Aldosterone in clinical nephrology—old hormone, new questions

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Introduction

There has been a resurgence of interest in the use of aldosterone blockade with spironolactone and eplerenone in patients with hypertension and renal disease. This, combined with observations made in patients treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), has resulted in many questions regarding aldosterone, a hormone many of us previously thought we understood. It has long been known that the renin–angiotensin–aldosterone system (RAAS) has a pivotal role in regulating sodium, potassium and fluid balance. Accordingly, in this classical volume-related pathway (Figure 1), liver-derived angiotensinogen is cleaved by renin to angiotensin I, which ACE or kininase II then converts to the active principal angiotensin II. Angiotensin II then stimulates thirst, vasoconstriction and adrenal production of aldosterone that promote renal tubular sodium reabsorption and kaliuresis. We now know that this is a simplistic view of a much more complex system, with many redundancies in the pathways, and multiple non-volume-related effects demonstrated both experimentally and clinically, as outlined by Ritz and Tomaschitz [1]. In many respects, this has raised as many questions as it has answers.

Aldosterone breakthrough

The widespread use of ACEIs and ARBs to treat hypertension, and to reduce proteinuria in renal disease, has resulted in the observation that despite continuing these drugs, plasma aldosterone levels, which almost invariably fall initially, rise again to pre-treatment levels or above in a high proportion of patients—a phenomenon known as aldosterone breakthrough [2]. The proportion of patients in whom aldosterone breakthrough is observed varies between series, but may be as high as over 50%. The mechanism for aldosterone breakthrough is currently obscure, as is the source of the aldosterone, which though likely of adrenal origin could possibly be contributed to by cells outside the adrenal glands. This possibility derives from experiments suggesting that the hormone can also be produced in other organs such as the heart, brain and kidneys. Though cardiac synthesis is now questionable [3,4], aldosterone production in the kidney seems to be likely, having been demonstrated in the renal cortex [5] and in particular by mesangial cells [6]. These non-adrenal aldosterone producing mechanisms seem to contribute little to circulating aldosterone levels, though they may have local relevance.

Non-volume effects of aldosterone

As outlined by Ritz and Tomaschitz [1], the actions of aldosterone are not confined to the distal nephron, but via various mechanisms other than the traditional mineralocorticoid receptor (MR) and alternative intracellular pathways [7], it can affect many other renal cells including afferent arterioles [8,9], fibroblasts [10], mesangial cells [11] and podocytes [12], with potentially deleterious pro-inflammatory and pro-fibrotic effects [10,11,13,14]. Many of these may be abrogated by the aldosterone antagonists...
spironolactone or eplerenone, indicating the role of the MR in some of these processes.

Recently, there has been interest in the amelioration of proteinuria by aldosterone blockade and in the role of podocytes in proteinuria. Accordingly, any direct effects of aldosterone on podocytes might be relevant. Though much of the data in both animals and man are confused by concurrent hypertension, proteinuria, renal failure, drugs interfering with the RAAS or combinations thereof, this was at least partially untangled in one experimental study that also demonstrated the presence of MR on podocytes [12]. Podocyte injury was clearly seen in salt-loaded uninephrectomized rats infused with aldosterone. Severe hypertension, heavy proteinuria and podocyte damage in these animals were abrogated by eplerenone, but not when blood pressure was normalized with hydralazine, suggesting that aldosterone rather than high blood pressure per se might be directly responsible [12].

**Aldosterone antagonism in proteinuria**

In 2001, we reported a small series of patients with glomerular disease already taking ACEI in whom addition of spironolactone 25 mg daily resulted in a 55% reduction in proteinuria by 4 weeks [15]. Since then, there have been at least 10 randomized controlled trials (RCTs) (Table 1) as well as a systematic review of various publications including RCTs, case series and pilot studies confirming this effect [16]. Whether the effect is as great or occurs at all in patients not already established on ACEI or ARB seems not to have been established or whether very high dose ARB would have a similar effect has not been clarified. The reduction in proteinuria–albuminuria commences rapidly within 2–4 weeks [15,17,18] and persists for at least 12 months [17,19,20]. The reported extent of the reduction in proteinuria is substantial, ranging between 30 and 50% and occurs in a wide variety of chronic proteinuric glomerular diseases. Though antiproteinuric effects have been demonstrated in patients in whom aldosterone breakthrough has occurred [21], the effect seems not confined to this sub-group, since it occurs in a far higher proportion of patients than does aldosterone breakthrough [22]. In one larger RCT, there was a correlation between baseline proteinuria and aldosterone levels and the observed decrease in proteinuria with spironolactone therapy [17], while others found no such correlation, albeit in smaller studies [23].

**How does aldosterone blockade reduce proteinuria?**

There are many potential mechanisms, all of which may play a role in some patients in different situations and after different periods of treatment. The effect appears not generally proportionate to observed reductions in blood pressure. In most RCTs, this was well controlled prior to the addition of aldosterone blockade. It is likely that the rapid initial fall in proteinuria is due to an alteration in glomerular haemodynamics. This would be consistent with the observation that patients with aldosterone secreting adenomas have a slightly elevated GFR and albumin excretion rates that normalize after adrenalec- tomy [24,25]. Though many RCTs have failed to demonstrate a reduction in GFR with aldosterone blockade in proteinuria, or only showed a statistically insignificant trend to reduction, a small early reduction in GFR between 1 and 3 months has been demonstrated by some [17,20], followed by a slower decline over the following 12 months when compared with patients on conventional therapy where the decline in GFR was steady over that period. That the spironolactone-induced initial decline in GFR was functional rather than structural is supported by the observation that in patients with reduced GFR in whom spironolactone was ceased due to hyperkalaemia, the GFR returned to baseline levels [20]. However, the reductions in GFR were proportionately far less than the reduction in proteinuria. In one study, the impact of the change in GFR was estimated by calculating the fractional clearance of albumin (albumin excretion/plasma albumin × GFR). A 35% reduction in fractional excretion of albumin was reported, consistent with a mechanism whereby the reduction in albuminuria far exceeded any change in GFR. In the same study, albuminuria fell by 35%, while EDTA clearance showed only a statistically insignificant trend to decrease [23].

The rapid reduction in protein excretion may be due to alterations in the diameter of glomerular afferent and efferent arterioles, similar to the mechanism by which angiotensin II blockade reduces proteinuria. The most obvious scenario would be a blockade of the vasoconstrictor effects of aldosterone. However, this may be unlikely as these vasoconstrictor actions of aldosterone have been reported to be unaffected by spironolactone [8]. Other possibilities include blockade of angiotensin II induced hypertrophy [26] or a reduction in aldosterone mediated up-regulation of angiotensin II receptors in the glomerular arterioles [27]. These would reduce the effects of angiotensin II on the glomeruli, resulting in similar effects to ARB, i.e. a reduction in albuminuria associated with a minor decrease in GFR. In addition if the aldosterone blockade leads to any natriuresis, this could potentiate the antiproteinuric effects.
Table 1. Randomized controlled trials, using aldosterone antagonists spironolactone and eplerenone to target proteinuria

<table>
<thead>
<tr>
<th>Reference</th>
<th>DM/CKD</th>
<th>GFR/Cr</th>
<th>ACEI/ARB</th>
<th>SP/EP</th>
<th>WKS</th>
<th>↓ UAC or urine protein</th>
<th>BP</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parallel group RCT</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Bianchi et al. [17]</td>
<td>83 CKD</td>
<td>GFR &gt; 60 mL/min/1.73 m²</td>
<td>ACEI ± ARB</td>
<td>SP 25 mg</td>
<td>52 wks</td>
<td>−54%</td>
<td>NC</td>
<td>GFR</td>
</tr>
<tr>
<td>Chrysostomou et al. [19]</td>
<td>DM CKD 41</td>
<td>Cr &lt; 200 µmol/L</td>
<td>ACEI ± ARB</td>
<td>SP 25 mg</td>
<td>12 wks blind 52 wks open</td>
<td>−45%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Epstein et al. [18]</td>
<td>268 DM</td>
<td>GFR &gt; 70 mL/min/1.73 m²</td>
<td>ACEI ± ARB</td>
<td>EP 50–100 mg</td>
<td>12 wks</td>
<td>−45%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>van den Meiracker et al. [20]</td>
<td>59 DM</td>
<td>Cr &lt; 265 µmol/L</td>
<td>ACEI or ARB</td>
<td>SP 25–50 mg</td>
<td>52 wks</td>
<td>−44%</td>
<td>Fall</td>
<td>NC</td>
</tr>
<tr>
<td>Furumatsu et al. [34]</td>
<td>32 CKD</td>
<td>CrCL &gt; 30 mL/min</td>
<td>ACEI + ARB</td>
<td>SP 25 mg</td>
<td>52 wks</td>
<td>−58%</td>
<td>NC</td>
<td>GFR</td>
</tr>
<tr>
<td><strong>Crossover RCT</strong></td>
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<tr>
<td>Rachmani et al. [57]</td>
<td>46 DM</td>
<td>Cr &lt; 160 µmol/L</td>
<td>ACEI</td>
<td>SP 50–100 mg</td>
<td>24 wks</td>
<td>−52.2%</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Rossing et al. [58]</td>
<td>20 DM</td>
<td>GFR &gt; 30 mL/min/1.73 m²</td>
<td>ACEI ± ARB</td>
<td>SP 25 mg</td>
<td>8 wks</td>
<td>−33%</td>
<td>Fall</td>
<td>Small fall</td>
</tr>
<tr>
<td>Schjoedt et al. [23]</td>
<td>20 DM</td>
<td>GFR &gt; 30 mL/min/1.73 m²</td>
<td>ACEI ± ARB</td>
<td>SP 25 mg</td>
<td>8 wks</td>
<td>−30%</td>
<td>Insignificant Fall</td>
<td>Insignificant fall</td>
</tr>
<tr>
<td>Schjoedt et al. [59]</td>
<td>20 Type I DM</td>
<td>GFR &gt; 30 mL/min/1.73 m²</td>
<td>ACEI ± ARB</td>
<td>SP 25 mg</td>
<td>8 wks</td>
<td>−32%</td>
<td>Fall</td>
<td>Insignificant fall</td>
</tr>
<tr>
<td>Saklayen et al. [60]</td>
<td>24 DM</td>
<td>Cr &lt; 2.0 mg/dl</td>
<td>ACEI or ARB</td>
<td>SP 25 mg</td>
<td>4 wks</td>
<td>−57%</td>
<td>Fall</td>
<td>Insignificant fall</td>
</tr>
<tr>
<td>Tyllicki et al. [22]</td>
<td>18 CKD</td>
<td>GFR &gt; 45 mL/min/1.73 m²</td>
<td>ACEI + ARB</td>
<td>SP 25 mg</td>
<td>8 wks</td>
<td>−55.3%</td>
<td>NC</td>
<td>NC</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trials; SP: spironolactone; EP: eplerenone; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; DM/CKD: Number of patients with chronic kidney disease (CKD) or diabetes (DM); Wks: weeks; NC: no change.
effects of angiotensin II, much as diuretics potentiate and salt loading abrogates the antihypertensive effects of ACEI [28].

Blockade of the multitude of pro-fibrotic and pro-inflammatory effects of aldosterone [14,29–33] could affect glomerular haemodynamics and may be increasingly important in the longer term with the reduction of progressive renal injury, hence proteinuria. Reductions in urinary excretion of type IV collagen after 1 year [34] and the amino-terminal peptide of type III collagen (PIIINP) after 8 weeks [22] have been shown to accompany the antiproteinuric effect [22].

Finally, a direct effect on podocytes has been suggested, since as detailed above, rat podocytes have been shown to express MR, and aldosterone-induced podocyte injury could be demonstrated independent of blood pressure [12].

A question remaining is whether this reduction in protein excretion and abrogation of pro-fibrotic and pro-inflammatory pathways means that aldosterone blockade will reduce progressive renal injury. Only three RCTs have studied the effects of aldosterone blockade over a 12-month period, and of these only two had the power to question effects on GFR [17,20]. In both, a small but statistically significant initial fall in GFR occurred in the first 1–3 months, followed by a reduced rate of fall over the next 12 months, while GFR fell steadily in the control arm, reminiscent of the pattern seen with ACEI/ARB treatment of proteinuric chronic kidney disease (CKD). It is thus far too early to judge whether aldosterone blockade has any long-term renoprotective effect, though as reviewed by Ritz and Tomaschitz [1], suggestive evidence is accumulating.

**Aldosterone blockade in hypertension**

Important insights have come from addressing two questions in hypertension. Is there evidence to suggest that aldosterone has a role in so-called essential or primary hypertension? Is there evidence that aldosterone blockade with spironolactone or eplerenone is effective in the treatment of hypertension? Though still controversial [35,36], a series of papers published since 1994 [37] has suggested some patients with ‘primary’ hypertension have inappropriately high aldosterone levels for their renin level. This leads to a high aldosterone to renin ratio (ARR). In difficult-to-control essential hypertensives, recent studies suggest that in 6–19% of these patients such inappropriate hyperaldosteronism is resistant to such steps as salt loading or fludrocortisone administration [38–42]. Of interest, the majority of these patients are seen to have normal adrenal glands on CT scanning. The mechanism is not known, and the value of detecting the syndrome and the appropriate treatment is controversial.

Having established an association between inappropriately high aldosterone levels and high blood pressure, the question arises as to whether high aldosterone levels predict future hypertension, supporting a causal role. The Framingham study has contributed to this debate as mentioned by Ritz and Tomaschitz [1]. First, it reported that serum aldosterone levels predicted the development or worsening of hypertension [43]. More recently came the observation that even after adjusting for other variables, a high ARR is predictive of later development or worsening of hypertension [44]. The risk of developing or worsening of hypertension over 3 years (sex and age adjusted) was progressively higher with each tertile increase in aldosterone level, and decreased with each tertile decrease of renin level, such that in the highest ARR quartile the risk for both was more than doubled.

A host of uncontrolled studies have suggested that aldosterone antagonism with spironolactone or eplerenone is effective in reducing blood pressure, particularly in difficult-to-control hypertensives, usually already on ACEI or ARB [45–49]. This effect seems independent of whether or not the patients have non-suppressible hypoaldosteronism [46]. Previously used in a dosage of 100–400 mg/day [50] with a correspondingly high side effect profile, interest has been rekindled by the many reports of the efficacy of lower doses of spironolactone (25–50 mg/day) and the introduction of eplerenone, an aldosterone analogue with minimal androgenic and progesterone like effects, hence less risk of gynaecomastia, a significant problem with chronic high-dose spironolactone. A large multicentre randomized-placebo-controlled study compared 8 weeks of eplerenone (total 50–400 mg/day) with spironolactone (50 mg twice a day) and placebo in 409 mild-to-moderate hypertensives not on any other known blood pressure modifying agents. Both eplerenone and spironolactone were effective, with a similar BP reduction (16/9 mmHg approximately) [45]. Other papers report smaller series of patients in which low-dose spironolactone (25–50 mg/day) has been effective in treating patients with difficult-to-control hypertension, usually already taking ACEI or ARB [46,48,51]. The mechanism remains controversial. Counterintuitively, it does not seem to be consequent upon aldosterone breakthrough. In a RCT of eplerenone or placebo added to ACEI or ARB monotherapy, eplerenone was shown to be effective in lowering BP and, importantly, this effect bore no relationship to baseline plasma renin, aldosterone or ARR [52].

The aldosterone antagonist could be acting as a diuretic. While considered unlikely by some [53], because of the low doses required and the lack of influence of circulating aldosterone levels, others consider this likely [54]. Evidence for this point of view comes from the observation that the diuretic, amiloride, which also inhibits the epithelial sodium channel by which aldosterone regulates sodium resorption, has been shown to be equally as effective as spironolactone in lowering BP in hypertensive African Americans not on ACEI or ARB. Moreover, there was no added benefit when both were given together [55].

**Unresolved questions**

The unresolved questions raised are many. How does aldosterone breakthrough occur? Is systemic aldosterone breakthrough relevant to the antiproteinuric and antihypertensive effects of aldosterone blockade? What are the mechanisms of these effects, which do not seem volume related?

Importantly, we must be concerned about the risk of hyperkalaemia when adding aldosterone blockade to our routine therapeutic regimens in both glomerular disease...
and hypertension. The increasing enthusiasm in the nephrology world for double (ACE/ARB) or even triple (ACE/ARB/Aldosterone blockers) RAAS blockade must be tempered with serious caution, since life-threatening hyperkalaemia can occur [56]. In most studies of aldosterone blockade, particularly in patients in whom GFR is already reduced, hyperkalaemia or a rise in mean plasma K is observed. That RCTs are poorly designed to demonstrate safety or adverse effects is well known. It is thus premature to advocate aldosterone blockade in the wider nephrology context until we have much better data from large-scale studies.

Conflict of interest statements. None declared.

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Phosphate levels—time for a rethink?

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Introduction

There has been great concentration on measurement and manipulation of circulating phosphate concentrations; however, little recent thought has been given as to whether we should pay attention to when this is measured. There is a large body of evidence to indicate that this could be important, since there are pronounced fluctuations during the day in normal individuals and with dialysis sessions in haemodialysis (HD) patients, yet there is a paucity of data particularly regarding the circadian rhythm in patients with chronic kidney disease (CKD).

Why do we measure serum phosphate levels?

Serum phosphate concentration (Ps) has been clearly demonstrated to be a strong risk factor for morbidity and mortality in patients with CKD both before requiring maintenance dialysis therapy and when on chronic HD. A 2-year observational study of 6407 prevalent HD patients in the community sample.