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Mineralocorticoid receptor antagonists in dialysis patients

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Abstract

Mineralocorticoid receptor (MR) antagonists are known to have beneficial effects in patients with cardiovascular disease without renal failure. However, there have been few published studies on the effectiveness of MR antagonists in dialysis patients, and most of the studies were small-sized. The present review focuses on the effectiveness of MR antagonists and the risk of hyperkalemia in dialysis patients. Severe hyperkalemia due to treatment with MR antagonists in dialysis patients is not common, particularly in peritoneal dialysis (PD) patients, and the prospect of cardioprotective effects has been hopeful in both hemodialysis (HD) and PD patients. Further studies are required to establish optimal protocols for the use of MR antagonists in these patients without adverse effects.

Keywords: Mineralocorticoid receptor antagonist, Cardiovascular disease, Dialysis patients, Aldosterone, Peritoneal fibrosis

Background

The number of patients with end-stage renal disease (ESRD) who are undergoing dialysis is increasing. Although dialysis treatment techniques have improved, cardiovascular mortality in dialysis patients is still 10 to 20 times higher than in the general population [1]. In addition, data from the Japanese Society of Dialysis at the end of 2013 showed that heart failure constituted 26.8% of the main causes of death in dialysis patients in Japan [2]. Mineralocorticoid receptor (MR) antagonists have been reported to improve the prognosis of chronic heart failure [3, 4], heart failure after acute myocardial infarction [5], and left ventricular (LV) hypertrophy [6] among patients without renal failure. In contrast in the patients with advanced renal failure, MR antagonists have not been recommended because of concern of causing hyperkalemia [7, 8]. This review article summarizes the beneficial effects of MR antagonists for patients with cardiovascular disease as discussed in recent reports, and evaluates the efficacy of treatment with MR antagonists and risk of hyperkalemia in patients receiving hemodialysis (HD) and peritoneal dialysis (PD).

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Mechanisms

Since 1960 spironolactone has been used as a potassium-sparing diuretic to control edema, hypertension, ascites of cirrhosis, and primary aldosteronism by inhibiting the mineralocorticoid (aldosterone) receptor [9]. Aldosterone acts on epithelial cells such as renal collecting duct tubules and intestinal mucosa, and controls the extracellular fluid volume by increasing sodium reabsorption [10–12]. Because aldosterone is located in the most downstream area of the renin-angiotensin-aldosterone system, it has been thought to indirectly cause cardiovascular disorders through the increase of extracellular fluid volume and hypertension [13]. In large cohort studies, MR antagonists showed reduction of mortality in the patients with severe heart failure and acute myocardial infarction complicated by left ventricular dysfunction. These effects were suggested not to be related to hemodynamic effects. [3, 5]. Patients with primary aldosteronism are known to have a higher incidence of LV hypertrophy, stroke, and microalbuminuria than patients with essential hypertension. In addition, the occurrence rate of LV hypertrophy is higher in patients with primary aldosteronism than in patients with other types of secondary hypertension [14]. These reports suggest that aldosterone can cause direct organ damage independent of blood pressure.

The MR has been shown to be expressed in many organs such as the brain, heart, and blood vessels; and the MR produces a variety of actions in each organ (Table 1) [15–17]. The effects of aldosterone on the cardiovascular system have been widely reported in relation to vascular remodeling [18, 19], endothelial dysfunction [20, 21], increased oxidative stress [22], vascular inflammation promotion [23], and cardiomyocyte hypertrophy [24], either by aldosterone alone or through cooperative action with angiotensin II or salt intake [25, 26].

In the heart, aldosterone has been reported to play a role in inducing cardiac hypertrophy. In particular, aldosterone with salt-loading induces cardiac hypertrophy associated with fibrosis, which is attenuated by MR blockade [24, 27]. Aldosterone and high salt administration for 4 weeks was observed to induce upregulation for nuclear factor (NF)-κB, nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase), and oxidative stress, leading to increases in monocyte chemoattractant protein-1 (MCP-1), intracellular adhesion molecule 1 (ICAM1), tumor necrosis factor alpha (TNF-α), and macrophage infiltration in the perivascular area of the intramyocardial coronary arteries and at sites of myocardial injury [22].

The MR, which is expressed not only in the endothelial cells but also in the vascular smooth muscle cells [28], has been reported to be involved in vascular injury. For vascular endothelial cells, aldosterone and the MR are related to endothelial dysfunction, coagulation, inflammation and fibrosis, nitric oxide (NO) synthesis, and oxidative stress [29]. Endothelial dysfunction is one of the factors of atherosclerosis. Aldosterone exacerbates neointimal thickening after balloon injury and is blocked by spironolactone [30]. Aldosterone has been reported to induce a prothrombotic condition by upregulation of plasminogen activator inhibitor-1 [31]. Aldosterone was also shown to induce inflammation through upregulation of oxidative stress, which was ameliorated by spironolactone [32]. Aldosterone was found to downregulate NO production in vascular endothelial cells, resulting in inhibition of vascular relaxation, which was attenuated with MR blockade [33, 34]. Interestingly, in vivo studies in rabbits with high cholesterol diets showed that eplerenone reduced superoxide generation and improved endothelial function [35]. Also, in monkeys receiving high cholesterol diets, eplerenone improved endothelium-dependent relaxation [36]. In the recent report, MR in endothelial cells was shown to play a role in regulating endothelial function in hypertension using the mice with MR specifically deleted in the endothelial cells [37].

In vascular smooth muscle cells, aldosterone induced proliferation [38] and oxidative stress [39]. Aldosterone activated the mitogen-activated protein (MAP) kinases and NADPH oxidase through c-Src, leading to damage of vascular smooth muscle cells [39]. In addition, spironolactone inhibited the progression of aortic calcification in rats with adenine-induced chronic kidney disease (CKD) because of suppression of osteogenic transition and apoptosis in the aorta [40]. Recently, arterial stiffness was shown to be modulated by MR activation in vascular smooth muscle cells using a mouse with conditional inactivation of MR in these cells [41]. The main functions of aldosterone are summarized in Table 1.

Table 1 Effects of aldosterone in associated disorders [25]

Effects of aldosterone	Myocardial fibrosis and remodeling
	Vascular injury and fibrosis
	Reduced vascular compliance
	Impaired baroreceptor function
	Endothelial dysfunction
	Catecholamine potentiation
	Ventricular arrhythmias
	Progressive renal disease
	K^+ and Mg^{2+} loss
	Sodium reabsorption and water retention
	Prothrombotic effects (Increasing PAI-1)
Aldosterone-associated disorders	Hypertension
	Heart failure and cardiac hypertrophy
	Stroke
	Ischemia and arteriosclerosis
	End-stage renal disease
	Peritoneal fibrosis

PAI-1 plasminogen activator inhibitor-1

Effects of the MR antagonists in hemodialysis patients

There have been many reports about the cardioprotective effects of MR antagonists and the concomitant risk of hyperkalemia in HD patients (Table 2).

Risk of hyperkalemia

In a 1983 study, spironolactone at 300 mg/day was administered to 9 HD patients for 3 weeks. At the end of the study, plasma potassium levels were significantly increased [42]. However, the patients in this study had received a higher dose of spironolactone than that used commonly. Saudan et al. [43] reported 14 HD patients who received low-dose spironolactone at 12.5 mg × 3/week after dialysis sessions for 2 weeks. Then, the dose was increased to 25 mg × 3/week and continued for 2 weeks in comparison with 21 HD control patients. The serum potassium levels did not significantly differ between the two groups (4.9 ± 0.7 in the spironolactone group and 4.9 ± 0.3 mEq/l in the control group). Hussain et al. [44] reported that 15 HD patients with serum

Table 2 Effects of MR antagonists in hemodialysis patients

Author	Number of patients	Administration period	Study duration	Results	Change of plasma potassium
Papadimitriou et al. [42]	9 HD patients	Spironolactone 300 mg/day	3 weeks	Blood pressure remained unchanged.	Plasma potassium levels increased.
Saudan et al. [43]	14 HD patients	Spironolactone 12.5 mg × 3/week for 2 weeks; then increased 25 mg × 3/week for 2 weeks	4 weeks		Serum potassium levels did not differ between spironolactone group and control group (4.9 ± 0.7 vs. 4.9 ± 0.3 mEq/l, N.S.).
Hussain et al. [44]	15 HD patients	Spironolactone 25 mg/day	28 days		4.6 ± 0.6 at baseline 4.9 ± 0.9 mEq/l at study completion ($P = 0.14$). One patient developed hyperkalemia (K = 7.6 mEq/l).
Nitta et al. [55]	5 HD patients	Spironolactone 50 mg/day	3.1 ± 1.2 years	ACI decreased. Plasma osteopontin decreased.	
Gross et al. [45]	8 HD patients	Spironolactone 50 mg × 2/day	2 weeks	Systolic blood pressure reduced. Plasma aldosterone and renin activity were not significantly different from placebo group.	Spironolactone group 5.0 ± 0.8 versus placebo group 4.7 ± 0.5 mEq/l ($P > 0.05$).
Taheri et al. [48]	8 HD patients with heart failure and LVEF ≤45%	Spironolactone 25 mg × 3/week	6 months	LVEF and LV mass improved.	Potassium level increased by 21% in the spironolactone group.
McGill et al. [49]	13 HD patients	Spironolactone 25 mg/day	9 months	Cardiac MRI was not improved..	There was no incidence of hyperkalemia (K > 6.0 mEq/l).
Matsumoto et al. [53]	61 HD patients	Spironolactone 25 mg/day	6 months		Potassium levels were 4.96 ± 0.72 at baseline and 5.18 ± 0.72 mEq/l at 6 months ($P < 0.05$). No patients developed over 6.8 mEq/l.
Vukusich et al. [56]	33 HD patients	Spironolactone 50 mg × 3/week	2 years	CIMT decreased.	No patients developed hyperkalemia, but the potassium levels in the spironolactone group increased ($P < 0.001$).
Shavit et al. [46]	8 HD patients	Eplerenone 25 mg × 2/day	4 weeks	Systolic blood pressure reduced.	Plasma potassium concentration was 4.67 ± 0.2 at baseline and 4.86 ± 0.38 mEq/l after 4 weeks ($P = 0.48$).
Flevari et al. [50]	14 HD patients	Spironolactone 25 mg × 3/week	4 months	Blood pressure controlled, the reactive hyperemia and heart rate variability improved. LV dimensions and mass were not improved.	The potassium level increased from 4.4 ± 0.2 to 5.5 ± 0.3 mEq/l ($P < 0.05$). Two patients took cation exchange resin due to hyperkalemia (K > 6 mEq/l).
Matsumoto et al. [52]	157 HD patients	Spironolactone 25 mg/day	3 years	Death or hospitalization for CCV events and all-cause mortality reduced.	Potassium level was 5.16 at baseline vs. 5.14 mEq/l after 3 years. Three patients discontinued in spironolactone because of hyperkalemia.
Walsh et al. [47]	77 HD patients	Eplerenone 50 mg/day	13 weeks	Discontinuation of the drug because of hyperkalemia or hypotension was not different.	Nine patients developed hyperkalemia (K > 6.5 mEq/l) in the eplerenone group compared with two patients in the placebo group.

Table 2 Effects of MR antagonists in hemodialysis patients *(Continued)*

Feniman-De-Stefano et al. [51]	8 HD patients	Spironolactone 25 mg/day	6 months	LV mass index decreased.	There was no significant difference between spironolactone and placebo groups (5.0 ± 0.31 in the spironolactone group vs 4.9 ± 0.24 mEq/l in the control group, $P = 0.568$).
Lin et al. [54]	125 HD + PD patients	Spironolactone 25 mg/day	2 years	CCV events and the rates of death from all causes reduced. LV mass index, LVEF, and FMD were improved.	Potassium level rose from 4.12 ± 0.42 to 5.32 ± 0.68 mEq/l after 2 years, but was not significantly elevated compared with the control group ($P = 0.13$).

ACI aortic calcification index, *CCV* cardiovascular and cerebrovascular, *CIMT* carotid intima-media thickness, *EF* ejection fraction, *ESRD* end-stage renal disease, *FMD* flow-mediated dilation, *HD* hemodialysis, *LV* left ventricular, *MR* mineralocorticoid receptor, *MRI* magnetic resonance imaging, *PD* peritoneal dialysis, *N.S.* not significant

potassium levels <5.6 mEq/l were treated with spironolactone at 25 mg/day for 28 days. The mean potassium levels did not significantly increase (before - 4.6 ± 0.6 mEq/l; after - 4.9 ± 0.9 mEq/l, $P = 0.14$); however, the potassium level of one patient rose to 7.6 mEq/l, and this patient was dropped from the study. Gross et al. [45] reported a randomized, double-blinded, placebo-controlled study in which 8 HD patients were administered spironolactone 50 mg × 2/day or placebo for 2 weeks; after a 3-week washout period, the patients crossed over in the treatment arms for 2 more weeks. After administration of spironolactone for 2 weeks, systolic blood pressure was significantly reduced from 142.0 ± 19.6 to 131.4 ± 18.2 mmHg ($P < 0.05$). In contrast, plasma potassium levels were not different between spironolactone treatment and placebo groups (5.0 ± 0.8 vs 4.7 ± 0.5 mEq/l, P = n.s.). Similar trials were reported using eplerenone, another MR antagonist. Shavit et al. [46] treated 8 HD patients with low-dose eplerenone at 25 mg × 2/day for 4 weeks. After 4 weeks, the systolic blood pressure was reduced from 166 ± 14 to 153 ± 10 mmHg ($P < 0.05$); however, there was no significant change in the potassium level (before - 4.67 ± 0.2 mEq/l, after - 4.86 ± 0.38 mEq/l, $P = 0.48$). In addition, Walsh et al. [47] conducted a randomized, double-blinded, placebo-controlled study of 154 HD patients. In the study, 77 and 77 patients were treated with eplerenone 50 mg/day or placebo, respectively, and followed for 13 weeks. Nine patients developed hyperkalemia (K > 6.5 mEq/l) in the eplerenone group compared with two patients in the placebo group (relative risk, 4.5; 95% confidence interval, CI 1.0–20.2); however, there was no significant difference in the dropout rate from adverse events (hyperkalemia or hypotension) between the two groups.

Effects on cardiovascular disease

The effects of MR blockade on cardiac function in HD patients have also been reported. First, Taheri et al. [48] conducted a randomized, double-blinded, placebo-controlled study in 16 HD patients with heart failure and low LV ejection fraction (EF) ≤45%, who received spironolactone at 25 mg × 3/week ($n = 8$) or placebo ($n = 8$). After 6 months, the mean EF significantly increased in the spironolactone group compared with the placebo group (6.2 ± 1.64 vs. 0.83 ± 4.9%, $P = 0.046$), and the mean LV mass decreased in the spironolactone group compared with the placebo group (-8.4 ± 4.72 vs. 3 ± 7.97%, $P = 0.021$). The potassium level increased by 21% in the spironolactone group, but the incidence of hyperkalemia was not significantly increased. McGill et al. [49] conducted a small-sized study of 13 HD patients treated with spironolactone at 25 mg/day for 9 months and evaluated LV mass by cardiac magnetic resonance imaging. No improvements in LV mass were detected. Another research group reported a small-sized study with 14 HD patients without heart failure who received low-dose spironolactone at 25 mg × 3/week. After 4 months, blood pressure control, reactive hyperemia, and heart rate variability were significantly improved, while LV dimensions or mass were not improved [50]. Feniman-De-Stefano et al. [51] conducted a small-sized randomized, double-blinded, placebo-controlled study in which 17 HD patients were divided into 2 groups. Eight HD patients received spironolactone and 9 patients received placebo for 6 months; the spironolactone was administered at 12.5 mg/day for 1 week, after which the dose was increased to 25 mg/day. The LV mass index was significantly reduced from 77 ± 14.6 g/m$^{2.7}$ to 69 ± 10.5 g/m$^{2.7}$ ($P = 0.039$) in the spironolactone group, whereas in the placebo group there was an increase from 71 ± 14.2 to 74 ± 17.4 g/m$^{2.7}$ ($P > 0.05$).

Matsumoto et al. [52] conducted a large-scale randomized trial in HD patients. These investigators performed a pilot study to evaluate the safety of spironolactone. Sixty-one HD patients received spironolactone at 25 mg/day for 6 months. The mean potassium level was significantly higher at the end of the study than at baseline, but no patients developed a potassium level >6.8 mEq/l [53]. Based on the safety of this pilot study, Matsumoto et al. [52] conducted a 3-year follow-up randomized trial. One hundred fifty-seven HD patients who received spironolactone at 25 mg/day were compared with 152 control patients. The composite rate of death or hospitalization due to cardiovascular and cerebrovascular (CCV) events during 3 years was 5.7% in the spironolactone group and 12.5% in the control group. Death from all causes was 6.4% in the spironolactone group and 19.7% in the control group. The average potassium level did not increase significantly; however, 3 patients in the spironolactone group discontinued the study because of developing hyperkalemia during the study. Lin et al. [54] also reported a multicenter, randomized, placebo-controlled study in which 125 HD + PD patients received spironolactone at 25 mg/day and 128 patients received placebo for 2 years. Death from CCV events occurred in 4.0% of the spironolactone group vs 11.7% in the control group. All-cause mortality was 9.6% in the spironolactone group and 19.5% in the control group. LV mass index, LVEF, and flow-mediated dilation were significantly improved from baseline in the spironolactone group but not in the control group. The potassium level rose from 4.12 ± 0.42 to 5.32 ± 0.68 mEq/l but was not significantly elevated compared with the control group. Three patients in the spironolactone group experienced an increase in their plasma potassium levels up to 6.0~6.5 mEq/l.

The effects of spironolactone on blood vessels have also been reported. Nitta et al. [55] reported a small

study in which 5 HD patients received spironolactone for 3.1 ± 1.2 years and were evaluated for the aortic calcification index (ACI) by abdominal computed tomography scan. The mean ACI was significantly decreased from 27.0 ± 12.8 to 18.6 ± 11.8% ($P = 0.003$). Vukusich et al. [56] performed a randomized, double-blinded, placebo-controlled trial in 33 HD patients who received spironolactone at 50 mg × 3/week and in 33 HD control patients. After 2 years, carotid intima-media thickness significantly improved in the spironolactone group compared with the placebo group.

Taken together, hyperkalemia does not commonly occur in HD patients who receive treatment with MR antagonists; however, attention should be paid to serum potassium levels. Cardioprotective effects have been shown in many reports. Two reports described an improvement in mortality [52, 54]; therefore, MR antagonists hold promise for improving the prognosis in HD patients.

Effects of MR antagonists in peritoneal dialysis patients

Cardioprotective effects and risk of hyperkalemia in peritoneal dialysis patients

The number of reports on MR antagonists with respect to their cardioprotective effects and adverse effects in PD patients, summarized in Table 3, has been fewer than the number of reports in HD patients. In 2002, Hausmann et al. [57] first reported a 73-year-old patient on PD who received spironolactone at 25 mg/day, in whom the EF improved from 32 to 46% after 10 months. Taheri et al. [58] conducted a small-sized randomized, double-blinded, placebo-controlled study in which 18 PD patients with heart failure received spironolactone at 25 mg ($n = 9$) or placebo ($n = 9$) every other day for 6 months. The EF in the placebo group did not change (before - 33.3 ± 11.7 vs after - 34.2 ± 11.6, $P = 0.363$); however, the EF in the spironolactone group significantly improved (before - 25.7 ± 7.3 vs after - 33.3 ± 7.8, $P = 0.002$). Although there was no significant difference in the serum potassium level between the spironolactone and placebo groups, one patient in the spironolactone group developed hyperkalemia with K = 5.70 mEq/l. After the Taheri study, Yongsiri et al. [59] reported a small-sized, randomized, double-blinded, placebo-controlled, crossover study that focused on changes in potassium levels. Twenty-four PD patients with hypokalemia received spironolactone at 25 mg/day for 4 weeks. The serum potassium levels did not change significantly (4.23 ± 0.64 vs 3.90 ± 0.59 mEq/l in the patients who received spironolactone, $P = 0.077$), but one patient in the spironolactone group developed hyperkalemia with K = 5.6 mEq/l.

Because most of the studies on the effects of spironolactone in dialysis patients have been small-sized, we conducted a multicenter, open-label, prospective, randomized trial to investigate the add-on effects of MR antagonists in PD patients [60]. One hundred fifty-eight PD patients treated with an angiotensin-converting

Table 3 Effects of MR antagonists in peritoneal dialysis patients

Author	Number of patients	Administration period	Study duration	Results	Change of plasma potassium
Hausmann et al. [57]	One PD patient	Spironolactone 25 mg/day	10 months	LVEF increased.	Potassium level was below 5.1 at pretreatment and below 5.5 mEq/l after spironolactone treatment.
Taheri et al. [58]	9 PD patients with heart failure	Spironolactone 25 mg every other day	6 months	LVEF increased.	There was no significantly difference between spironolactone and placebo groups ($P > 0.05$). One patient in the spironolactone group developed hyperkalemia (K = 5.70 mEq/l).
Ito et al. [60]	78 PD patients	Spironolactone 25 mg/day	2 years	LV mass index and LVEF improved.	Potassium levels were significantly higher in the spironolactone group after 6 and 12 months ($P < 0.05$). Two patients in the spironolactone group developed hyperkalemia (K = 6.0 mEq/l), and one patient (K = 6.1 mEq/l) in the control group.
Yongsiri et al. [59]	24 PD patients with hypokalemia	Spironolactone 25 mg/day	4 weeks		Potassium levels 4.23 ± 0.64 at base line and 3.90 ± 0.59 mEq/l after 4 weeks ($P = 0.077$). One patient in the spironolactone group developed hyperkalemia (K = 5.6 mEq/l).
Yelken et al. [72]	23 PD patients	Spironolactone 25 mg/day	6 months	Dialysate CA125 increased. Residual GFR declined.	Potassium level 4.3 ± 0.5 at baseline and 4.4 ± 0.6 mEq/l after 6 months ($P = 0.488$).
Vazquez-Rangel et al. [73]	9 PD patients	Spironolactone 25 mg/day	6 months	CD20 and collagen IV levels in peritoneal biopsy specimens decreased.	Potassium levels 4.8 ± 0.4 in the spironolactone group and 4.4 ± 0.5 mEq/l in the control group ($P = 0.2$).

CA125 cancer antigen 125, *EF* ejection fraction, *GFR* glomerular filtration rate, *LV* left ventricular, *MR* mineralocorticoid receptor, *PD* peritoneal dialysis

enzyme inhibitor or an angiotensin type 1 receptor antagonist were enrolled from 12 hospitals in the Tokai area in Japan. Seventy-eight PD patients received spironolactone at 25 mg/day for 2 years, and 80 patients as the control group did not receive spironolactone. The rate of change in the LV mass index and LVEF in the spironolactone group improved significantly compared with the control group (LV mass index - $P = 0.01$, EF - $P = 0.02$). In the present study, the effects of spironolactone were clearly shown in the males, whereas we could not show usefulness in the females because an insufficient number of females was enrolled. Serum potassium levels were significantly elevated in the spironolactone group at 6 months and 12 months after treatment with spironolactone. Only two patients in the spironolactone group developed hyperkalemia (maximum K level 6.0 mEq/l); on the other hand, one patient in the control group developed hyperkalemia (K level 6.2 mEq/l). There was no significant difference in the occurrence of hyperkalemia between the two groups ($P = 0.62$). Moreover, hypokalemia (potassium level < 3.0 mEq/l) occurred in 25% of the control group and 15.4% of the spironolactone group [60].

Protective effects on the peritoneal membrane in PD patients

Peritoneal membrane deterioration associated with peritoneal fibrosis and neoangiogenesis is one of the important problems for patients receiving long-term PD [61]. Peritoneal injury is caused by bioincompatible peritoneal dialysis solution [62–64], peritonitis [65–67], and uremia [68, 69]. MR antagonists have been reported to ameliorate peritoneal fibrosis in a rat peritonitis model [70, 71].

Two reports have discussed the effects of spironolactone on the peritoneal membrane in PD patients. Yelken et al. [72] reported 23 PD patients who received spironolactone at 25 mg/day for 6 months. After spironolactone administration, mean dialysate cancer antigen 125 significantly increased ($P = 0.028$), while the potassium level did not change significantly (4.3 ± 0.5 at baseline vs 4.4 ± 0.6 mEq/l after 6 months, $P = 0.488$). Vazquez-Rangel et al. [73] conducted a randomized, double-blinded, placebo-controlled study. Nine PD patients received spironolactone at 25 mg/day for 6 months and underwent peritoneal biopsies when the PD catheter was placed and at the conclusion of follow-up. Spironolactone decreased the CD20 and collagen IV levels in the peritoneal biopsy specimens in the patients who received spironolactone compared with the placebo group. There was no significant difference in the potassium level between the 2 groups. The effects of MR antagonists on the peritoneal membrane in PD are still obscure. Future studies are necessary to determine whether MR blockade is useful for ameliorating peritoneal damage in PD patients.

These reports indicate that the risk of severe hyperkalemia is not significantly increased in patients receiving MR treatment, and the cardioprotective effects produced by MR antagonists are promising in PD patients.

Conclusions

Recent evidence has suggested that administration of low-dose MR antagonists does not significantly elevate the risk of hyperkalemia, and that cardioprotective effectiveness is provided by MR antagonists in both HD and PD patients. Moreover, MR antagonists are expected to improve mortality in ESRD dialysis patients. Since most of the studies have been small size and used short observation periods, further large-scale clinical studies are required to establish the protocol for use of MR antagonists in dialysis patients.

Abbreviations

ACI: Aortic calcification index; CCV: Cardiovascular and cerebrovascular; CKD: Chronic kidney disease; EF: Ejection fraction; ESRD: End-stage renal disease; HD: Hemodialysis; ICAM1: Intracellular adhesion molecule 1; LV: Left ventricular; MAP: Mitogen-activated protein; MCP-1: Monocyte chemoattractant protein-1; MR: Mineralocorticoid receptor; NADPH oxidase: Nicotinamide adenine dinucleotide phosphate-oxidase; NF: Nuclear factor; NO: Nitric oxide; PD: Peritoneal dialysis; TNF-α: Tumor necrosis factor alpha

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Availability of data and materials

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Authors' contributions

YI and MT planned the study, searched and collected the literatures, and wrote the manuscript. YS wrote the manuscript. FS and MM discussed the contents of manuscript with YI and MT. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Not applicable.

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