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Aldosterone Blockade in chronic Kidney Disease: Can it Improve Outcome?

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Abstract

Purpose of this review—The purpose of this review is to explain the rationale and limitations for use of mineralocorticoid receptor blockers for the treatment of chronic kidney disease (CKD) and its complications.

Recent Findings—Recent studies in animal models of CKD demonstrate that blockade of the mineralocorticoid receptor using spironolactone or eplerenone decreases inflammation, oxidative stress, proteinuria and glomerular and tubular injury. Patients with CKD are at very high risk for progression of kidney disease and major cardiovascular events. Recent studies in patients with chronic kidney disease demonstrate that administration of low doses of mineralocorticoid receptor blockers (MRB) added onto an angiotensin converting enzyme inhibitor-based regimen reduces proteinuria-a risk marker for both progressive kidney disease and cardiovascular events. However, incident hyperkalemia, unwanted side effect dampened enthusiasm for this approach. There are no large-scale, long-term outcome trials examining whether MRB can slow progression of kidney disease or prevent cardiovascular events.

Summary—At this time it is unknown whether mineralocorticoid receptor blockade can improve outcomes in patients with chronic kidney disease. To move this field forward and determine whether these agents can improve the lives of patients with kidney disease novel strategies to prevent or ameliorate hyperkalemia are needed.

Keywords

mineralocorticoid receptor; spironolactone; eplerenone; outcome trials

Introduction

Chronic kidney disease is defined as presence of abnormal structure or function of the kidney persisting for longer than 3 months or a reduction in estimated glomerular filtration to a level less than 60 ml/min/1.73 m^2. Chronic kidney disease is difficult to detect, is associated with excessive cardiovascular morbidity and mortality and despite optimal treatment often progressive to end-stage renal disease. Diabetes mellitus is the leading attributable cause for end stage kidney disease and nearly 50% of new cases of end-stage

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kidney disease are attributed to diabetes.[1] Unfortunately most patients with kidney disease in diabetes progress to kidney failure or die prematurely from cardiovascular disease despite tighter glycemic control, blood pressure lowering and use of drugs that block the renin-angiotensin system.[2–6] Treatment with angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) slow progression of kidney disease; however used alone or in combination these classes of drugs have not been proven to reduce cardiovascular morbidity and mortality.[7, 8] There is an urgent need to find novel therapies to improve cardiovascular and renal outcomes in patients with diabetic nephropathy, a highly prevalent and vulnerable patient population. No treatment regimens have been shown to stop progression of kidney disease or prevent cardiovascular events in patients with diabetes mellitus, including anemia treatment.[9] Several recent studies suggest that administration of therapeutic agents that block the mineralocorticoid receptor may improve outcomes in those with chronic kidney disease. The purpose of this review is to explain the rationale and limitations of mineralocorticoid receptor blockers as well as their potential future application to prevent adverse renal and cardiovascular outcomes in patients with chronic kidney disease.

Effects of aldosterone on salt transport and blood pressure regulation

Aldosterone is well known to increase sodium reabsorption and potassium secretion by the kidney. It exerts its main effects on sodium and potassium balance by binding to the mineralocorticoid receptor (MCR) located in the distal convoluted tubule, connecting segment and cortical collecting duct in the kidney. The net effect is that aldosterone functions homeostatically to maintain normal sodium and potassium balance as well as blood pressure and circulating blood volume.[10] In addition mineralocorticoid receptors are also present in glomerular endothelial cells, mesangial cells and podocytes as well as the renal and systemic vascular endothelial tissues.[11, 12] In the systemic vasculature, heart and kidney aldosterone has mitogenic effects on a number of cell types and therefore has the potential for a pathological role in cardiovascular and kidney disease.[13]

Pathologic role of aldosterone in kidney and cardiovascular disease

Aldosterone has been shown to play a major pathologic role in causing cardiovascular and renal injury through multiple mechanisms including inflammation, oxidative stress, activation and enhancement of angiotensin II and accelerated fibrosis.[11, 12, 14–16] After binding to the mineralocorticoid receptor, aldosterone is translated into the nucleus, where the complex dissociates and binds to regulatory regions of multiple genes that stimulate production of proteins involved in both sodium and potassium transport as well as inflammation and oxidative stress. Activation of serum- and glucocorticoid-inducible kinase 1 (Sgk1) and epithelial sodium channel subunit and glucocorticoid induced leucine zipper is followed by downstream actions that promote both ion transport and inflammation. Hence activation of NADPH oxidase in turn activates NF-b and AP-1 leading to upregulation of intercellular adhesion molecule -1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor -beta (TGF-b). In the kidney the upregulation of these molecules contributes to vascular injury, tubulointerstitial inflammation and subsequent fibrosis, and glomerular

injury during aldosterone infusion accompanied by high salt intake in animal models. In addition, aldosterone inhibits nitric oxide synthase thereby reducing nitric oxide availability in the kidney and vasculature.[17]

Experimental models of chronic kidney have demonstrated a key role for aldosterone-mediated glomerular and tubular injury and inflammation. This injury is medicated in part by activation of oxidative stress molecules, upregulated in part by NADPH oxidase, including proinflammatory cytokines including IL-6, MCP-1, ICAM-1, osteopontin and TGF-beta a potent profibrotic cytokine.[18–2324] Blockade of the mineralocorticoid receptor using drugs like spironolactone and eplerenone attenuate or abrogate these effects.[16, 22] It is important to note that high salt intake in combination with aldosterone excess or activation of the mineralocorticoid receptor is necessary to induce renal and vascular inflammation and fibrosis in animal models.[25–2722, 28, 29]

The beneficial effects of aldosterone blockade are believed to be, in part, by improvement in endothelial dysfunction. Aldosterone infusion leads to increased reactive oxygen species (ROS) that stems from increased activity of NADPH throughout the vasculature, a major source of superoxide anion and this effect is attenuated by MCR antagonism or systemic antioxidants and improve endothelial dependent vasodilation (a measurement of endothelial dysfunction) to near normal levels in a model for atherosclerosis. }[30] In humans with heart failure administration of low dose spironolactone increases nitric oxide bioactivity and improves endothelial vasodilator dysfunction.[31] In patients with diabetic nephropathy administration of spironolactone but not amlodipine reduced both urinary F2-isoprotane and MCP-1 despite similar effect on blood pressure.[32] Obesity may be accompanied by hypertension and increased biomarkers for inflammation and oxidative stress. In obese patients with resistant hypertensive patients and sleep apnea, inappropriately high plasma levels of aldosterone have been observed and implicated in the pathogenesis of this syndrome.[33] Adipocytokines have been implicated in excess secretion of aldosterone in vitro.[22, 28, 34] Also, blockade of the MCR by eplerenone attenuates proteinuria and glomerular injury in an obese rat model of human metabolic syndrome.[22, 28] Therefore, in the absence of an aldosterone-secreting tumor, the pathological role of aldosterone in kidney and cardiovascular disease is observed when diseases such as underlying diabetes, obesity, or chronic kidney disease are present.

Two major clinical trials using drugs that block the mineralocorticoid receptor in heart failure patients, The Randomized Aldactone Evaluation Study (RALES) included 1663 patients with severe heart failure and a low left ventricular ejection fraction randomized to receive spironolactone or placebo superimposed on conventional CHF therapy.[35] The trial was stopped after 24 months owing to a 30% lower risk of death in the group receiving spironolactone. Similarly the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) enrolled 6642 patients with left ventricular systolic dysfunction and heart failure after myocardial infarction randomized to either placebo or eplerenone. Compared to placebo, eplerenone treatment was associated with a reduction in cardiovascular and all cause mortality or hospitalizations for cardiovascular events.[36] Notably, widespread use in patients with heart failure is associated with significant morbidity and mortality.[37] And, there are no large-scale outcome trials of MRA added onto

standard of care in patients with chronic kidney disease in part because the development of hyperkalemia has curbed enthusiasm for adding this class of agents onto an ACEi or ARB-based regimen.

In summary, aldosterone activation of the mineralocorticoid receptor particularly during high salt intake induces hypertension, vascular, cardiac and renal injury that is mediated by upregulation of oxidative stress and inflammatory molecules. These actions can be attenuated or abrogated by administration of mineralocorticoid blockade with spironolactone and eplerenone. Therefore, these mineralocorticoid receptor blockers have the potential to benefit patients with chronic kidney disease because of their blood pressure and proteinuria lowering effects and their life-saving effects in those with heart failure.

Aldosterone Blockade in Chronic Kidney Disease

Blockade of the renin-angiotensin aldosterone system with ACEi or ARB have been shown to improve renal outcomes in patients with chronic kidney disease including type 1 and type 2 diabetes mellitus, hypertensive nephrosclerosis and non-diabetic proteinuric renal diseases.[2, 4, 38–40] However, RAAS blockade with either of these strategies may also be incomplete leading to a reactivation of the downstream effects of ANG II, including aldosterone release, also known as aldosterone escape. This phenomenon is associated with failure to improve left ventricular hypertrophy and failure to slow declining glomerular filtration rate in some studies.[8]

Mineralocorticoid receptor blockers such as spironolactone and eplerenone have the potential to prevent onset and progression of kidney disease and associated cardiovascular complications. In this section the effects on blood pressure, proteinuria and markers of cardiovascular function are reviewed. Proteinuria is a hallmark of diabetic nephropathy and a marker for progressive kidney disease and cardiovascular morbidity and mortality.[41, 42] Several small, short-term, clinical trials have examined the effects of adding spironolactone or eplerenone to an ACEi- and/or ARB-based regimen in patients with proteinuric kidney diseases. These studies have consistently shown that adding MRB therapy reduces proteinuria in patients on long-term ACEI or ARB therapy and persistent proteinuria as reviewed by Bomback et al. They systematically reviewed of 15 studies of 436 patients with proteinuric kidney disease that included case reports and randomized controlled trials illustrating that addition of either spironolactone or eplerenone to ACEI and/or ARB therapy resulted in reduction in proteinuria ranging from 5% to 54%.[43] Table 1 illustrates the results of addition of MRB in randomized double-blind placebo controlled trials reported so far.[44, 4546–49] As shown in the table in general the addition of an MRB to an ACEi or ARB based regimen is associated with a 33–55% reduction in proteinuria or albuminuria with varying effects on systemic blood pressure.

To determine whether combined blockade of the renin-angiotensin aldosterone system can reduce proteinuria, my laboratory randomly assigned 81 patients with diabetes and chronic kidney disease and persistent albuminuria despite a supramaximal dose of lisinopril 80 mg once daily to receive either losartan 100 mg once daily or spironolactone 25 mg once daily or placebo once daily for 48 weeks. Both clinic and ambulatory blood pressure was

measured repeatedly over the trial and the primary outcome was the change in albuminuria comparing the experimental groups to placebo. We found that urine albumin to creatinine ratio decreased 55% in those assigned to spironolactone as compared to 27% with losartan and 13% with placebo. The decrease in urine albumin to creatinine ratio in comparison to placebo was 34.0% (95% CI: −51.0%, −11.2%, p=0.007) in those assigned to spironolactone and by contrast was only 16.8% (95% CI: −37.3%, +10.5%, p = 0.20) in those assigned to losartan. Both the clinic and ambulatory BP were similar among groups throughout the study. We concluded that at similar BP, spironolactone but not losartan, afforded greater renoprotection in patients with diabetic nephropathy when added onto a supramaximal dose of lisinopril.

Mechanism of antiproteinuric effect of mineralocorticoid blockade

The mechanism by which aldosterone blockade reduces proteinuria is incompletely understood. Blockade of the mineralocorticoid receptor is accompanied by lowering of systemic blood pressure that in turn is well known to lower proteinuria in patients with chronic kidney disease and uncontrolled hypertension. Indeed administration of either spironolactone or eplerenone to patients with chronic kidney disease and proteinuria is accompanied by significant reduction in blood pressure. In addition, administration of spironolactone in some studies is accompanied by a reduction in glomerular filtration rate which might in turn lower the filtered load and urine protein excretion rate.[43, 49] In addition, alterations in dietary protein and sodium intake and in those with diabetes alterations in glycemia can alter the rate of protein excretion in patients treated with these agents. To exclude changes in blood pressure, glomerular filtration rate, dietary factors and glycemic control as factors explaining the antiproteinuric effect of spironolactone, we performed repeated measures of twenty-four hour creatinine clearance our urine sodium and urea nitrogen and A1c over 48 weeks in our randomized controlled trial (see above). We found that the effect of spironolactone on proteinuria was not explained by these factors in our patients with diabetic nephropathy.

Mineralocorticoid receptor is present in glomerular podocytes of diabetic rats.[50] Recently, Fujita and colleagues have examined the effect of aldosterone on podocyte function in experimental animal models.[51] In these studies Rac-1 a Rho GTPase was shown to activate the MCR and increased MCR nuclear translocation in podocytes. Moreover, in a mouse model of renal injury with proteinuria, a Rac specific inhibitor decreased MCR activity, translocation, proteinuria and podocyte damage. These studies suggested that Rac1 could be a therapeutic target for chronic kidney disease. Nishiyama et al demonstrated that addition of eplerenone to telmisartan in obese rats with diabetic nephropathy reduced proteinuria and glomerular sclerosis and podocyte injury despite no change in systemic blood pressure.[52] The human and experimental animal data strongly suggest that the antiproteinuric effect of MRB is at least in part mediated by a direct effect on the glomerular basement membrane and is not dependent solely on reduction in systemic blood pressure, glomerular filtration or dietary factors.

In summary, taken together with the results of prior studies and the RALES and EPHESUS trials, these findings suggest that the addition of an MRB to an ACEI or ARB may be an

effective treatment strategy for slowing kidney disease progression and preventing or effectively treating heart failure in CKD populations. However, the effect of MRB administration on cardiovascular outcomes in those with CKD has not been studied in a prospective randomized trial in proteinuric or non-proteinuric kidney disease. One reason is the concern for hyperkalemia.

Hyperkalemia: The rate-limiting step?

Preliminary studies from my laboratory in patients with diabetic nephropathy demonstrated that the addition of 25 mg once daily of spironolactone to standard care lowered albuminuria independent of ambulatory and clinic blood pressure, dietary sodium, potassium and protein, and glomerular filtration rate (see above). Post-hoc analysis revealed a mean increase of 0.4 mEq/L in potassium one week after an initial dose of spironolactone 12.5 mg daily and this increased further at the trial maintenance dose of 25 mg daily despite the lack of significant changes in plasma aldosterone level. However, we recognized in our patients that hyperkalemia was more common in those randomized to spironolactone as compared to placebo or losartan. Post-hoc analysis revealed a 0.4 mEq/L increase in potassium one week after an initial dose of spironolactone 12.5 mg daily and this increased further at the trial maintenance dose of 25 mg daily despite the lack of significant changes in plasma aldosterone level. Although this apparent dose response could be directly linked to more potent blockade of the mineralocorticoid receptor, other mechanisms could be involved.

One possibility is that spironolactone acts via WNKs (with-no-lysine [K]), enzymes that regulate potassium secretion through alterations in collecting duct sodium channels, are involved. WNKs (with-no-lysine [K]) are a family of protein kinases that have unusual protein kinase domains due to the atypical placement of the catalytic lysine.[53] WNK kinases function as true protein kinases and catalyze the phosphorylation of endogenous and exogenous substrates.[54–56] WNK proteins are broadly expressed in tissues and at least some splice forms display tissue-specific expression.[57, 58] Mutations of WNK1 and 4 cause Gordon's syndrome an autosomal-dominant disease characterized by hypertension, hyperkalemia, hyperchloremia, and metabolic acidosis.[59] The full-length WNK1 has a broad tissue distribution and a shorter alternatively spliced WNK1 isoform is exclusively expressed in the kidney and known as kidney-specific WNK1, KS-WNK1.[57, 58] In the cortical collecting duct WNK1 inhibits potassium secretion by inhibition of the ROMK channel. KS-WNK1 antagonizes the inhibition of ROMK mediated by WNK1.[60, 61] Recent studies suggest that the ratio of WNK1 to KS-WNK1 is an important mediator for regulation of renal K^+ secretion. An increase in the WNK1 to KS-WNK1 ratio (as in K^+ deficiency and Gordon's syndrome) would decrease renal K^+ secretion by inhibiting ROMK but increase Na^+ reabsorption by activating epithelial sodium channel (ENaC) and sodium chloride cotransporter (NCC). Thus, the ratio of WNK1 to KS-WNK1 regulates (inhibits) ROMK.[62] It remains to be determined whether MRB by spironolactone or eplerenone also inhibit potassium secretion by modifying WNK-1 and KS-WNK-1 expression or activity. Two recent preliminary reports suggested that WNKs are important in the pathogenesis of hyperkalemia and hypertension in diabetic nephropathy.[63, 64] Together with data from heart failure studies our results provide a strong rationale for adding an MRB on to an ACEi-based

regimen for improving both cardiovascular and renal outcomes in patients with diabetic nephropathy.

Recently, Khosla et al identified important predictors of risk for development of hyperkalemia during add-on therapy with MRB. They evaluated 46 patients with resistant hypertension and stages 2 or 3 CKD during addition of aldosterone blockade preexisting BP-lowering regimens over a 6 week period and found a significant increase in mean serum potassium of 0.4 mEq/l and a 17.3% incidence of hyperkalemia defined as a serum potassium >5.5 mEq/l. Factors that predicted incident hyperkalemia included a baseline estimated GFR of $\leq$ 45 ml/min/1.73 m^2, a reduction in systolic BP reduction of >15 mm Hg and a decline in eGFR of >30%. They concluded that caution should be advised when using aldosterone blockade for BP control in people with advanced stage 3 nephropathy and a serum potassium of >4.5 mEq/l for safety reasons.[65]

In summary, hyperkalemia is an important problem complicating the current management of chronic kidney disease and a barrier to determining the beneficial effect of MRB on cardiovascular and renal outcome in this patient population. It is not known whether a lower dose of the MRA spironolactone may be effective for mitigating hyperkalemia, lowering blood pressure and albuminuria, because this strategy has never been tested in patients with diabetic nephropathy.

Conclusion and Future Directions

Patients and clinicians are desperately seeking ways to prevent cardiovascular and kidney complications of type 2 diabetes. Many clinicians are adding ARBs and MRAs onto ACEi-based regimens in patients with diabetic nephropathy in hopes of lowering proteinuria and preventing cardiovascular and kidney complications, but there are no studies to guide them. They are especially concerned with the appropriate use of MRAs given the concerns over hyperkalemia. A trial using low-dose spironolactone or eplerenone is needed to determine whether the beneficial effects on blood pressure and proteinuria can be achieved safely without causing significant hyperkalemia. Such as study would provide crucial information needed to assist in the management of these patients and to design a large-scale outcomes trial to determine whether addition of spironolactone to standard of care can improve patient outcomes. This could pave the way for a large-scale outcome trial designed to determine whether adding on a mineralocorticoid blocker can prevent progression of kidney disease and reduce cardiovascular morbidity and mortality in those with chronic kidney disease.

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Table 1

Double-blind randomized placebo-controlled trials of addition of spironolactone or eplerenone to an ACEi-based regimen in chronic kidney disease

Study groups					
Control	**Experimental**	**Δ Proteinuria or albuminuria**	**Δ BP lower vs. placebo**	***n***	**Weeks**
ACEi + placebo [44]	ACEi + spironolactone	−33%	Yes	21	8
ACEi + placebo [45]	ACEi + spironolactone	−32%	No	20	8
ACEi + placebo [46]	ACEi + eplerenone	−48%	Yes	268	12
ACEi + placebo [47]	ACEi + spironolactone	−40%	Yes	59	48
ACEi + placebo [48]	ACEi + spironolactone	−45%	Yes	27	12
ACEi + placebo [49]	ACEi + spironolactone	−55%	No	81	48

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; MRB, mineralocorticoid blocker.