, leading to secondary hypertension.[3] These sequences inevitably increase renal perfusion pressure and induce glomerular hyperfiltration.[4] Furthermore, chronic exposure to excessive aldosterone induces endothelial dysfunction and increases small vessel resistance.[5] Therefore, long-standing PA may induce renal structural damage, leading to a significant decline in renal function.[4]

However, it is difficult to accurately evaluate renal function in patients with PA because glomerular hyperfiltration and aldosterone escape usually conceal mild renal function impairment.[6] If these phenomena disappear after PA treatment, a significant decline in estimated glomerular filtration rate (eGFR) may occur, especially when serum aldosterone levels suddenly

drop following surgical treatment.[7] Early detection of concealed chronic kidney disease (CKD) and identification of risk factors of renal impairment before surgical treatment of PA are crucial clinical issues because CKD is a well-known risk factor of cardiovascular event and mortality.[8] Despite the clinical importance of renal impairment that may be revealed after surgical treatment of PA, there have been few studies investigating risk factors of postoperative (PO) renal impairment in patients with PA.[7,9]

Our study was designed to investigate renal function changes after unilateral adrenalectomy in patients with PA compared to the control group with other adrenal diseases receiving the same surgery, in order to identify preexisting risk factors of PO renal impairment in patients with PA.

2. Methods

2.1. Patient selection and follow-up

Adult patients (≥18 years old) who underwent unilateral adrenalectomy in Sungkyunkwan University School of Medicine, Samsung Medical Center, between January 2002 and June 2013 were enrolled. A total of 668 patients underwent unilateral adrenalectomy during this period: 142 patients with PA and 526 patients with other adrenal diseases. After excluding patients with preexisting end-stage renal disease, cancer, and insufficient data, 136 patients were finally included in the PA group and 422 patients were included in the control group. Patients in the control group had adrenal disease such as pheochromocytoma (170 of 422 patients, 40.3%), Cushing disease (91 of 422 patients, 21.6%), adrenal cyst (53 of 422 patients, 12.5%), nonfunctioning adenoma (49 of 422 patients, 11.6%), ganglioneuroma (18 of 422 patients, 4.3%), myelolipoma (17 of 422 patients, 4.0%), schwannoma (10 of 422 patients, 2.3%), pseudocyst (7 of 422 patients, 1.7%), and others (7 of 422 patients, 1.7%: 2 angiomyolipoma, 1 hemangioma, 1 hematoma, 1 lipoma, 1 lymphangioma, 1 paraganglioma). The study protocol was approved by the Institutional Review Board of Samsung Medical Center in compliance with the Declaration of Helsinki (IRB number: 201309028).

In order to analyze the baseline characteristics of patients, preoperative clinical data including age, sex, body mass index (BMI), systolic and diastolic blood pressure (BP), number and type of antihypertensive agents, duration of hypertension, underlying comorbidities (e.g., diabetes mellitus, coronary artery disease, and dyslipidemia), and the presence of left ventricular hypertrophy were extracted from electronic medical records. Laboratory data including hemoglobin, serum creatinine, serum potassium, serum cholesterol, serum uric acid, albuminuria examined by dipstick test, and plasma aldosterone concentration with plasma renin activity were also collected.

Renal function was assessed with eGFR, which was calculated based on the modified Modification of Diet in Renal Disease equation using serum creatinine. Renal function was serially compared between control and PA groups from preoperative baseline to 3 days, 2 weeks, 6 months, and up to 2 years after surgery.

2.2. Definitions

PA was diagnosed based on the following criteria[1,10]: elevated aldosterone to renin ratio (ARR) >30 ng/dL/(ng/[mL·h]), serum aldosterone above the median of the normal range, and abnormal results in confirmatory tests such as saline loading test, captopril challenge test, or fludrocortisone suppression test. A final

diagnosis of aldosterone-producing adenoma type PA was determined by localization of tumor using abdominal computed tomography or magnetic resonance imaging. Subsequent adrenal venous sampling was performed in most patients with unilateral adrenal lesion for confirmation of lateralization. Mineralocorticoid antagonists, β-blockers, and renin–angiotensin system inhibitors were discontinued at least 2 weeks before both screening and confirmatory diagnostic tests. Pathological results of all surgically removed lesions were consistent with adrenocortical adenoma (131 of 136 patients, 96.3%) or nodular adrenal cortical hyperplasia (5 of 136 patients, 3.7%).

eGFR was calculated using the modified Modification of Diet in Renal Disease formula as follows[11]: $175 \times$ (serum creatinine)$^{-1.154} \times$ (age)$^{-0.203} \times 0.742$ (if female). To evaluate serial changes in renal function, PO eGFR, ΔeGFR, and percentage change eGFR were compared. PO eGFR was determined as the last checked eGFR within 6 months after adrenalectomy. ΔeGFR was defined as preoperative eGFR minus PO eGFR. Percentage change eGFR was calculated as follows: (ΔeGFR/preoperative eGFR) $\times 100$.

PO renal impairment was defined as PO eGFR decline of >25% from preoperative eGFR. CKD was defined as an eGFR <60 mL/min/1.73 m^2.

2.3. Statistical analyses

Continuous variables following normal distribution were expressed as mean ± standard deviation (SD) or mean ± standard error of mean as appropriate. Continuous variables not following normal distribution were expressed as median (interquartile range). Categorical variables were expressed as number (percentage). The significance of differences between the control and the PA groups was determined by unpaired t test or Mann–Whitney test as appropriate. Categorical variables were compared using χ^2 tests or linear-by-linear association. One-way analysis of variance (ANOVA) followed by Bonferroni correction or Kruskal–Wallis test was used for comparing >2 groups as appropriate. Paired t test and Wilcoxon signed rank test were performed for comparing values before and after surgery. Repeated measures ANOVA was used to compare differences in eGFR at each time point. Multivariate regression analyses with stepwise selection procedure were performed to identify risk factors for renal impairment after adrenalectomy in all patients and in the PA group. A P value <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS statistics 23 (IBM Corporation, Armonk, NY).

3. Results

3.1. Baseline characteristics of study population

Baseline characteristics of the control (n=422) and the PA (n=136) groups including clinical features and laboratory data are summarized in Table 1. The mean age of the control and PA groups was 46.6±13.24 and 48.0±11.16 years, respectively. The proportion of males was similar in both groups (control: 48.3% vs. PA: 47.1%). The PA group showed higher BP (control: 124.7/75.8 mmHg vs. PA: 155.2/93.4 mmHg, $P < 0.001$), longer duration of hypertension (control: 2 [0.9, 7] years vs. PA: 7 [3, 10] years, $P < 0.001$), and significantly lower levels of serum potassium (control: 4.1±0.39 mmol/L vs. PA: 2.9±0.63 mmol/L, $P < 0.001$) than the control group. Serum cholesterol level was lower in the PA group (control: 186.8±38.38 mg/dL vs. PA: 172.7±33.96 mg/dL, $P < 0.001$), but serum uric acid level was

Table 1

Baseline characteristics of the study population.

	Control group (n = 422)	Total PA	PA group (n = 136)			P^*	$P^\dagger$
			PA1 (n = 55) (eGFR ≥90)	PA2 (n = 67) (60 ≤ eGFR < 90)	PA3 (n = 14) (eGFR <60)		
Age, y	46.6 ± 13.24	48.0 ± 11.16	42.0 ± 10.95‡,§	51.9 ± 9.73‡	53.1 ± 7.60§	0.202	<0.001
Male, %	204 (48.3%)	64 (47.1%)	22 (40.0%)	35 (52.2%)	7 (50.0%)	0.795	0.393
Hospital days	8 (6, 11)	6 (5, 8)	6 (5, 6)	7 (5, 9)	7.5 (5, 11)	<0.001	0.074
BMI, kg/m²	24.5 ± 3.67	24.4 ± 2.87	24.3 ± 2.92	24.4 ± 3.01	24.3 ± 2.11	0.284	0.990
Systolic BP, mmHg	124.7 ± 17.04	155.2 ± 22.94	153.3 ± 17.56	156.4 ± 25.63	157.0 ± 28.69	<0.001	0.722
Diastolic BP, mmHg	75.8 ± 11.97	93.4 ± 15.74	96.5 ± 12.69	92.0 ± 17.31	87.9 ± 17.35	<0.001	0.115
Mean BP, mmHg	92.1 ± 12.62	114.0 ± 16.86	115.4 ± 13.44	113.5 ± 18.83	110.9 ± 19.48	<0.001	0.636
Hemoglobin, g/dL	13.5 ± 1.73	13.3 ± 1.54	13.3 ± 1.47	13.3 ± 1.49	13.2 ± 2.08	0.204	0.965
Serum potassium, mmol/L	4.1 ± 0.39	2.9 ± 0.63	3.0 ± 0.55	2.9 ± 0.67	2.6 ± 0.66	<0.001	0.209
Serum creatinine, mg/dL	0.87 ± 0.53	0.89 ± 0.31	0.71 ± 0.12‡,§	0.92 ± 0.13‡,‖	1.46 ± 0.62§,‖	0.629	<0.001
eGFR, mL/min/1.73 m²	89.0 ± 19.64	85.6 ± 21.80	105.3 ± 15.01‡,§	76.9 ± 8.86‡,‖	49.4 ± 12.73§,‖	0.082	<0.001
Serum cholesterol, mg/dL	186.8 ± 38.38	172.7 ± 33.96	173.7 ± 34.91	173.3 ± 31.97	166.2 ± 40.88	<0.001	0.753
Serum uric acid, mg/dL	4.9 ± 1.53	5.0 ± 1.49	4.7 ± 1.54¶	5.1 ± 1.33	5.9 ± 1.66¶	0.222	0.012
PAC, ng/dL	NA	32.1 (21.1, 54.1)	32.4 (23.5, 51.0)	30.8 (20.3, 50.8)	44.0 (32.7, 86.4)	NA	0.063
PRA, ng/mL·h	NA	0.10 (0.04, 0.25)	0.10 (0.03, 0.23)	0.10 (0.03, 0.26)	0.12 (0.1, 0.30)	NA	0.544
ARR, ng/dL/(ng/[mL·h])	NA	295 (117.6, 1166.3)	282.8 (103.6, 1211.0)	300.0 (114.4, 1179.0)	311.8 (195.6, 1055.2)	NA	0.987
Hypertension, number (%)	148 (35.1)	136 (100)	55 (100)	67 (100)	14 (100)	<0.001	NA
Duration of hypertension, y	2 (0.9, 7)	7 (3, 10)	4 (1, 8)‡,§	9 (5, 11)‡	10 (6.8, 10.8)§	<0.001	<0.001
DM, number (%)	82 (19.4)	19 (14.0)	4 (7.3)	11 (16.4)	4 (28.6)	0.150	0.029
CAD, number (%)	15 (3.6)	13 (9.6)	2 (3.6)	7 (10.4)	4 (28.6)	0.005	0.008
Dyslipidemia, number (%)	68 (16.1)	29 (21.3)	10 (18.2)	12 (17.9)	7 (50.0)	0.163	0.063
LVH, number (%)	50 (11.8)	41 (30.2)	9 (16.4)	28 (41.8)	4 (28.6)	<0.001	0.034
Albuminuria, %	12 (2.8%)	7 (5.1%)	2 (3.6%)	3 (4.5%)	2 (14.3%)	0.273	0.206

Continuous variables following normal distribution are expressed as mean ± standard deviation. Continuous variables not following normal distribution are expressed as median (interquartile range). Categorical variables are expressed as number (percentage). Unpaired t test or Mann–Whitney test was used for comparing the control group with the PA group. One-way ANOVA followed by Bonferroni correction or Kruskal–Wallis test followed by Mann–Whitney test was performed for PA1 versus PA2 versus PA3. Categorical variables were compared using χ^2 tests or linear-by-linear association. ANOVA = analysis of variance, ARR = aldosterone to renin ratio, BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, LVH = left ventricular hypertrophy, NA = not applicable, PA = primary aldosteronism, PAC = plasma aldosterone concentration, PRA = plasma renin activity.

* Control group versus total PA group.

† PA1 versus PA2 versus PA3 (between subgroups of the PA group).

‡ $P < 0.001$ for PA1 versus PA2.

§ $P < 0.001$ for PA1 versus PA3.

‖ $P < 0.001$ for PA2 versus PA3.

¶ $P < 0.05$ for PA1 versus PA3.

comparable between 2 groups (control: 4.9 ± 1.53 mg/dL vs. PA: 5.0 ± 1.49 mg/dL, $P = 0.222$). The proportion of patients with hypertension (control: 35.1% vs. PA: 100%, $P < 0.001$), coronary artery disease (control: 3.6% vs. PA: 9.6%, $P = 0.005$), and left ventricular hypertrophy (control: 11.8% vs. PA: 30.2%, $P < 0.001$) was higher in the PA group. However, baseline eGFR were similar, indicating comparable preoperative renal function between groups.

The PA group was further divided into 3 groups based on preoperative eGFR (Table 1). Patients with low preoperative eGFR were older (PA1: 42.0 ± 10.95 years old vs. PA2: 51.9 ± 9.73 years old vs. PA3: 53.1 ± 7.60 years old, $P < 0.001$) and had a much longer duration of hypertension ($P < 0.001$). Diabetes mellitus, coronary artery disease, and left ventricular hypertrophy were also higher in patients with low preoperative eGFR. However, BP was comparable among the 3 groups (mean BP, PA1: 115.4 ± 13.44 mmHg vs. PA2: 113.5 ± 18.83 mmHg vs. PA3: 110.9 ± 19.48 mmHg, $P = 0.636$). Serum potassium and ARR were also comparable among the 3 subgroups of PA.

3.2. Overall outcome of PA group after adrenalectomy

PA group showed significant improvement of hypertension (means of systolic/diastolic BP 129.9/85.8 mmHg at 6 months after surgery; Table 2). All patients were prescribed with antihypertensive agents at the first visit. The number of patients with monotherapy and that with combination therapy were 22 (16.2%) and 114 (83.8%), respectively. The number of patients who no longer required antihypertensive agents was 66 (48.5%). Serum potassium of PA group was normalized from 2.9 ± 0.63 to 4.6 ± 0.42 mmol/L after the operation.

In order to evaluate PO BP control, repeated measures ANOVA was performed using PO BP of patients with available data at all PO time points (118 of 136 patients). Hypertension was improved at 3 days after operation (systolic/diastolic BP, preoperative: 155.2 ± 22.94/94 ± 15.45 vs. PO 3 days: 135.1 ± 13.64/85.4 ± 10.20 vs. PO 2 weeks: 132.7 ± 15.41/87.8 ± 10.54 vs. PO 6 months: 129.9 ± 13.89/85.8 ± 10.61, $P < 0.001$). There were no significant differences in BP since 3 days after operation (supplemental Fig. 1, http://links.lww.com/MD/B82).

3.3. Renal impairment revealed after adrenalectomy in the PA group

The PA group showed significantly lower eGFR 3 days, 2 weeks, and 6 months after unilateral adrenalectomy compared to the control group (Fig. 1A). There were no significant differences between eGFR of PO 2 weeks and 6 months within both control

Table 2

Preoperative and postoperative characteristics of the PA group.

	Preoperative	**Postoperative**	**P**
Systolic BP, mmHg	155.2±22.94	129.9±13.89	<0.001
Diastolic BP, mmHg	93.4±15.74	85.8±10.61	<0.001
Numbers of antihypertensive agents	2.3±0.90	0.7±0.88	<0.001
Patients who discontinued antihypertensive agents, %	0 (0%)	66 (48.5%)	<0.001
Serum potassium, mmol/L	2.9±0.63	4.6±0.42	<0.001
ARR, ng/dL/(ng/[mL·h])	295 (117.5, 1166.3)	5.5 (1.7, 19.9)	<0.001

Continuous variables following normal distribution are expressed as mean±standard deviation. Continuous variables not following normal distribution are expressed as median (interquartile range). Categorical variables are expressed as number (percentage). Paired *t* test was performed for comparison between preoperative characteristics and postoperative characteristics except ARR. Wilcoxon signed rank test was performed for ARR. Systolic and diastolic BP, numbers of antihypertensive agent, and patients who discontinued antihypertensive agents were assessed at 6 months after operation. Systolic and diastolic BP was measured in patients with sufficient follow-up data (118 of 136 patients). Serum potassium and ARR were measured at 2 weeks after operation. ARR = aldosterone to renin ratio, BP = blood pressure, PA = primary aldosteronism.

and PA groups. PO serial changes in renal function in each PA subgroup are shown in Fig. 1B. All 3 subgroups exhibited a significant decrease in PO eGFR. However, there were no differences in the degree of renal impairment evaluated with percentage change eGFR among the PA subgroups.

PO renal impairment was significant in the PA group and 3 PA subgroups, whereas there was no difference in PO eGFR of the control group compared to the preoperative eGFR (preoperative vs. PO eGFR, paired *t* test; control: 89.0±19.64 vs. 90.5±23.10 mL/min/1.73 m^2, $P=0.166$; PA: 85.6±21.80 vs. 70.0±23.64 mL/min/1.73 m^2, $P<0.001$, Wilcoxon signed rank test; $P<0.001$ for PA1 and PA2, $P=0.001$ for PA3; Fig. 1C).

The PA group had greater ΔeGFR (mean±SD of [preoperative eGFR − PO eGFR], control: −1.5±22.36 mL/min/1.73 m^2 vs. PA: 15.6±18.57 mL/min/1.73 m^2, $P<0.001$) and percentage change eGFR (mean±SD of [{ΔeGFR/preoperative eGFR}× 100], control: −3.8%±25.02% vs. PA: 18.2%±20.37%, $P<0.001$) compared to the control group. The PA group also showed greater ΔeGFR and percentage change eGFR compared to patients with hypertension in the control group (ΔeGFR, control: 0.9±21.01 mL/min/1.73 m^2 vs. PA: 15.6±18.57 mL/min/1.73 m^2, $P<0.001$; percentage change eGFR, control: −0.6%±22.91% vs. PA: 18.2%±20.37%, $P<0.001$).

Three patients in the PA group had reversible acute kidney injury (AKI) after unilateral adrenalectomy. They were diagnosed with ischemic AKI and recovered after proper conservative management. One patient showed PO renal impairment. Although nonsteroidal anti-inflammatory drugs were prescribed in 16 of 136 patients with PA, there was no case of toxic AKI. PO ileus occurred in 10 patients and infection occurred in 1 of 136 patients. The PO lowest BP was within normal BP range (mean 117.8/73.3 mmHg). These factors, which are regarded as possible causes of AKI, did not show correlation with PO CKD development in the PA group.

Subgroup analysis for patients with long-term follow-up results for 2 years after surgery was performed. A total of 94 patients of the control group and 42 patients of the PA group were included. Renal function was not significantly changed after PO 2 weeks in the PA group. Patients in the control group did not show significant changes in eGFR for 2 years after surgery (supplemental Fig. 2, http://links.lww.com/MD/B82).
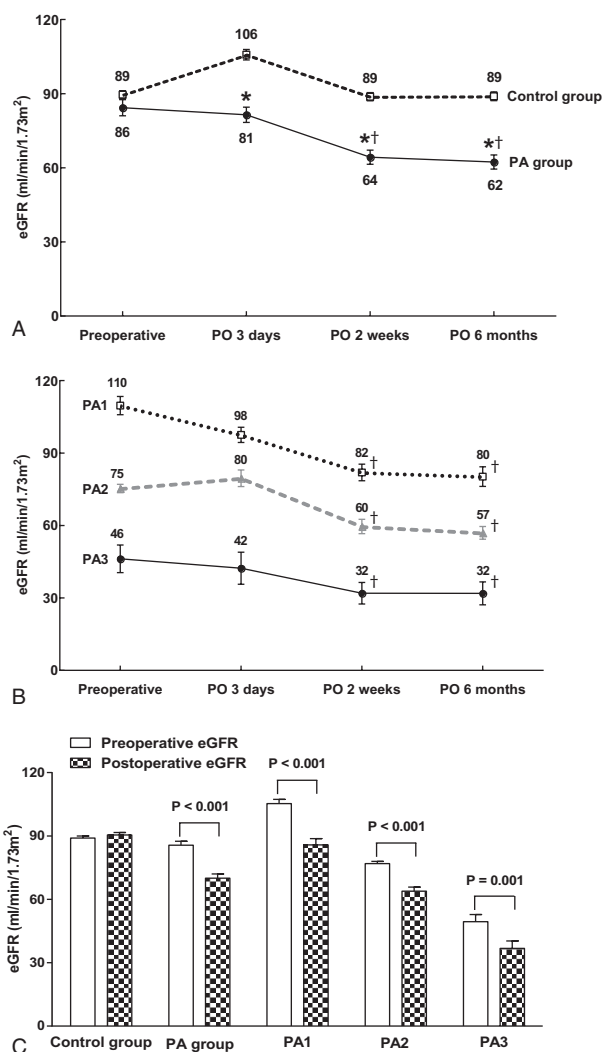

Figure 1. Serial follow-up of renal function in the control and PA groups. (A) There was no difference in preoperative eGFR between the control and the PA groups. In the PA group, eGFR measured 2 weeks and 6 months PO was significantly decreased compared to preoperative eGFR. The PA group showed lower eGFR compared to the control group 3 days, 2 weeks, and 6 months PO. The significant eGFR decline in the PA group compared to that in the control group was consistent at each PO time point according to repeated measures ANOVA (F[2.70, 665.83]=57.63, $P<0.001$). (*) $P<0.05$ compared to the control group at the same time point; (†) $P<0.05$ compared to preoperative eGFR in the same group. (B) Renal impairment after unilateral adrenalectomy in each PA subgroup. The PA group was divided into 3 subgroups according to preoperative eGFR: PA1, eGFR ≥90 mL/min/1.73 m^2; PA2, 60 mL/min/1.73 m^2 ≤ eGFR < 90 mL/min/1.73 m^2; PA3, eGFR <60 mL/min/1.73 m^2. eGFR significantly decreased in all PA subgroups 2 weeks and 6 months PO according to repeated measures ANOVA (F[2.70, 159.15]= 34.02, $P<0.001$). Among 3 subgroups, there were no differences in the degree of PO renal impairment evaluated with 1-way ANOVA ($P=0.218$). (†) $P<0.05$ compared to preoperative eGFR in the same subgroup. (C) Comparison of preoperative and PO eGFR in the control group, the PA group, and each PA subgroup. PO eGFR was significantly lower than preoperative eGFR in the PA group and all PA subgroups, whereas there was no difference between preoperative and PO eGFR in the control group. ANOVA = analysis of variance, eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), PA = primary aldosteronism, PO = postoperative.

3.4. Risk factors for postoperative eGFR decline in all patients

In order to identify risk factors for PO eGFR decline and verify that eGFR would decrease more in the PA group than in the

Table 3

Risk factors for postoperative eGFR decline evaluated by ΔeGFR and percentage change eGFR in all patients.

	ΔeGFR				Percentage change eGFR			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	β coefficient	P	β coefficient	P	β coefficient	P	β coefficient	P
PA	17.107	<0.001	8.303	0.007	21.987	<0.001	12.343	<0.001
Age	0.140	0.063	0.388	<0.001	0.240	0.005	0.457	<0.001
Duration of hypertension	1.037	<0.001	0.606	0.002	1.375	<0.001	0.642	0.004
Systolic BP	0.196	<0.001			0.266	<0.001		
Diastolic BP	0.206	0.001			0.269	<0.001		
BMI	0.163	0.554			0.327	0.294		
Serum potassium	−10.247	<0.001	−4.878	0.006	−12.769	<0.001	−6.384	0.002
Preoperative eGFR	0.376	<0.001	0.554	<0.001	0.316	<0.001	0.528	<0.001
Serum uric acid	0.539	0.394	1.686	0.002	1.203	0.093	2.141	<0.001
Serum cholesterol	−0.023	0.375			−0.022	0.449		
ARR	0.003	0.009			0.003	0.004		
DM	2.455	0.326			2.318	0.413		
CAD	3.146	0.475			6.945	0.164		
LVH	5.088	0.050			6.836	0.020		
Albuminuria	2.467	0.642			2.164	0.719		

Values are based on univariate regression analysis and multivariate regression model with stepwise selection. ARR = aldosterone to renin ratio, BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), LVH = left ventricular hypertrophy, PA = primary aldosteronism.

control group after adrenalectomy, multivariate regression analysis was performed using group, age, duration of hypertension, preoperative BP, BMI, serum potassium, preoperative eGFR, serum cholesterol, serum uric acid, ARR, albuminuria, left ventricular hypertrophy, and several comorbid conditions such as diabetes mellitus and coronary artery disease. Multivariate regression analysis for ΔeGFR and percentage change eGFR indicated that the PA group had greater ΔeGFR (control vs. PA; β = 8.303, P = 0.007) and percentage change eGFR (control vs. PA; β = 12.343, P < 0.001) (Table 3).

Moreover, multivariate regression analysis for percentage change eGFR revealed old age (β = 0.457, P < 0.001), long-standing hypertension (β = 0.642, P = 0.004), low levels of serum potassium (β = −6.384, P = 0.002), high preoperative eGFR (β = 0.528, P < 0.001), and high levels of serum uric acid (β = 2.141, P < 0.001) as risk factors for PO eGFR decline after adrenalectomy. Analysis for ΔeGFR also showed similar results with the analysis for percentage change eGFR.

3.5. Risk factors for postoperative renal impairment and CKD development in patients with PA

Multivariate regression analysis in the PA group revealed old age (β = 0.602, P < 0.001), long-standing hypertension (β = 0.785, P = 0.016), low levels of serum potassium (β = −10.801, P < 0.001), high preoperative eGFR (β = 0.243, P = 0.002), and high levels of serum uric acid (β = 2.966, P = 0.005) as risk factors for PO eGFR decline evaluated by percentage change eGFR (Table 4). Serum cholesterol and albuminuria tended to be associated with PO eGFR decline only in the univariate analysis.

In the PA group, 53 patients (39.0%) showed PO renal impairment, which was defined as PO eGFR decline of >25%. According to the multivariate logistic regression analysis, long-standing hypertension, low BMI, low levels of serum potassium, and high preoperative eGFR were identified as risk factors for PO renal impairment. (Fig. 2A). Among 89 patients with preoperative eGFR ≥60 mL/min/1.73 m^2, 29 patients (32.6%)

Table 4

Risk factors for postoperative eGFR decline evaluated by percentage change eGFR in the PA group.

	Univariate analysis		Multivariate analysis	
	β coefficient	P	β coefficient	P
Age	0.597	<0.001	0.602	<0.001
Duration of hypertension	1.163	<0.001	0.785	0.016
Systolic BP	−0.002	0.981		
Diastolic BP	−0.084	0.451		
BMI	−0.447	0.466		
Serum potassium	−9.862	<0.001	−10.801	<0.001
Preoperative eGFR	0.009	0.908	0.243	0.002
Serum uric acid	3.080	0.008	2.966	0.005
Serum cholesterol	0.093	0.073		
ARR	−0.002	0.122		
DM	3.495	0.049		
CAD	−1.205	0.840		
LVH	0.883	0.818		
Albuminuria	13.993	0.077		

Values are based on univariate regression analysis and multivariate regression model with stepwise selection. ARR = aldosterone to renin ratio, BMI = body mass index, BP = blood pressure, CAD = coronary artery disease, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate (mL/min/1.73 m^2), LVH = left ventricular hypertrophy, PA = primary aldosteronism.
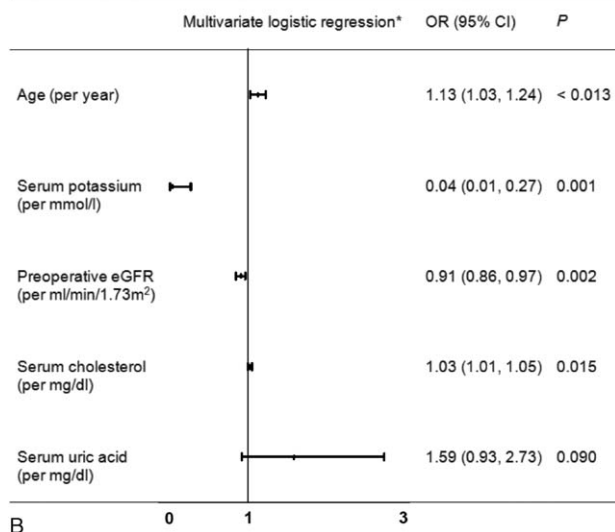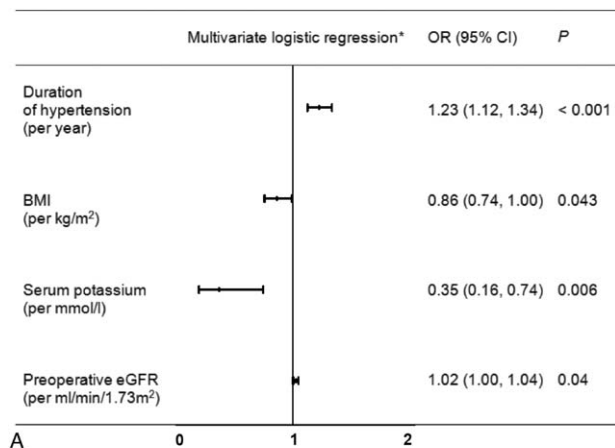
Figure 2. Risk factors for postoperative renal impairment and chronic kidney disease development in patients with primary aldosteronism. (A) Duration of hypertension and preoperative eGFR increased OR. Low BMI and low levels of serum potassium were associated with postoperative renal impairment. (B) Old age, low serum potassium, low preoperative eGFR, and high serum cholesterol were associated with postoperative CKD development. (*) Adjusted by age, duration of hypertension, preoperative blood pressure, BMI, serum potassium, preoperative eGFR, serum cholesterol, serum uric acid, serum aldosterone to renin ratio, albuminuria, left ventricular hypertrophy, diabetes mellitus, and coronary artery disease. BMI = body mass index, CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate (mL/min/1.73 m²), OR = odds ratio.

Figure 3. Postoperative change in the proportion of chronic kidney disease in patients with PA. Before unilateral adrenalectomy, only 12.7% of the PA group had chronic kidney disease (defined as eGFR <60 mL/min/1.73 m²). After surgery, the proportion of chronic kidney disease increased to 41.2%. eGFR = estimated glomerular filtration rate (mL/min/1.73 m²), PA = primary aldosteronism.

4. Discussion

In this study, we demonstrated that significant renal impairment was revealed in patients with PA after unilateral adrenalectomy. These data were confirmed by comparing serial changes in the renal function of patients with PA with those of patients with non-PA adrenal disease who underwent the same surgery and multivariate model adjusted with several comorbidities. Approximately 40% of patients with PA showed a PO eGFR decline of >25%, and the prevalence of CKD significantly increased after adrenalectomy. Furthermore, we identified risk factors for PO renal impairment after adrenalectomy in these patients with PA. Old age, long-standing hypertension, low BMI, low serum potassium, and high serum uric acid or cholesterol were predictors for PO renal impairment and/or PO CKD development. High preoperative eGFR was identified as a risk factor for PO renal impairment, whereas low preoperative eGFR was a risk factor for PO CKD development.

Previous studies reported that glomerular hyperfiltration and aldosterone escape phenomena due to inappropriate aldosterone excess help maintain eGFR, concealing renal function decline as well as structural changes.[4,6,12,13] When excessive aldosterone was decreased to within the normal range with appropriate treatment, by either adrenalectomy or aldosterone antagonist administration, renal impairment was revealed and persisted.[4] Because the increasing prevalence of CKD is a serious public health problem associated with cardiovascular events and mortality,[8,14] early identification of patients with PA at risk of renal impairment after treatment is crucial. However, there have been few reports investigating renal function changes and risk factors for renal impairment in patients with PA after treatment, particularly after adrenalectomy, compared with the control group who received adrenalectomy for other adrenal diseases. Our study, which included a sufficient number of patients, demonstrated that patients with PA develop significant renal impairment after adrenalectomy compared to patients with other adrenal diseases. These findings imply that unilateral adrenalectomy does not cause renal function impairment, per se, but does reveal hidden renal damage related to excessive aldosterone, which leads to renal impairment in patients with PA.

Chronic hypertension and the direct effects of aldosterone induce structural damage to both renal and cardiovascular tissues.[15,16] Plasma aldosterone concentration is inversely correlated with renal function in the general population[17]

developed CKD (eGFR < 60 mL/min/1.73 m²) postoperatively. Multivariate logistic regression analysis showed that old age, low serum potassium, low preoperative eGFR, and high serum cholesterol were associated with PO CKD development (Fig. 2B).

Changes in the proportion of CKD after unilateral adrenalectomy in the PA group are shown in Fig. 3. Only 12.7% (13 of 102 patients with available laboratory data 2 weeks or 6 months PO) exhibited eGFR <60 mL/min/1.73 m² before surgery. However, the proportion of patients with eGFR <60 mL/min/1.73 m² increased to 41.2% (42 of 102 patients) PO. Six patients in the PA1 group (patients with preoperative eGFR ≥90 mL/min/1.73 m²) showed severe PO renal impairment (eGFR <60 mL/min/1.73 m²).
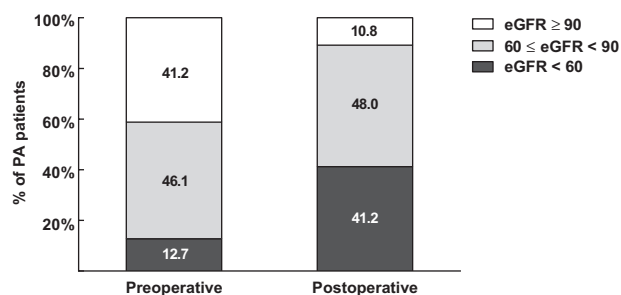
and aldosterone contributes to renal tubulointerstitial fibrosis and scarring.[18] In our study, eGFR of the PA group declined from 85.6±21.80 to 70.0±23.64 mL/min/1.73 m² after unilateral adrenalectomy within 6 months. The proportional PO changes in eGFR were −18.2%±20.37% in the PA group. The proportion of CKD in the PA group increased from 12.7% to 41.2% after operation. Kuo et al demonstrated that relative glomerular hyperfiltration occurred in untreated patients with PA to a greater extent than in patients with essential hypertension.[14] Danforth et al investigated the renal pathology of patients with PA and reported that PA caused renal parenchymal damage and that preoperative renal evaluation did not reflect histopathological changes in the kidney.[19] Our data support the apparent presence of concealed renal damage in patients with PA, which appeared as a PO decrease in eGFR of approximately 20% compared to preoperative eGFR. Furthermore, our data indicate that PA patients with normal eGFR may have a 30% chance of masked CKD before surgical treatment. However, there was no significant correlation between ARR and PO renal impairment.

There were no significant differences between eGFR 2 weeks PO and 6 months PO in the PA group. These results were comparable to those of a recent report showing that significant renal function decline developed within 1 month after unilateral adrenalectomy in 45 patients with PA.[20] Therapeutic effects of adrenalectomy including decline of ARR and improvement of hypertension were evident within 2 weeks after adrenalectomy in the PA group of our study. Rapid disappearance of aldosterone excess after adrenalectomy may have eliminated glomerular hyperfiltration that concealed preexisting renal impairment in patients with PA. Additional decline of eGFR may not occur once masked renal impairment is revealed within 2 weeks after adrenalectomy. This is supported by our subgroup analysis with long-term data demonstrating that renal function did not change between 6 months and 1 year as well as between 1 and 2 years in the PA group. Our results confirmed that renal impairment that occurred within 2 weeks PO persisted in patients with PA, suggesting the necessity of close monitoring of renal function and careful management to avoid volume depletion and nephrotoxic factors such as nonsteroidal anti-inflammatory drugs, especially within the first 2 weeks PO. The degree of renal function decline evaluated with percentage change eGFR was similar between the 3 subgroups of patients with PA divided by preoperative eGFR in this study. These data suggest that the absolute decrement in eGFR is greater in patients with higher preoperative eGFR, implying that close monitoring of renal function and adequate management are also needed in PA patients with good preoperative renal function.

The risk factors for PO renal impairment and PO CKD development in the PA group were also investigated in this study. Old age, long-standing hypertension, low levels of serum potassium, and high levels of uric acid were identified as risk factors for PO eGFR decline in the PA group. In addition to low BMI, long-standing hypertension and low levels of serum potassium were identified as risk factors for PO renal impairment (PO eGFR decline of >25%). Old age, serum potassium, and serum cholesterol were predictive factors for PO CKD development. Regarding preoperative renal function as predictive factors, high preoperative eGFR and low preoperative eGFR were associated with PO renal impairment and CKD development, respectively. Previous studies demonstrated that PO eGFR decline was inversely correlated with baseline glomerular hydrostatic pressure.[6] Thus, the renal function of patients with higher preoperative eGFR may be more likely to be overestimated

before treatment compared to that in other patients. Preoperative low eGFR was associated with the development of PO CKD. PO eGFR decreased to <60 mL/min/1.73 m² in 48.9% of patients with preoperative eGFR between 60 and 90 mL/min/1.73 m². Long-standing hypertension was a predictor for PO eGFR decline as well as significant PO renal impairment. Studies reported that PA was responsible for 6% to 11% of patients with newly diagnosed hypertension.[21,22] Prolonged exposure to excessive aldosterone could be associated with a greater risk of cardiovascular event.[23,24] Early correction of aldosterone excess states was reported to prevent or reverse aldosterone's effects on target organs.[25] Our data and those of previous reports support the importance of thorough screening and appropriate treatment for PA in all patients with newly diagnosed hypertension to prevent the progression of renal impairment. Hypokalemia in patients with PA was a predictor for PO renal impairment and CKD development in our analyses. A previous study reported that low serum potassium correlated with lower eGFR in patients with PA.[21] Low serum potassium has been shown to be associated with eGFR decline after treatment of PA.[9] In contrast, no correlation between hypokalemia and PO CKD development was found in another study.[20] Despite mixed results of previous studies, our data strongly suggested hypokalemia as a predictive factor for glomerular hyperfiltration and concealed renal impairment before treatment of PA. Hyperuricemia is a known risk factor for the progression of CKD[26–28] and also was a risk factor for PO eGFR decline in patients with PA in our study. High cholesterol was linked to PO CKD development. These data are compatible with several previous reports showing the correlation between dyslipidemia and PO CKD development,[7] higher prevalence of dyslipidemia in the CKD population,[29] and progressive renal damage by dyslipidemia.[30,31] Iwakura et al recently reported that high urinary albumin excretion was associated with eGFR decline after treatment of PA.[9] Excessive aldosterone and subsequent long-standing hypertension may be associated with increased urinary albumin excretion followed by CKD.[21,32] Although there was no significant relationship between preoperative urinary albumin excretion measured with dipstick test and PO renal impairment or CKD in this study, the impact of urinary albumin excretion on renal function changes in PA needs to be investigated through further studies including a larger number of patients and using more accurate diagnostic tests, such as the urinary albumin to creatinine ratio.

There are some limitations in this study. First, because the number of unilateral adrenalectomies performed annually for treatment of PA is relatively small, a retrospective design was chosen. A total of 136 patients with PA over a 10-year period were included in our study, which is the largest sample size of any PA study investigating renal impairment thus far. In addition, the statistical power of our study was strengthened by comparing PA patients with the control group receiving the same surgery. Second, the extent of urinary albumin excretion was not thoroughly analyzed, because only the results of urine dipstick tests were available in our patients. Quantitative tests for urinary albumin or protein excretion were performed only in selected cases. Third, both control and PA groups were followed until 6 months PO, which is a relatively short duration for assessing the long-term outcomes of renal damage. However, there were no significant differences in eGFR 2 weeks and 6 months PO, so a 6-month PO follow-up period may be sufficient for analyzing the effects of adrenalectomy on renal function in patients with PA. To overcome this limitation, additional analysis with patients who

had eGFR follow-up data for 2 years after surgery was performed.

In conclusion, significant renal impairment was revealed after surgery in patients with PA. Old age, long-standing hypertension, low levels of serum potassium, low BMI, and high levels of serum uric acid or cholesterol were risk factors for PO renal impairment and/or CKD development in patients with PA. Our study suggests the necessity of thorough risk assessment and serial follow-up of renal function in all patients with PA even when their renal function is within normal range, as well as careful management of PA patients with high risk. Further prospective studies are needed to improve renal outcomes in PA patients with risk factors.

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