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Clinical Research Article

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Increased Dosage of MRA Improves BP and Urinary Albumin Excretion in Primary Aldosteronism With Suppressed Plasma Renin

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Abstract

Purpose: Excessive aldosterone secretion causes a high risk of cardio-cerebrovascular events. Mineralocorticoid receptor antagonist (MRA) is 1 of the treatment strategies for primary aldosteronism (PA). However, current MRA treatment is insufficient because MRA-treated patients with suppressed plasma renin activity (PRA) < 1 ng/mL/h still had a higher risk of cardiovascular disease than those with unsuppressed PRA. This is a prospective interventional study to determine the effects of an increase in MRA dosage on blood pressure (BP) control and urinary albumin excretion (UAE) in MRA-treated PA patients.

Methods: Thirty-four PA patients were recruited, and 24 patients (6 male, 18 female) completed this study. Serum potassium concentration was assessed every two months to adjust the dosage of MRA safely for 6 months. The primary outcomes were the changes in BP and UAE between baseline and 6 months.

Results: Systolic BP (SBP) and $\log_{10}$UAE decreased significantly as the daily dose of MRA increased. Diastolic BP (DBP) tended to decrease. We divided the PA patients into two groups (baseline PRA < 1 ng/mL/h and baseline PRA ≥ 1 ng/mL/h) according to PRA. In the group with baseline PRA < 1 ng/mL/h but not that with baseline PRA ≥ 1 ng/mL/h, SBP, DBP and $\log_{10}$UAE after 6 months were significantly lower than those at baseline.

Conclusions: The increase in MRA dosage improved BP and UAE in PA patients with suppressed PRA.

Key Words: primary aldosteronism, mineralocorticoid receptor antagonist, plasma renin activity, blood pressure, urinary albumin excretion

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Primary aldosteronism (PA) is a major cause of secondary hypertension [1,2]. Since aldosterone hypersecretion not only induces a rise in blood pressure (BP) but also damages the myocardium and arterial walls directly, PA patients have higher risks of cardio-cerebrovascular (CCV) events than those with essential hypertension (EH) [3]. Furthermore, as a result of excessive aldosterone secretion, which causes fibrosis and vasculopathies in the kidneys, kidney function deterioration and the elevation of urinary albumin excretion (UAE) have been detected in PA patients [4-6]. Therefore, PA patients should undergo adrenalectomy (ADX) or be treated with mineralocorticoid receptor antagonist (MRA) to reduce the risk of CCV events and inhibit the progression of renal complications [7,8].

The principle of PA treatment is that ADX is indicated for unilateral disease, and MRA [spironolactone (SPL) and eplerenone (EPL)] treatment is indicated for bilateral disease or in the case of ADX refusal [2,9,10]. ADX improves BP or reduces the daily dose of antihypertensive medication as well as ARR [the ratio of plasma aldosterone concentration (PAC)/plasma renin activity (PRA)] in most PA patients with unilateral disease [11]. However, MRA treatment also improves BP and hypokalemia [9,10] but does nothing to change the aldosterone secretion or might even increase it. Therefore, it is difficult to evaluate whether the effect of MRA treatment is the same as that of ADX.

In an Endocrine Society Clinical Practice Guideline [2], the therapeutic target of MRA treatment is a relatively higher normalizing serum potassium concentration and a decrease in BP to eliminate the vascular, cardiac, and renal effects of aldosterone excess. Recently, a retrospective cohort study reported that PA patients who had reversed the suppression of PRA (≥1 ng/mL/h) had lower incidences of cardiovascular events than PA patients who still had suppressed PRA (<1 ng/mL/h) [12]. This report suggests that current MRA treatment is insufficient and that an increase in MRA dosage may be necessary to protect against damage to aldosterone target organs and reduce cardiovascular events in PA patients.

We therefore conducted a prospective study to determine the effects of an increase in MRA dosage on BP control and UAE in PA patients.

Materials and Methods

Patients

This prospective interventional study was conducted at Osaka University Hospital, a single referral center, between April 2018 and December 2019. Written informed consent was obtained from all patients. This study was approved by the Osaka University Clinical Research Review Committee (no. 17215). Thirty-four PA patients which were both bilateral and unilateral subtype were recruited to this study. Three patients withdrew their consent, and 4 patients dropped out due to polyuria, palpitation, pancreatoduodenectomy, and acute renal failure, respectively. Polyuria might be caused by diuretic effect of MRA, but other adverse events were irrelevant to MRA titration. Acute renal failure was caused by dehydration of gastroenteritis before the MRA dosage was titrated upward. Another 3 patients did not increase their MRA dosage because their serum potassium concentrations were ≥4.6 mEq/L during the study period. Finally, 24 patients (6 male, 18 female) completed this study. The median age of these patients was 60 (48-74) years, and the median body mass index was 25.2 (22.4-31.6) kg/m^2. The median duration of hypertension was 6 (2-13) years, and the median duration of MRA treatment (after PA diagnosis) was 2 (1-4) years. Fifteen patients were treated with SPL, and the remainder were treated with EPL. The patients took 1 (0-1) antihypertensive medications in addition to MRA. All patients had normal serum potassium at baseline. The prevalence of diabetes mellitus was 16.7% (4 patients), dyslipidemia was 54.2% (13 patients) and ever smoking was 41.7% (10 patients).

Study Design

The diagnosis of PA was based on the criteria defined by the Japan Endocrine Society [1] and the Japan Society of Hypertension [13]. PA patients who were ≥20 years of age and had been taking MRA (below the maximum dosage) for more than 6 months were recruited to this study. Exclusion criteria were serum potassium ≥ 4.6 mEq/L, heart disease (above New York Heart Association classification III), liver disease (aspartate transaminase and/or alanine transaminase ≥ 100 IU/mL), kidney disease (creatinine ≥ 2.0 mg/dL), and other serious problems such as malignant diseases. We assessed serum potassium concentrations every 2 months to adjust the dosage of MRA (SPL or EPL that PA patients had already been taking) safely for 6 months. SPL is considered twice as potent as EPL [2]. Therefore, the dosing was calculated by multiplying SPL total daily dose by 2 and EPL total daily dose by 1 [12]. The MRA dosage was gradually titrated upward until serum potassium reached 4.6 to 5.0 mEq/L. The same dosage of MRA was maintained on the condition that serum potassium was 4.6 to 5.0 mEq/L. When serum potassium was ≥5.5 mEq/L, the dosage of MRA was reduced. Other antihypertensive medications such as calcium-channel blocker (15 cases), angiotensin-converting enzyme inhibitor or angiotensin α receptor blocker (4 cases), beta blocker (1 case), and diuretics (1 case) were used not changed during this study.

The primary outcomes were the changes in BP and UAE between baseline and 6 months. We also monitored estimated glomerular filtration rate (eGFR) and electrolytes.

Quality of life (QOL) was evaluated using the Short Form 36 Health Survey (SF-36) at baseline and after 6 months. The SF-36 comprises 35 items evaluating 8 domains: physical functioning, role limitations due to physical problems (role physical), bodily pain, general health perception, vitality, social functioning, role limitation due to emotional problems (role emotional), and mental health [14,15].

Laboratory Measurements

BP was measured twice by a doctor using upper-arm cuff device based on the cuff-oscillometric principle with the supine position after few minutes of rest at the same time of day. The data on second measurement were adopted for analysis. Urinary samples (spot) and venous blood samples were obtained in the fasting condition in the morning. UAE was measured by immunonephelometry. PAC was determined by chemiluminescent enzyme immunoassay (Accuraseed Aldosterone, FUJIFILM Wako Pure Chemical, Co., Tokyo, Japan) [16]. The reference range of PAC measured in the supine position was 3.0 to 15.9 ng/dL. PRA was measured by a PRA enzyme immunoassay kit (Yamasa, Co., Choshi, Japan) [17]. The reference range of PRA in the supine positive group was 0.2 to 2.3 ng/mL/h.

Statistical Analysis

Data are expressed as median (interquartile range). The paired data between baseline and 6 months were compared by the Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables. Differences between baseline PRA < 1 ng/mL/h group and baseline PRA ≥ 1 ng/mL/h group were compared by the Wilcoxon test for continuous variables and by chi-square test for categorical variables. Linear regression analysis was used to show relationship between BP and UAE. Statistical significance was accepted at the $P < 0.05$ significance level. All statistical analyses were performed using JMP Pro software for Windows (ver.14, SAS Institute, Cary, NC, USA).

Results

Effects of the Upward Titration of MRA Dosage on Clinical Parameters in PA Patients

The changes in the clinical parameters after the upward titration of MRA dosage are shown in Table 1. The daily dose of MRA significantly increased [50 (50-75) vs 150 (100-200) mg/d, $P < 0.01$]. The upward titration of MRA dosage significantly increased PRA [1.0 (0.6-2.3) vs 2.6 (1.4-5.0) ng/mL/h, $P < 0.01$) and decreased ARR [17.8 (11.6-48.7) vs 10.3 (5.2-19.9), $P < 0.01$]. There was no difference in PAC between baseline and 6 months [25.5 (17.2-36.4) vs 26.2 (13.9-33.4), $P = 0.88$].

The changes in BP and UAE as primary outcomes are shown in Figure 1. SBP [136 (124-148) vs 127 (120-139) mmHg, $P < 0.01$] and $\log_{10}$UAE [1.1 (0.8-1.4) vs 0.8 (0.6-1.1) mg/gCr, $P < 0.01$] decreased significantly as the daily dose of MRA increased. DBP [76 (69-89) vs 72 (68-82) mmHg, $P = 0.06$] tended to decrease. There was no relationship between ΔUAE and ΔSBP or ΔDBP (Fig. 2A and 2B).

Interestingly, serum potassium concentration significantly increased after 2 months compared with baseline [4.4 (4.1-4.6) vs 4.2 (4.1-4.4) mEq/L, $P < 0.01$], then decreased after 4 months, and were almost the same as at baseline after 6 months [4.2 (4.0-4.4) vs 4.2 (4.1-4.4) mEq/L, $P = 0.89$] (Table 1). Although eGFR significantly decreased after 2 and 4 months compared with baseline [62.3 (54.7-73.4) vs 69.0 (57.2-80.3) mL/min/1.73 m^2, $P < 0.01$; 64.6 (53.7-75.6) vs 69.0 (57.2-80.3) mL/min/1.73 m^2, $P < 0.01$, respectively], there was no significant difference in eGFR between 6 months and baseline [63.9 (52.2-77.8) vs 69.0 (57.2-80.3) mL/min/1.73 m^2, $P = 0.08$] (Table 1). Both serum sodium and chloride were significantly lower after 6 months than at baseline [140 (138-141) vs 141 (139-142) mEq/L, $P < 0.01$; 105 (103-105) vs 105 (104-107) mEq/L, $P = 0.02$, respectively] (Table 1). There were no patients with hyponatremia or hypochloremia during this study period. Metabolic parameters such as body mass index, abdominal circumference, and hemoglobin A1c were not significantly different between baseline and 6 months [25.2 (22.4-31.6) vs 24.7 (22.1-31.3) kg/m^2, $P = 0.19$; 88.0 (82.0-95.8) vs 87.0 (83.0-95.0) cm, $P = 0.66$; 5.7 (5.5-6.0) vs 5.8% (5.5%-6.2%), $P = 0.53$, respectively).

With regard to QOL, there was no difference in any of the 8 domains of SF-36 between baseline and 6 months (Table 1).

Comparison of Clinical Parameters Between the Patient Groups With Baseline PRA < 1 ng/mL/h and Baseline PRA ≥ 1 ng/mL/h After the Upward Titration of MRA Dosage

Based on the report by Hundemer et al [12], we divided the 24 PA patients into 2 groups: 1 patient group with baseline PRA < 1 ng/mL/h (n = 12) and the other with baseline PRA ≥ 1 ng/mL/h (n = 12) (Table 2). There was no difference in baseline clinical characteristics except PRA and ARR between the 2 groups (Table 2). The duration of MRA treatment for the 2 groups were 2 (1-4) years in the PRA < 1 ng/mL/h group and 2 (1-7) years in the PRA ≥ 1 ng/mL/h group ($P = 0.79$). The MRA dosage significantly increased in both groups after 6 months compared to baseline [group with baseline PRA < 1 ng/mL/h: 50 (50-69) vs 175 (113-200) mg, $P < 0.01$; group with baseline PRA ≥ 1 ng/mL/h: 50 (50-94) vs 100 (100-200) mg, $P < 0.01$].

Table 1. Changes of clinical parameters between baseline and after 6 months of the upward titration of MRA dosage

	Baseline	After 2 months	After 4 months	After 6 months	P
MRA equivalent potency total daily dose, mg	50 (50-75)	100 (100-138)**	100 (100-200)**	150 (100-200)	<0.01
Spironolactone total daily dose, mg	25 (25-50)	50 (50-75)**	75 (50-100)**	100 (75-125)	<0.01
Eplerenone total daily dose, mg	50 (50-50)	100 (50-100)*	100 (88-100)**	100 (100-100)	<0.01
Plasma aldosterone concentration, ng/dL	25.5 (17.2-36.4)	—	—	26.2 (13.9-33.4)	0.88
Plasma renin activity, ng/mL/h	1.0 (0.6-2.3)	—	—	2.6 (1.4-5.0)	<0.01
Plasma renin activity ≥ 1, ng/mL/h	50.0%	—	—	83.3%	0.01
ARR, ng/dL/ng/mL/h	17.8 (11.6-48.7)	—	—	10.3 (5.2-19.9)	<0.01
ARR < 20, ng/dL/ng/mL/h, %	54.2	—	—	79.2	0.01
Serum potassium, mEq/L	4.2 (4.1-4.4)	4.4 (4.1-4.6)**	4.3 (4.0-4.4)	4.2 (4.0-4.4)	0.89
Serum potassium ≥ 4.6 mEq/L, %	4.2	33.3*	12.5	16.7	0.18
Serum sodium, mEq/L	141 (139-142)	140 (139-141)	140 (138-141)	140 (138-141)	<0.01
Serum chloride, mEq/L	105 (104-107)	105 (103-107)	105 (104-108)	105 (103-105)	0.02
Urinary sodium/ potassium excretion ratio	1.5 (1.0-2.4)	-	-	2.1 (1.3-3.4)	0.06
Urinary albumin/creatinine excretion ratio, mg/gCr	12.1 (6.6-25.0)	-	-	6.5 (4.1-12.2)	0.03
eGFR, mL/min/1.73 m^2	69.0 (57.2-80.3)	62.3 (54.7-73.4)**	64.6 (53.7-75.6)**	63.9 (52.2-77.8)	0.08
SF-36					
Physical functioning	95.0 (85.0-100.0)	—	—	95.0 (85.0-100.0)	0.30
Role physical	100.0 (81.3-100.0)	—	—	93.8 (82.9-100.0)	0.59
Bodily pain	84.0 (72.0-100.0)	—	—	92.0 (61.3-100.0)	0.50
General health perception	62.0 (45.5-72.0)	—	—	59.5 (52.0-75.8)	0.76
Vitality	65.7 (46.9-79.7)	—	—	62.5 (45.4-75.0)	0.59
Social functioning	100.0 (87.5-100.0)	—	—	100.0 (78.1-100.0)	0.65
Role emotional	91.7 (77.1-100.0)	—	—	100.0 (75.0-100.0)	0.57
Mental health	75.0 (60.0-85.0)	—	—	77.5 (60.0-90.0)	0.23

Data are median (first and third quartiles) values unless otherwise noted. eGFR was obtained using the following equation: estimated glomerular filtration rate (mL/min/1.73 m^2) = 194 × serum creatinine (−1.094) × age (−0.287) × 0.739 (if female). *P*-values indicate baseline vs after 6 months.
Abbreviations: ARR, plasma aldosterone concentration/plasma renin activity ratio; eGFR, estimate glomerular filtration rate; MRA, mineralocorticoid receptor antagonist.
*$P < 0.05$, **$P < 0.01$; vs baseline.

The changes in BP and UAE are shown in Figure 1. In the patient group with baseline PRA < 1 ng/mL/h but not the group with baseline PRA ≥ 1 ng/mL/h, SBP, DBP and $\log_{10}$UAE at 6 months were significantly lower than those at baseline [SBP 137 (123-150) vs 125 (121-136) mmHg, $P = 0.02$; DBP 78 (71-90) vs 72 (67-81) mmHg, $P = 0.04$; $\log_{10}$UAE: 1.1 (0.8-1.4) vs 0.8 [0.5-1.0] mg/gCr, $P < 0.01$). There was no relationship between ΔUAE and ΔSBP or ΔDBP in the patient group with baseline PRA < 1 ng/mL/h (Fig. 2C and 2D).

Although PAC, serum potassium concentration, and eGFR did not change in either group, PRA after 6 months significantly increased in the patient group with baseline PRA < 1 ng/mL/h compared to baseline (Table 2). Serum sodium and chloride were lower at 6 months than at baseline in the patient group with baseline PRA < 1 ng/mL/h but not in the group with baseline PRA ≥ 1 ng/mL/h (Table 2).

Discussion

Previous studies reported that MRA treatment is effective in reducing BP and UAE in PA patients [9,10,18-20]. We demonstrated that the upward titration of MRA dosage until the upper limit of normal serum potassium concentration was reached brought additional clinical benefit to PA patients who had already been treated with MRA. In particular, the upward titration of MRA dosage was safe from the point of view of serum potassium concentration, eGFR, and QOL and decreased BP and UAE in PA patients with PRA < 1 ng/mL/h.

Karagiannis at el [9] reported the effects of EPL or SPL on BP after a 2-week drug washout period in patients with bilateral idiopathic hyperaldosteronism. They assessed BP every 4 weeks, and the doses were gradually increased up to 400 mg for SPL and 200 mg for EPL if the patient's BP was not less than 140/90 mmHg. They showed that both EPL and SPL were effective in reducing BP in patients with idiopathic hyperaldosteronism.

High BP is the most important risk factor for CCV diseases [21]. Therefore, BP-lowering treatment reduces the risk of CCV diseases [22,23]. On the other hand, previous studies demonstrated that UAE is an independent predictor of cardiovascular events in patients with hypertension and reduction in UAE by hypertensive treatment is associated with reduced risk of cardiovascular events [24]. Our results

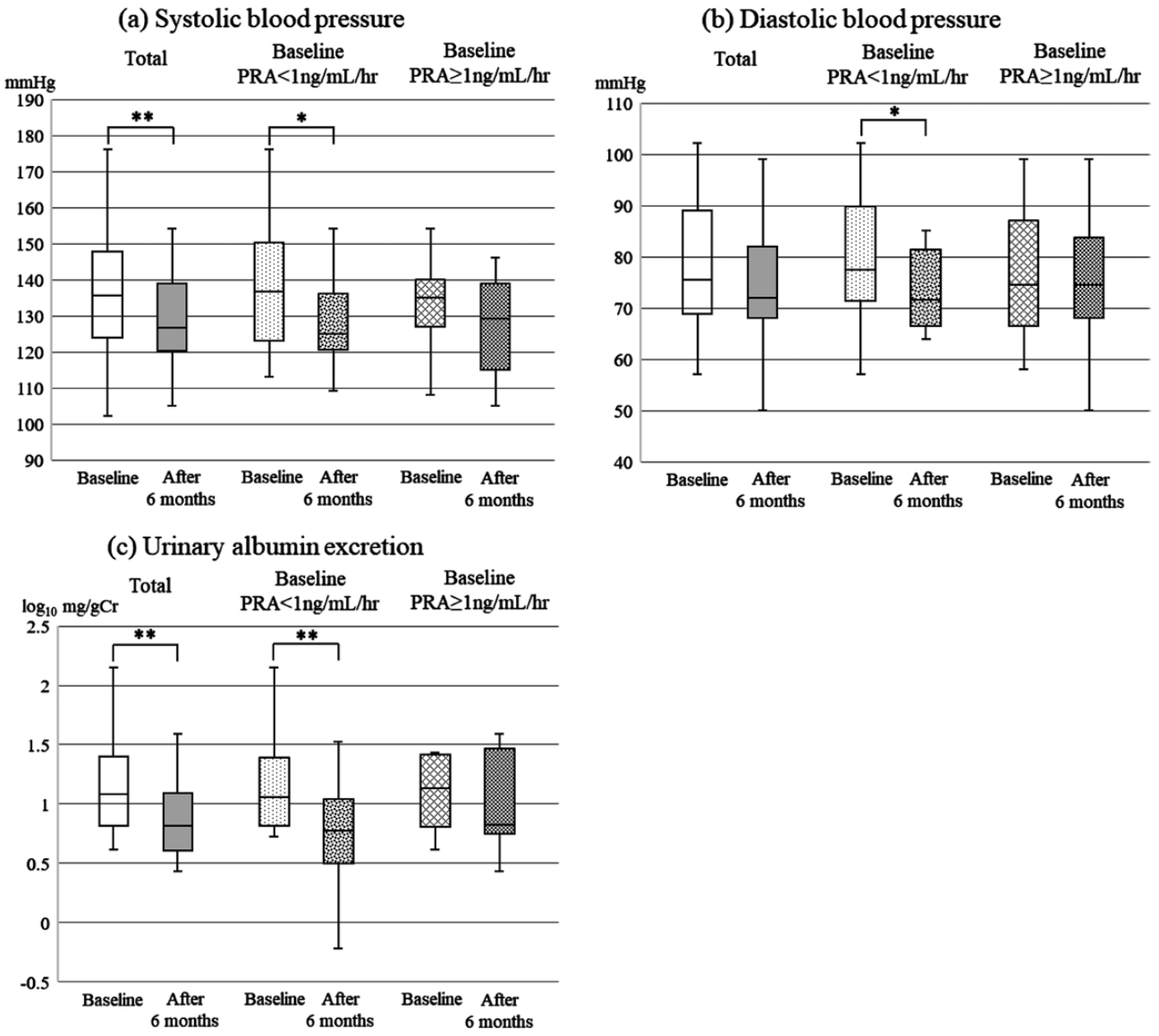

Figure 1. Changes in blood pressure and urinary albumin excretion between baseline and after 6 months of the upward titration of mineralocorticoid receptor antagonist dosage in primary aldosteronism patients. Changes in (A) systolic blood pressure, (B) diastolic blood pressure, and (C) urinary albumin excretion in 24 patients, 12 with baseline plasma renin activity (PRA) < 1 ng/mL and 12 with baseline PRA ≥ 1 ng/mL, are shown. $^{*}P < 0.05$, $^{**}P < 0.01$.

suggested that the upward titration of MRA dosage improved BP and UAE and could be expected to reduce the risk of CCV events in PA patients.

Excessive aldosterone secretion is one of risk factor for chronic kidney disease (CKD) in addition to hypertension and UAE, which are known risk factors. In the kidneys, excessive aldosterone exposure causes an increase in intravascular volume and hyperfiltration and leads to elevated eGFR in the early stage [8,25]. Persistent exposure to excessive aldosterone induces renal fibrosis, vascular disease, and podocyte injury [4,5,26]. Consequently, eGFR declines and UAE rises in the late stage [6,27]. The treatments for PA have been shown to stop the excessive aldosterone-induced hyperfiltration in the kidneys. As a result, eGFR and UAE were improved [19,27]. Hundemer et al [20] reported no difference in the annual decline in eGFR or the incidence of CKD between PA patients treated with ADX and age- and eGFR-matched EH patients. However, PA patients treated with MRA had a greater decline in eGFR and a higher risk for CKD despite similar BP control as EH patients and PA patients with ADX. Although they showed that MRA treatment was associated with a higher risk for developing CKD than ADX in PA, our results suggest that the adequate titration of MRA dosage may suppress the development of CKD and CCV diseases because low eGFR and high UAE are associated with coronary heart disease and mortality [28-30].

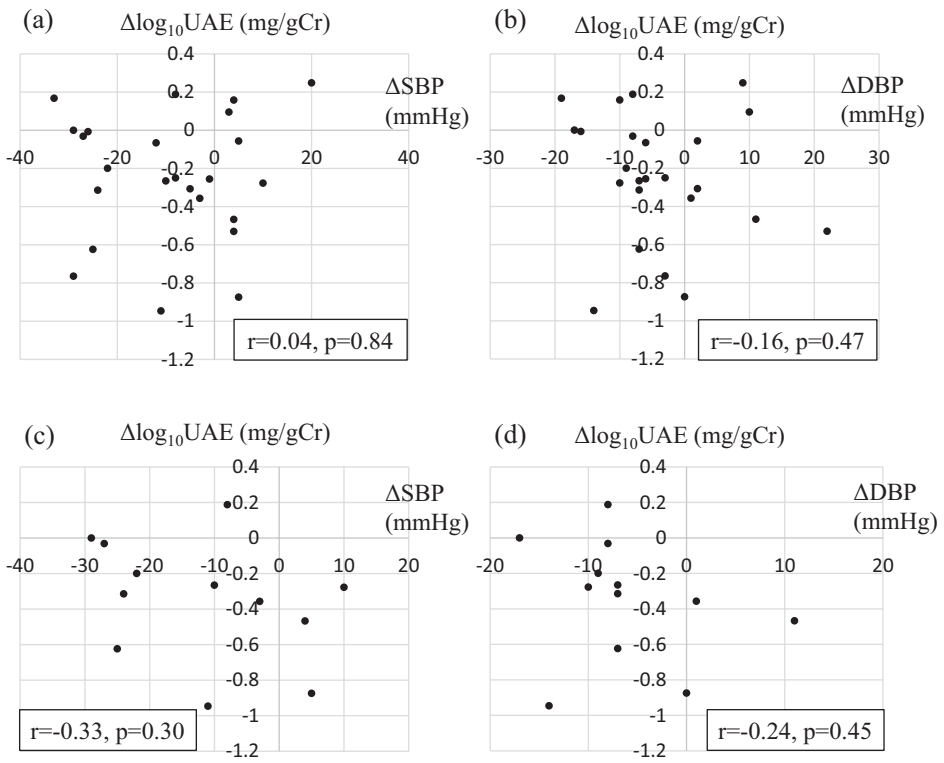

Figure 2. Relationship between Δlog_{10}UAE and ΔBP in 24 primary aldosteronism patients and 12 patients with baseline plasma renin activity (PRA) < 1 ng/mL/h. Correlations between (A) Δlog_{10}UAE and ΔSBP in all 24 PA patients, (B) Δlog_{10}UAE and ΔDBP in all 24 PA patients, (C) Δlog_{10}UAE and ΔSBP in patients with baseline PRA < 1 ng/mL, and (D) Δlog_{10}UAE and ΔDBP in patients with baseline PRA < 1 ng/mL are shown.

PRA suppression in PA indicates excessive MR activation and volume expansion [2]. Our results showed that SBP, DBP, and log_{10}UAE after 6 months of the upward titration of MRA dosage were significantly lower than those at baseline in PA patients with baseline PRA < 1 ng/mL/h but not those with baseline PRA ≥ 1 ng/mL/h. Compared with patients with EH, MRA-treated PA patients with suppressed PRA (<1 ng/mL/h) have a higher risk of cardiovascular events, whereas those with unsuppressed PRA (≥1 ng/mL/h) have no significant risk [12]. These results suggest that unsuppressed PRA indicates the full blockage of MR activation by excessive aldosterone, and PA patients with suppressed PRA should be considered for an increase in MRA dosage. Improvement of BP and UAE with increasing MRA dosage may play an important role in decreasing the risk of cardiovascular events in PA patients with baseline PRA < 1 ng/mL/h. Both of renin-angiotensin system blockade and antidiabetic therapy are beneficial to reducing UAE [31,32]. In our study, 2 of 4 patients with diabetes mellitus were treated by antidiabetic drugs: 1 patient with metformin and the other patient with alogliptin plus metformin. An angiotensin-converting enzyme inhibitor or angiotensin 2 receptor blocker was used in 4 patients. Although our results demonstrated that the increase in MRA dosage improved UAE in PA patients, continued renin-angiotensin system blockade and antidiabetic therapy might be the positive additive effect on the improvement of UAE.

There was no significant an increase in PAC after 6 months of the upward titration of MRA dosage compared to baseline in this study. Previous studies showed that the initiation of MRA treatment increased PAC [10]. However, Pecori et al reported that MRA treatment led to a significant increase in PRA but not PAC, which is the same result as this study [33]. They also suggested that only a complete desuppression of the renin-angiotensin axis may effectively stimulate aldosterone secretion because patients with PAC increase ≥ 10 ng/dL display higher levels of PRA than patients with no or a smaller increase of PAC [33]. Our data and this report suggest that PRA might be a better marker for MRA treatment compared to PAC.

MRA treatment is known to decrease GFR and elevate serum potassium concentrations [9,10]. Although serum potassium concentration was significantly increased until 2 months and eGFR was significantly decreased until 4 months in our study, there was no difference in serum potassium concentration or eGFR between baseline and 6 months. We speculate that some adaptation mechanism by MRA treatment might have led to these results.

There is the possibility that MRA treatment affects QOL due to excessive antialdosterone action (deficiency of mineralocorticoid). We showed that the serum sodium

Table 2. Comparison of clinical parameters between patient group with baseline PRA < 1 ng/mL/h and base line PRA ≥ 1 ng/mL/h after the upward titration of MRA dosage

	PRA < 1 ng/mL/h (n = 12)			PRA ≥ 1 ng/mL/h(n = 12)		
	Baseline	After 6 months	P	Baseline	After 6 months	P
Sex male/female (% male)	3/9 (25.0)	—	—	3/9 (25.0)	—	—
Age, years	58 (50-70)	—	—	65 (45-76)	—	—
Duration of hypertension, years	7 (3-12)	—	—	4 (1-17)	—	—
Duration of MRA treatment, years	2 (1-4)	—	—	2 (1-7)	—	—
Spironolactone/eplerenone (% spironolactone)	9/3 (75.0)	—	—	6/6 (50.0)	—	—
Number of antihypertensive medications	1 (0-1)	—	—	0 (0-2)	—	—
Diabetes mellitus, %	8.3	—	—	25.0	—	—
Dyslipidemia, %	50.0	—	—	58.3	—	—
Ever smoker, %	58.3	—	—	25.0	—	—
MRA equivalent potency total daily dose, mg	50 (50-69)	175 (113-200)	<0.01	50 (50-94)	100 (100-200)	<0.01
Spironolactone total daily dose, mg	25 (25-44)	100 (75-125)	<0.01	38 (25-50)	100 (66-131)	0.03
Eplerenone total daily dose, mg	50 (50-50)	100 (100-100)	0.25	50 (44-56)	100 (94-100)	0.03
Plasma aldosterone concentration, ng/dL	22.7 (15.6-34.3)	23.3 (13.8-29.0)	0.64	26.6 (18.3-45.9)	27.3 (15.3-40.2)	0.62
Plasma renin activity, ng/mL/h	0.6 (0.4-0.8)	2.3 (0.7-3.2)	<0.01	2.2 (1.3-4.0)**	4.0 (1.6-7.2)	0.11
ARR, ng/dL/ng/mL/h	47.2 (20.1-65.7)	12.4 (5.9-23.1)	0.03	12.4 (8.0-15.3)**	7.0 (4.4-19.4)	0.06
ARR < 20, ng/dL/ng/mL/h, %	25.0	75.0	0.01	83.3*	83.3	1.00
Serum potassium, mEq/L	4.2 (4.1-4.5)	4.3 (4.0-4.6)	0.60	4.3 (4.1-4.4)	4.1 (3.9-4.4)	0.65
Serum sodium, mEq/L	141 (140-143)	140 (137-141)	<0.01	140 (138-141)	139 (138-141)	0.33
Serum chloride, mEq/L	106 (105-108)	105 (103-108)	0.03	105 (103-106)*	105 (102-105)	0.34
Urinary sodium/potassium excretion ratio	1.75 (1.40-2.68)	1.54 (1.24-3.32)	0.30	1.25 (0.98-2.43)	2.31 (1.41-3.39)	0.11
Urinary albumin/ creatinine excretion ratio, mg/gCr	11.3 (6.6-24.6)	6.0 (3.1-11.0)	0.04	13.7 (6.3-25.8)	6.6 (5.6-31.8)	0.38
eGFR, mL/min/1.73 m^2	73.1 (60.9-84.7)	67.9 (56.2-78.4)	0.08	63.2 (52.2-73.0)	59.7 (46.9-74.9)	0.58

Data are median (first and third quartiles) values unless otherwise noted.
Abbreviations: ARR, plasma aldosterone concentration/plasma renin activity ratio; eGFR, estimate glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; PRA, plasma renin activity.
*$P < 0.05$, **$P < 0.01$; baseline PRA ≥ 1 ng/mL/h vs baseline PRA < 1 ng/mL/h.

and chloride concentrations after 6 months of the upward titration of MRA dosage were significantly lower than those at baseline. However, there was no patient with hyponatremia or hypochloremia and no difference in QOL between baseline and 6 months. Based on these results, we conclude that the upward titration of MRA dosage until the patient reaches the upper limit of normal serum potassium concentration is safe and does not affect QOL.

Conclusion

In conclusion, the increase in MRA dosage improved BP and UAE in PA patients with suppressed PRA (<1 ng/mL/h). The PRA level as well as BP and serum potassium are useful indicators to use when titrating the MRA dosage for the inhibition of excessive aldosterone action.

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Disclosure Summary

The authors declare no conflicts of interest.

Additional Information

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Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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