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Renal aspirin: will all patients with chronic kidney disease one day take spironolactone?

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Over the past two decades, aldosterone has emerged as a key agent in the pathophysiology of congestive heart failure and, more recently, progressive kidney dysfunction.¹ In addition to its effects of promoting sodium retention (and potassium excretion) in epithelial tissues, aldosterone activates mineralocorticoid receptors in the nonepithelial tissues of the heart, kidney, and peripheral vasculature to foster inflammation and fibrosis. As these nonepithelial routes of kidney injury have been uncovered, so too has the remarkable efficacy of mineralocorticoid receptor blockade in countering a variety of renal insults. The results of recent animal and human studies of aldosterone blockade in various kidney diseases prompt speculation that low doses of spironolactone, an inexpensive, generic medication with few and easily recognizable adverse effects, could become a staple therapy for all patients with chronic kidney disease (CKD).

Treatment of diabetic and hypertensive kidney disease, the two leading causes of CKD, relies heavily on blockade of the renin–angiotensin–aldosterone system (RAAS) with angiotensin-converting-enzyme inhibitors (ACEIs) and/or angiotensin receptor blockers (ARBs). In clinical trials of ACEIs and ARBs, aldosterone levels—after an initial decline—increase in 30–50% of patients during the first year of therapy. This ‘aldosterone breakthrough’ might increase the risks of proteinuria, a decline in glomerular filtration rate (GFR), and development of left ventricular hypertrophy.² Patients with CKD who do not respond to ACEIs and/or ARBs—as indicated by persistent proteinuria, refractory hypertension, and declining GFR—could benefit from an additional level of RAAS blockade achieved by targeting aldosterone. Indeed, a growing body of evidence suggests that, when added to conventional RAAS blockers, mineralocorticoid receptor blockers such as spironolactone and eplerenone yield up to 50% reductions in proteinuria.³ These effects, moreover, are achieved with relatively low doses of drug (e.g. 12.5–25.0 mg/day spironolactone), which are generally insufficient to cause diuresis or a substantial drop in blood pressure.

Immunosuppressive medications are the mainstays of therapy for nondiabetic glomerular diseases. However, these diseases can advance to a chronic, fibrotic phase with considerable loss of renal function and, in some cases, progression to end-stage disease. Accordingly, ACEIs and ARBs have become standard adjunctive therapy for glomerular diseases, but aldosterone blockade remains underexplored in this setting. In small numbers of patients with nondiabetic glomerular diseases, spironolactone has yielded substantial reductions in proteinuria,

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Competing interests

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comparable to those seen in diabetic nephropathy.³ In a murine model of lupus glomerulonephritis, spironolactone significantly reduced the incidence of nephrotic-range proteinuria, and treated animals showed less severe glomerular injuries than controls.⁴

Obesity and the metabolic syndrome are frequently associated with elevated aldosterone levels.⁵ In dogs that were fed high-fat diets, treatment with eplerenone significantly limited elevations in blood pressure, increases in cumulative sodium balance, and hyperfiltration-associated rises in GFR.⁶ A rat model of metabolic syndrome indicated a positive correlation between circulating aldosterone concentrations and proteinuria. Although nonobese hypertensive rats had little to no proteinuria, rats with metabolic syndrome had exaggerated proteinuria despite similar blood pressure elevations. Proteinuria in the rat metabolic syndrome model was accompanied histologically by podocyte injury that, along with proteinuria, improved after mineralocorticoid receptor blockade.⁷

Calcineurin inhibitor (CNI) toxicity is an important cause of chronic allograft nephropathy. In rat models of both acute and chronic CNI nephrotoxicity, coadministration of spironolactone with ciclosporin prevented CNI-associated declines in renal blood flow, GFR, and creatinine clearance. Histological specimens also showed marked reductions in CNI-induced afferent arteriolopathy and tubulointerstitial fibrosis.⁸ In a more clinically relevant scenario, administration of spironolactone in rats with pre-existing ciclosporin toxicity significantly reduced the rate of GFR decline and progression of tubulointerstitial fibrosis.⁹ These studies suggest that mineralocorticoid receptor blockade counter-balances the renal vasoconstriction induced by CNIs and that aldosterone's profibrotic effects on the kidney might be exaggerated in CNI toxicity.

Aldosterone blockade has also surfaced as a potential treatment for renal ischemia–reperfusion injury, a leading cause of acute kidney injury in both native and transplanted kidneys. In a rat model of ischemia–reperfusion-induced kidney injury, pretreatment with spironolactone substantially decreased reductions in renal blood flow and creatinine clearance compared with untreated rats. On histological examination, the lesions of ischemia–reperfusion injury that were evident in untreated kidneys were virtually absent in spironolactone-treated animals.¹⁰ A number of potential mechanisms support spironolactone's efficacy in attenuating such injury. Rats subjected to renal ischemia–reperfusion exhibit markedly elevated serum aldosterone levels compared with sham-operated animals. Mineralocorticoid receptor blockade prevents the effective nitric oxide deficiency that is caused by ischemia–reperfusion injury and, unchecked, reduces renal plasma flow and extends renal injury. Finally, spironolactone might halt a reperfusion-induced increase in oxidative stress, via upregulation of antioxidant enzymes.

The RAAS has long been implicated in the pathogenesis of renal disease, but only recently has aldosterone's role in progressive CKD received attention. Specifically, in the presence of normal to high sodium intake, inappropriately 'normal' or frankly elevated aldosterone levels result in renal damage.¹¹ This proinflammatory interaction between aldosterone and salt, described in both animals and humans, calls for increased attention to aldosterone blockade in Western societies that do not foster salt restriction. In the experiments mentioned above, animals were fed normal to high amounts of salt to exaggerate both the fibrotic properties of aldosterone and the beneficial effects of mineralocorticoid receptor blockade. This 'stacking of the deck' might be a reasonable approximation of the dietary sodium habits of patients with CKD.

The bulk of the evidence discussed here is from animal studies, and translation to clinical practice would be premature without well-designed, long-term clinical trials. The risk of hyperkalemia with mineralocorticoid blockade, particularly in patients with reduced GFR who

might already be on ACEIs and/or ARBs, cannot be understated. Hypotension, GFR decline, and—with spironolactone—gynecomastia in men and menstrual irregularities in women are other important adverse events to consider. These risks could potentially be minimized by use of mineralocorticoid receptor blockade earlier in CKD or by use of lower drug doses, but this theory needs to be tested in clinical studies. At least six studies of aldosterone blockade in CKD are ongoing or recently completed, of which three were specifically designed to evaluate safety.

Any beneficial therapy comes with risks, however—even one as widely used as aspirin. This drug, a mainstay in the prevention and management of cardiovascular and cerebrovascular disease, is often prescribed in an 81 mg ('baby') dose to minimize the risk of bleeding. We propose that spironolactone, at a 'baby' dose of 12.5 mg per day, could become the CKD equivalent of aspirin. Whereas today, in primary care and cardiology offices, patients often ask their physicians if they should be taking aspirin, perhaps someday nephrologists will ask whether their patients with CKD should be receiving the 'renal aspirin', spironolactone.

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