Aldosterone Blockade in Chronic Kidney Disease

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Summary: Although blockade of the renin-angiotensin-aldosterone system with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers has become standard therapy for chronic kidney disease (CKD), renewed interest in the role of aldosterone in mediating the injuries and progressive insults of CKD has highlighted the potential role of treatments targeting the mineralocorticoid receptor (MR). Although salt restriction is an important component of mitigating the profibrotic effects of MR activation, a growing body of literature has shown that MR antagonists, spironolactone and eplerenone, can reduce proteinuria and blood pressure in patients at all stages of CKD. These agents carry a risk of hyperkalemia, but this risk likely can be predicted based on baseline renal function and mitigated using dietary modifications and adjustments of concomitant medications. Data on hard outcomes, such as progression to end-stage renal disease and overall mortality, still are lacking in patients with CKD.
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The role of the renin-angiotensin-aldosterone system (RAAS) in cardiovascular and renal disease is well established, and, more recently, a greater appreciation of the final element in that pathway, aldosterone, has emerged.[1–3] Indeed, the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) to interrupt the RAAS has become a mainstay of treatment in cardiac disease, including after myocardial infarction and in congestive heart failure.[4,5] In chronic kidney disease (CKD), particularly in patients with proteinuria, RAAS blockade with ACE inhibitors or ARBs is recommended by the Kidney Disease Improving Global Outcomes guidelines.[6,7] Less used, however, are mineralocorticoid-receptor antagonists (MRAs), even though they block a key component of this pathway.

Despite treatment with ACE inhibitors and ARBs, many patients with CKD have persistent proteinuria, a risk factor for progressive renal failure[8,9] and cardiovascular disease.[10] The role of aldosterone as the final mediator in the RAAS pathway and thus in the pathophysiology of cardiac, vascular, and renal disease[11] therefore has been subject to greater scrutiny, in the hopes that blockade can lead to improved meaningful clinical outcomes.

Aldosterone is a steroid hormone with mineralocorticoid activity produced by the adrenal glands in response to several stimuli, including angiotensin II, adrenocorticotropic hormone, and increased serum potassium levels. Classically, aldosterone serves to increase sodium reabsorption in the distal convoluted tubule of the kidney to maintain circulatory homeostasis and extracellular volume.[12] It has become increasingly clear, however, that aldosterone has myriad far-reaching effects on the kidney and other organs[13–18] in a nongenomic mode of action.[19] Blockade of this nonclassic pathway with the MRAs spironolactone and eplerenone thus has been explored for mitigating progression of kidney disease.

PROFIBROTIC EFFECTS OF ALDOSTERONE IN VARIOUS STATES OF KIDNEY INJURY

In addition to its effect on distal tubular salt and potassium handling, numerous animal studies have shown that aldosterone is involved intimately in vascular, myocardial, and renal fibrosis. Independent of changes in blood pressure and volume homeostasis, this nonepithelial MR activity plays a direct role in fibrosis and vascular toxicity.[13–18,20,21] Although early studies on RAAS blockade focused on the ability of ACE inhibitors and ARBs to prevent strokes and malignant nephrosclerosis in stroke-prone hypertensive rats,[16] focus has turned to aldosterone antagonists in reducing the deleterious profibrotic effects of unopposed aldosterone.

Cardiac fibrosis and hypertrophy occur in the presence of sodium intake and increased aldosterone levels, as well as in rat models of primary and secondary hyperaldosteronism, effects attenuated by aldosterone blockade.[12–14] In the remnant kidney model, aldosterone levels increased more than 10-fold from baseline, with an associated increase in systemic blood pressure and proteinuria. Dual RAAS blockade with ACE inhibition and ARBs reduces the

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aldosterone levels by approximately 65%, with improvement in blood pressure control and proteinuria; these benefits largely are circumvented by infusion of aldosterone, but once again are blocked by treatment with spironolactone.[15]

Imputing aldosterone as the major driver in renal vascular injury, its infusion completely negates the beneficial effects of ACE inhibition on proteinuria and renal damage in stroke-prone spontaneously hypertensive rats (SHR/A3N) placed on a high-salt diet.[22] Despite receiving an angiotensin II infusion and high-salt diet, rats with impaired nitric oxide synthesis largely are protected from renal damage after eplerenone treatment or adrenalectomy but display proteinuria, arteriolar fibrinoid necrosis, and focal thrombi within glomeruli after aldosterone administration.[1] Severe hypertension, proteinuria, evidence of stroke, and severe cerebrovascular lesions, cerebral edema and thrombotic microangiopathy, and ischemic retraction of glomerular tufts all befall stroke-prone SHRSP/A3N on a high-salt diet.[16]

Proinflammatory molecule expression, including cyclooxygenase-2, macrophage chemoattractant protein-1 (MCP-1), and osteopontin, all are increased significantly in the rat heart and kidney after MR activation[17,18,23] and correlate with vascular inflammation, coronary lesions,[17] and an influx of polymorphonuclear cells and monocytes.[1] Both cardiac[24,25] and renal cells[26,27] undergo apoptosis in the presence of mineralocorticoid activity, further contributing to end-organ damage.

In the kidney, increased expression of transforming growth factor (TGF)-β1,[23,27] plasminogen activator inhibitor-1 (PAI-1),[23,27,28] ED-1 macrophage marker,[18,23] and connective tissue growth factor,[27] promoters of inflammation, extracellular matrix accumulation, and fibrosis; thiobarbituric acid–reactive substances, a marker of reactive oxygen species (ROS); p22phox, Nox-4, and gp91phox, NAD(P)H oxidase-induced ROS; and the mitogen-activated protein kinases (ERK1/2), c-Jun-NH_2-terminal kinase (JNK), and big mitogen-activated protein kinase-1 (BMK1),[29] lead to hypertension and proteinuria.[18,29] Histologically, the kidneys develop glomerulosclerosis,[18,28,30] tubulointerstitial fibrosis[18,27] with tubular dilatation and proteinaceous casts,[18] and glomerular[18] and mesangial matrix expansion with cellular proliferation;[29,31] Degenerative changes in the arterioles and small arteries characterized by fibrinoid necrosis, thrombosis, and fibrosis;[18] and podocyte injury, as evidenced by foot process effacement, increased staining for desmin (a marker of podocyte injury), and reduced the expression of nephrin and podocin.[30,32]

A profibrotic milieu was confirmed in a biopsy series of 95 patients.[33] Serum aldosterone levels correlated with worsening renal function and renal scarring. Patients with more than 2 g/d urinary protein excretion had significantly higher levels of MR, sgk1, MCP-1 messenger RNA (mRNA), TGF-β1, and MR expression as compared with lower levels of proteinuria (increase as compared with nonproteinuric disease: MR 4.6×, sgk1 2.5×, MCP-1 mRNA 7.1×, and TGF-β1 3.8×).[33] Notably, spironolactone decreased urinary MCP-1 levels in patients with diabetic nephropathy.[34]

Treatment with eplerenone markedly attenuates inflammatory vascular and glomerular injury, reducing blood pressure and proteinuria, and preventing fibrosis.[1,16–18,29,32] Spironolactone mitigates glomerulosclerosis[35] and podocyte injury in subtotal nephrectomized rats compared with controls, despite achieving similar blood pressure control.[36] The improvement in blood pressure control with another antihypertensive agent, hydralazine, had no effect on renal pathology or proteinuria.[30,32]

Diabetic nephropathy, a proinflammatory condition leading to progressive renal injury, is in part mediated by aldosterone. Increased tubulointerstitial and glomerular TGF-β1 and PAI-1 expression in streptozocin-induced diabetic nephropathy results in periarteriolar, tubulointerstitial, and intraglomerular fibrosis.[37] Hyperglycemia potentiates MR activation, generation of ROS, and podocyte injury.[38] Treatment with spironolactone prevents fibrosis concurrent with reducing TGF-β1 and PAI-1 expression,[37,39] markedly attenuates arteriolar hyalinosis and glomerular lesions of mesangial matrix expansion,[40] and mitigates podocyte injury and ROS generation.[38] Likewise, increased TGF-β1, MCP-1 mRNA, urinary MCP-1, and albuminuria are present in Otsuka Long-Evans Tokushima Fatty rats, a genetic model of type 2 diabetes mellitus, and correlate with glomerulosclerosis.[41] Levels of these and other profibrotic makers, including connective tissue growth factor and collagen staining, are greatly reduced by spironolactone[41,42] or eplerenone, with the greatest improvement seen with the addition of an ACE inhibitor for dual RAAS blockade.[43] Similar to findings in aldosterone-infused rats,[18] staining for the inflammatory marker ED-1 macrophage marker is increased in both models of diabetic nephropathy, with significant reductions in the presence of spironolactone,[37,41] suggesting both an antifibrotic and anti-inflammatory role for MR blockade in diabetic nephropathy.[44]

Obesity and metabolic syndrome are states of relative hyperaldosteronism, leading to hypertension and renal injury, with weight loss leading to decreases in aldosterone levels.[45] Eplerenone mitigates the blood pressure increase and glomerular hyperfiltration (glomerular filtration rate [GFR] increase from 68.7 to 94.6 mL/min in the untreated group versus 54.7 to 69 mL/min among those treated) in dogs on a high-fat diet.[46] In a rat model of obesity and metabolic syndrome (SHR/NDmcr-cp, a derivative of the SHR