Original Paper

Effects of Spironolactone in Combination with Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Patients with Proteinuria

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Key Words

Spironolactone • Proteinuria • Aldosterone escape

Abstract

Background/Aims: This study aimed to investigate the potential beneficial anti-proteinuric effect of an add-on aldosterone blockade and the impact of the aldosterone escape phenomenon. **Methods:** We retrospectively analyzed data of 304 patients with persistent proteinuria, who were administered spironolactone (25 mg/day) after treatment with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) for >3 months. Patients were divided according to their aldosterone levels during ACEI/ARB treatment into an escape group (plasma aldosterone >80 pg/mL, N=95, 31.5%) and a non-escape group (plasma aldosterone ≤80 pg/mL, N=209, 68.5%) and according to their urine albumin-to-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR). **Results:** After 12 months, the UACR decreased significantly in patients with $1 \leq \text{UACR} < 3.5$ g/g Cr, $\text{UACR} \geq 3.5$ g/g Cr, and $\text{eGFR} \geq 60$ mL/min/1.73 m², and in the non-escape group. Severe hyperkalemia ($K \geq 7.0$ mEq/L) developed in 9 of 137 patients with $\text{eGFR} < 60$ mL/min/1.73 m² (6.5%) and in none of the 167 patients with $\text{eGFR} \geq 60$ mL/min/1.73 m². **Conclusions:** Proteinuria decreased significantly after add-on spironolactone treatment in patients with $1 \leq \text{UACR} < 3.5$ g/g Cr, $\text{UACR} \geq 3.5$ g/g Cr, and $\text{eGFR} \geq 60$ mL/min/1.73 m², and in the non-escape group. The anti-proteinuric effect of spironolactone may vary according to the degree of albuminuria, impaired eGFR, and aldosterone escape.

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Introduction

Proteinuria and albuminuria are independent predictors of kidney disease progression [1]. The renin-angiotensin system (RAS) has long been known to play an important role in the pathogenesis of chronic kidney disease [2], and hence, current standards of practice recommend blockade of the RAS with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) [3, 4]. However, additional treatment is needed as RAS blockade with ACEIs or ARBs attenuates but fails to abrogate progressive kidney disease [4].

Several studies have reported an increase in plasma aldosterone levels in a substantial portion of patients who were given RAS blockers over the long-term—after an initial decline [5–7]. This phenomenon, known as aldosterone escape, could have important clinical consequences since aldosterone by itself, independent of the RAS, is an important pathogenic factor in progressive kidney disease [8, 9]. In this context, adding mineralocorticoid receptor (MR) blockers to conventional RAS blockers has been suggested as an alternative treatment plan. However, no comparison studies between patients with and without aldosterone escape have been published.

Spironolactone has been commonly used in patients with liver cirrhosis or proteinuria in combination with ACEIs or ARBs, with proven effectiveness and safety after a long-term follow-up [10]. The well-documented mechanisms of spironolactone include glomerular hemodynamic change, pro-fibrotic and pro-inflammatory effects, and direct effects on podocytes [11]. Although the anti-proteinuric effect of spironolactone is well known, prophylactic treatment with spironolactone is not recommended in every patient with proteinuria because of the risk of hyperkalemia and a decline in the estimated glomerular filtration rate (eGFR) [12, 13].

The aim of this retrospective study was to investigate the potential beneficial anti-proteinuric effects of spironolactone and the impact of the aldosterone escape phenomenon.

Materials and Methods

Study population

We retrospectively analyzed the data of 304 patients who visited the kidney out-patient department of Chonnam National University Hospital from March 2012 to December 2013. This study was approved by the institutional review board of Chonnam National University Hospital, Gwangju, Korea (CNUH-2013-135). This institutional review board waived the need for consent given the retrospective design of the project.

We studied the effects of spironolactone (25 mg/day) in 304 patients who showed persistent proteinuria after treatment with ACEIs or ARBs for more than 3 months. As per the findings of a recent study [1], our hospital's practice pattern was to add spironolactone in the presence of persistent proteinuria (urine albumin-to-creatinine ratio [UACR] of >100 mg/dL or urine dipstick ≥1+, if UACR was unavailable), despite treatment with conventional RAS blockers. The chemical profiles, including UACR, were checked every 3 months to quantify the proteinuria.

Systolic and diastolic blood pressure, plasma aldosterone level, plasma renin activity, serum potassium, eGFR, and UACR were assessed at baseline, and at 6 months and 12 months after spironolactone add-on treatment. Other variables including age, sex, pre-existing diabetes, and spironolactone complications were also investigated. Serum creatinine levels were analyzed using the Jaffe method calibrated for isotope dilution mass spectrometry. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows: $\text{mL/min}/1.73 \text{ m}^2 = 141 \times \text{minimum (creatinine/k, 1)}^\alpha \times \text{maximum (creatinine/k, 1)}^{-1.209} \times 0.993^{\text{age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$, where κ is 0.7 for women and 0.9 for men and α is -0.329 for women and -0.411 for men [2].

Patients were divided into two groups according to their aldosterone levels during treatment with ACEIs or ARBs (an aldosterone escape group [plasma aldosterone >80 pg/mL, N=95, 31.5%] and an aldosterone non-escape group [plasma aldosterone ≤80 pg/mL, N=209, 68.5%]). Aldosterone escape was defined as plasma aldosterone level >80 pg/mL after treatment with ACEIs or ARBs for more than 3 months

Table 1. Demographic and clinical data at baseline according to group characteristics

	Total	UACR <1 (g/g Cr)	1≤UACR<3.5 (g/g Cr)	UACR ≥3.5 (g/g Cr)	P-value	eGFR ≥60 (mL/min/1.73 m ²)	eGFR <60 (mL/min/1.73 m ²)	P-value
N	304	204 (66.9 %)	89 (29.2 %)	11(3.6 %)		167 (54.8%)	137 (45.2 %)	
Men (%)	201 (66.1%)	144 (70.6 %)	48 (53.9 %)	9 (81.8 %)	0.019	108 (64.7%)	93 (67.9 %)	0.556
Age (years)	49±15.3	49±15.3	48±15.1	52±16.9	0.626	45±14.9	54±14.2	<0.001
Diabetes (%)	51 (16.7%)	22 (10.8 %)	24 (26.9 %)	5 (45.5 %)	<0.001	18 (10.8%)	33 (23.9 %)	0.002
SBP (mmHg)	122±15.4	121±14.2	123±14.7	135±33.9	0.013	120±13.4	124±17.2	0.023
DBP (mmHg)	74±12.4	74±12.4	76±12.7	74±15.7	0.267	74±12.7	75±11.9	0.289
eGFR (mL/min/1.73 m ²)	64±38.5	66±36.9	62±42.1	46±33.8	0.176	100±33.8	38±12.3	<0.001
UACR (mg/g Cr)	944±925.5	439±276.7	1974±932.0	4090±815.1	<0.001	869±762.0	1035±1088.3	0.135
Potassium (mg/dL)	4.4±0.52	4.3±0.50	4.5±0.55	4.6±0.43	0.080	4.2±0.38	4.6±0.55	<0.001
Aldosterone (pg/mL)	76±93.2	87.3±105.5	62.3±73.0	30.4±33.0	0.032	62.9±73.79	93.1±110.56	0.007

Data are presented as n (%) or mean ± SD. UACR, urine albumin to creatinine ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate

[3]. Patients were also divided into two groups according to their eGFR (eGFR ≥60 mL/min/1.73 m² [N=167, 54.8%] and eGFR <60 mL/min/1.73 m² [N=137, 45.2%]), and into three groups according to the degree of albuminuria (UACR <1g/g Cr, [N=204, 66.9%], 1≤UACR<3.5 g/g Cr, [N=89, 29.2%], and UACR ≥3.5 g/g Cr, [N=11, 3.6%]).

Statistical analyses

Analyses were performed using SPSS 18.0.0 (SPSS Inc., Chicago, IL, USA). Normally distributed variables are reported as mean with standard deviations and compared using Student's t-test and categorical variables as proportions or ratios. The baseline characteristics of the study participants were compared using independent t-test or chi-square, where appropriate. Within-group changes of outcome variables after 6 and 12 months were assessed using paired t-test. P-values < 0.05 were considered significant.

Results

Baseline characteristics of patients

304 patients (men 66.1%, age 49±15.3 years) were divided into two groups according to the degree of albuminuria, renal insufficiency, and aldosterone escape (Table 1). Patients with 1≤UACR<3.5 g/g Cr and UACR ≥3.5 g/g Cr had a higher systolic blood pressure, higher incidence of pre-existing diabetes, and lower serum aldosterone level than patients with UACR <1g/g Cr. Patients with eGFR ≥60 mL/min/1.73 m² were younger and had lower systolic blood pressure, serum potassium level, and serum aldosterone level. The patients with aldosterone escape had a lower incidence of pre-existing diabetes and lower UACR.

Changes in clinical variables after add-on spironolactone

Table 2 lists the baseline systolic and diastolic blood pressure, eGFR, serum creatinine, UACR, and serum potassium in all patients, in patients with 1≤UACR<3.5 g/g Cr and UACR ≥3.5 g/g Cr, and in patients with eGFR ≥60 mL/min/1.73 m² and at 6 months and 12 months after add-on spironolactone. In the group with 1≤UACR<3.5 g/g Cr and UACR ≥3.5 g/g Cr or eGFR ≥60 mL/min/1.73 m², the UACR at 6 months and 12 months showed a significant decline compared to the baseline levels (Fig. 1 A, B). In terms of the degree of proteinuria reduction, patients with UACR ≥3.5 g/g Cr showed greater reduction than patients with 1≤UACR<3.5 g/g Cr (reduction rate of UACR at 12 months; 57.2% in patients with UACR ≥3.5 g/g Cr vs. 29.7% in patients with 1≤UACR<3.5 g/g Cr) Figure 1 shows that the patients with UACR <1g/g Cr or eGFR <60 mL/min/1.73 m² or aldosterone escape did not demonstrate significant reduction in UACR. All groups showed a significant decline in the eGFR and serum creatinine over a period of 12 months. The anti-proteinuric effect of spironolactone has varied depending on diabetes in patients with eGFR ≥60 mL/min/1.73 m². UACR was significantly reduced at

6 months in patients with diabetes and eGFR ≥ 60 mL/min/1.73 m², but not in those without diabetes (Fig. 1 D).

Comparison between aldosterone escape group and aldosterone non-escape group

As shown in Table 3, there was a difference in the incidence of diabetes and UACR between the aldosterone escape group and aldosterone non-escape group at baseline. After 6 months and 12 months, the systolic and diastolic blood pressures were not significantly different from baseline. UACR

Table 2. Changes in the main clinical parameters before and after treatment with spironolactone

Variable	Baseline	6 months	12 months	P-value [§]	P-value [¶]
SBP (mmHg)					
All patients	122±15.4	119±15.7	120±13.9	0.038	0.239
1≤UACR<3.5 (g/g Cr)	122±14.4	118±15.9	123±14.5	0.062	0.886
UACR ≥3.5 (g/g Cr)	135±31.2	137±36.7	136±30.7	0.166	0.533
eGFR ≥60 (mL/min/1.73 m ²)	120±13.4	117±14.5	117±12.9	0.302	0.529
DBP (mmHg)					
All patients	74±12.4	73±13.2	74±13.1	0.195	0.732
1≤UACR<3.5 (g/g Cr)	76±12.2	74±12.2	75±14.1	0.142	0.860
UACR ≥3.5 (g/g Cr)	74±15.7	78±19.5	76±11.9	0.356	0.815
eGFR ≥60 (mL/min/1.73 m ²)	74±12.7	71±12.4	73±13.1	0.337	0.853
eGFR (mL/min/1.73 m²)					
All patients	72±40.9	67±41.2	61±36.7	0.006	<0.001
1≤UACR<3.5 (g/g Cr)	65±37.9	60±40.4	47±28.9	0.021	<0.001
UACR ≥3.5 (g/g Cr)	57±34.9	56±50.1	49±43.9	0.001	<0.001
eGFR ≥60 (mL/min/1.73 m ²)	100±33.8	95±36.3	86±32.4	0.877	0.156
Creatinine (mg/dL)					
All patients	1.4±0.71	1.5±0.80	1.6±0.95	<0.001	<0.001
1≤UACR<3.5 (g/g Cr)	1.5±0.78	1.7±0.85	1.9±0.81	0.033	<0.001
UACR ≥3.5 (g/g Cr)	1.5±0.54	1.8±0.74	2.0±0.82	0.046	0.009
eGFR ≥60 (mL/min/1.73 m ²)	0.9±0.22	0.9±0.26	1.0±0.30	<0.001	<0.001
UACR (mg/g Cr)					
All patients	944±925.5	762±838.3	678±932.6	0.007	0.001
1≤UACR<3.5 (g/g Cr)	1638±499.3	1301±894.4	1151±5032.1	<0.001	0.001
UACR ≥3.5 (g/g Cr)	4084±625.7	2827±1472.2	1744±1092.0	0.036	0.001
eGFR ≥60 (mL/min/1.73 m ²)	869±762.0	661±758.9	561±736.2	0.049	0.002
Potassium (mEq/L)					
All patients	4.4±0.52	4.7±0.68	4.7±0.69	<0.001	<0.001
1≤UACR<3.5 (g/g Cr)	4.5±0.55	4.8±0.77	5.2±0.75	<0.001	<0.001
UACR ≥3.5 (g/g Cr)	4.6±0.44	5.0±0.95	5.0±0.78	0.205	0.125
eGFR ≥60 (mL/min/1.73 m ²)	4.2±0.38	4.4±0.48	4.4±0.51	<0.001	<0.001

Data are presented as mean ± SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; §: comparison between baseline and 6 months; ¶: comparison between baseline and 12 months

was significantly decreased in the aldosterone non-escape group, but not in the aldosterone escape group. The plasma renin activity was significantly increased in both the aldosterone non-escape group and aldosterone escape group (Table 3).

Adverse events associated with spironolactone

Hyperkalemia, gynecomastia, hypotension, and gastrointestinal distress were reported as the side effects of spironolactone during the 12 months of administration. If the patient developed hyperkalemia (K ≥ 5.5 mEq/L), potassium lowering medication was initiated, and if the hyperkalemia was severe (K ≥ 7.0 mEq/L) [4], the spironolactone treatment was discontinued. Fifty-one patients (16.7%) with K ≥ 5.5 mEq/L were treated using gastrointestinal ion exchange with oral sodium polystyrene sulfonate for lowering potassium. Nine of the 137 patients with eGFR < 60 mL/min/1.73 m² (6.5%) and none of the 167 patients with eGFR ≥ 60 mL/min/1.73 m² developed severe hyperkalemia. Gynecomastia occurred in 8 of the 137 patients with eGFR < 60 mL/min/1.73 m² (5.8%) and in 2 of the 167 patients with eGFR ≥ 60 mL/min/1.73 m² (1.2%) (Figure 2).

Table 3. Patient characteristics before and after spironolactone therapy in the absence (non-escape group) and presence (escape group) of aldosterone escape

Variable	Non-escape group (N=209)				Escape group (N=95)			
	Baseline	6 months	12 months	P-value	Baseline	6 months	12 months	P-value
SBP (mmHg)	122±16.0	119±16.1	121±13.9	0.627	122±14.0	118±14.8	118±14.0	0.146
DBP (mmHg)	74±12.4	74±12.8	74±12.4	0.796	75±12.3	71±14.2	74±14.4	0.823
eGFR*	75±40.4	70±41.8	63±37.7	<0.001	67±41.5	61±39.2	57±33.9	0.004
UACR (mg/g)	1051±989.2	860±917.0	734±1001	0.002	707±716.4	535±562.5	553±750.9	0.336
Potassium (mEq/L)	4.3±0.52	4.7±0.73	4.7±0.70	<0.001	4.4±0.50	4.6±0.58	4.8±0.65	0.000
Aldosterone (pg/mL)	36.2±20.89	124±123.2	173±169.7	<0.001	165.1±124.52	221±166.8	232±179.1	0.014
Plasma renin activity**	5.25±7.42	10.3±9.11	12.8±11.6	<0.001	12.1±5.45	11.4±12.3	14.5±13.3	0.001

Data are presented as mean±SD; SBP, systolic blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration; UACR, urine albumin to creatinine ratio; P-value: for a comparison between baseline and 12 months; * (mL/min/1.73 m²); ** (ng/mL/h)

Fig. 1. Mean changes in the urine albumin-to-creatinine ratio over 12 months. * compared to baseline. † compared to 6 months.

Discussion

It is well known that aldosterone increases sodium and water reabsorption in the distal nephron and promotes tubular secretion of potassium [5]. Aldosterone also plays a major role in the regulation of the vasculature and has been associated with vascular smooth muscle cell hypertrophy, endothelial dysfunction, high blood pressure, proteinuria, and renal vascular injury [6]. For this

reason, we expected the aldosterone escape group to show a greater reduction in proteinuria after spironolactone was added to the treatment. Spironolactone is known to reduce proteinuria in CKD patients; however, it carries the risk of hyperkalemia and decreased

Fig. 2. Adverse events associated with spironolactone. Severe hyperkalemia indicates a serum potassium level ≥ 7.0 mEq/L.

eGFR. The indications for an add-on aldosterone blockade in patients with proteinuria have not yet been established. If the effect of treatment were different depending on serial aldosterone levels, measurement of serum aldosterone level might be helpful guide for the clinicians to decide to add on treatment of spironolactone. Our analysis revealed that an add-on spironolactone treatment was more effective in the aldosterone non-escape group compared to the aldosterone escape group. This is not in agreement with the results of a previous study, which found that the higher the plasma aldosterone level, the greater the anti-proteinuria in response to an aldosterone antagonist [1, 7]. Sato *et al* suggest that every patient with proteinuria and aldosterone escape should be treated prophylactically with an aldosterone antagonist [8]. Interestingly, recent studies have indicated that MR activation is important in the pathogenesis of cardiovascular and renal damage not only at the high-aldosterone status but also for low-aldosterone hypertension [9, 10]. In the present study, the aldosterone non-escape group had a higher incidence of diabetes and proteinuria, and these factors may be associated with the differences in the effects of spironolactone between the aldosterone escape and non-escape groups. Based on subgroup analysis, the present study revealed that under the same eGFR conditions (eGFR ≥ 60 mL/min/1.73 m²), the effect of proteinuria reduction was more prominent in patients with diabetes than in those without diabetes. Therefore, serum aldosterone level is probably not a crucial factor because the degree of proteinuria reduction was not associated with the serum aldosterone concentration ($r = -0.051$, $P = 0.456$).

Shibata *et al*. reported that podocytes were involved in the early glomerular damage seen in aldosterone-infused rats due to reactive oxygen species (ROS) and that spironolactone could be helpful in the recovery from podocyte injury [11]. In addition, other studies have demonstrated high glucose-induced expression of *Sgk1* through MR, which is upregulated in patients with diabetic nephropathy and have also demonstrated the activation of nicotinamide adenine dinucleotide phosphate oxidase and ROS production, which induced podocyte apoptosis and loss of function in *in vivo* and *in vitro* studies. Spironolactone inhibited all these effects by reducing tumor growth factor- β mRNA and by reducing renal fibrosis [12]. Spironolactone helps reduce the serum aldosterone level, and it affects the podocytes directly by diminishing the production of ROS. In this context, after spironolactone treatment, proteinuria was decreased in the patients with $1 \leq \text{UACR} < 3.5$ g/g Cr and $\text{UACR} \geq 3.5$ g/g Cr under the condition of podocyte injury. The present study showed that proteinuria reduction was more prominent in patients with eGFR ≥ 60 mL/min/1.73 m². We can therefore speculate that aldosterone antagonists may have anti-proteinuric and renoprotective effects only in the early stages of kidney damage and not in the advanced stage of renal failure. In accordance with previous studies [1], patients with eGFR < 60 mL/min/1.73 m² were at a higher risk for severe hyperkalemia. While 9 patients with eGFR < 60 mL/min/1.73 m² experienced severe hyperkalemia and discontinued the use of spironolactone, none of the patients with eGFR < 60 mL/min/1.73 m² experienced severe hyperkalemia. Taken together, an aldosterone antagonist can be recommended for patients with eGFR ≥ 60 mL/min/1.73 m² because of the low risk of hyperkalemia associated with its use.

The renin-angiotensin system (RAS) plays a central role in renal pathophysiology. Therefore, an extensive blockade of the RAS with an ACEI and ARB was expected to be more beneficial in renal disease; however, there is limited evidence regarding the effects of dual RAS inhibition. In the ONTARGET study, it was found that dual RAS inhibition in patients at high risk of cardiovascular events did not improve cardiovascular outcomes and led to an increased incidence of renal events due to acute renal failure [13, 14]. In addition, another previous study on patients with diabetes and overt proteinuria, who received the dual therapy with ACEI and ARB, was terminated early due to a greater number of observed acute kidney injury events and hyperkalemia [15]. In order to overcome the limitation of dual RAS inhibition with ACEI and ARB, many clinical studies have been conducted recently to investigate the efficacy of MR antagonists in reducing proteinuria and attenuating progressive renal disease [16].

A progressive decline in eGFR was observed in all groups, which is consistent with previous observations [17-19]. The proportion of patients that experienced a rise of 30% above baseline in serum creatinine after a median of 34 days was 39.1% [18]. In another study of 136 patients, the eGFR showed a decline from 74.39 to 64.16 mL/min/1.73 m² after 12 months of treatment with spironolactone [19]. Our data revealed that the eGFR reduces by about 18 mL/min/1.73 m² in patients with 1 ≤ UACR < 3.5 g/g creatinine, which is higher than the finding of previous studies however, this reduction seems to be transient and could be restored. In a previous study with an observational period of 48 months, the eGFR was shown to recover [20]. Additionally, the discrepancy in the degree of the declining eGFR among different studies could be due to the differences in the dosage of spironolactone, duration of treatment, and baseline characteristics including age, underlying disease, and racial and ethnic disparities. While the mechanisms underlying this early decline remain mostly obscure, it seems to be associated with hemodynamic alterations caused by suppression of genomic effects by aldosterone [18, 21]. This was estimated to be the hemodynamic effect of preventing vasoconstriction and reducing the blood volume of aldosterone antagonist, and impairment of renal auto-regulation [22, 23].

Conclusion

The clinical implication of our findings is that adding spironolactone to ACEIs or ARBs may have an additional benefit in patients with persisting proteinuria, who have an eGFR ≥ 60 mL/min/1.73 m², or UACR ≥ 1 g/g Cr, or belong to the aldosterone non-escape group.

Disclosure Statement

All the authors have no conflicts of interest to declare.

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