It is generally accepted as the optimal way to evaluate kidney function in studies on progressive CKD and it is therefore widely used [4,7,11,13,14]. The marked significance of this method is demonstrated in Figure 1 and Table 1 as only the rate in decline in GFR correctly expresses progression of renal failure.

The present knowledge on treatment of progressive CKD must continuously be extended. This implies the application of correct research methodology in clinical trials and meta-analyses. Failure to do so may at worst lead to exclusion of a potentially beneficial treatment.

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Secondary rise of albuminuria under AT1-receptor blockade—what is the potential role of aldosterone escape?

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Introduction

Inhibition of the renin–angiotensin system is the recommended standard therapeutic regimen in chronic kidney disease. The reasons for this choice are obvious. On the one hand angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs)
Aldosterone and proteinuria

Since the description of Conn in 1964 of 145 patients with primary hyperaldosteronism it is known that high plasma aldosterone levels are in most cases associated with proteinuria [5]. However, for a long time this symptom has been attributed to the deleterious effects of high blood pressure rather than direct effects of aldosterone on glomerular permselectivity. Today, there is clear evidence that aldosterone causes direct and blood pressure independent renal injury and proteinuria. In the remnant kidney model which is characterized by high plasma aldosterone levels, removal of the adrenals reduces proteinuria [6]. Furthermore, aldosterone infusion induces proteinuria even in the presence of ACE inhibitors and ARBs [7]. It is unknown to what extent these actions of aldosterone are mediated via genomic or non-genomic effects. Certainly several non-genomic effects of aldosterone have been reported which may contribute to its pro-proteinuric action [8]. The effects of aldosterone on the kidney include haemodynamic and non-haemodynamic mechanisms. Concerning the latter, aldosterone induces renal inflammation and fibrosis [9] via several pathomechanisms: increased Ca\(^{2+}\)-influx into renal cells [10], activation of MAP kinase [11], stimulation of PAI-1 [12], formation of reactive oxygen species [13] and expression of TGF-β [14]. Moreover, classical pharmacological experiments have demonstrated that aldosterone constricts renal efferent arterioles more potently than afferent arterioles [15] via endothelium-dependent mechanisms [16]. Furthermore, aldosterone potentiates Ang II-mediated signaling in smooth muscle cells. Differential vasoconstriction of efferent vs afferent arterioles as well as potentiation of the vasoconstrictor action of Ang II may contribute to hyperfiltration and proteinuria [17]. It is interesting to note that albuminuria is present even in young only moderately hypertensive patients with glucocorticoid remediable aldosteronism [18]. However, it is not well understood to what extent receptor-mediated molecular pathways are involved—an important point for the indication to use blockers of the mineralocorticoid receptor. For example, only some of the described renal effects of aldosterone effects are blocked by receptor antagonists, whilst others are not.

What is known about aldosterone escape under RAS blockade?

In a physiological setting, adrenal aldosterone formation and release is regulated mainly by Ang II (Figure 1). It is well established that ACE inhibitor therapy causes an initial decrease in Ang II levels, followed by a sustained secondary increase back to pretreatment levels. The most favoured explanation is that non-ACE enzymes are capable of cleaving Ang I to Ang II [19]. It is therefore tempting to consider that aldosterone escape is merely a consequence of Ang II escape. However, this assumption would not explain why aldosterone escape is a problem of ARB therapy as well. If all AT1-receptors are blocked, all stimulatory effects of Ang II on adrenal aldosterone secretion should be abrogated. Nevertheless, aldosterone escape...
has been documented even under ARB therapy. For instance, in the RESOLVD study in patients with heart failure, after 17 weeks of candesartan treatment, plasma aldosterone levels had decreased markedly, yet increased to pretreatment levels or even higher after prolonged therapy for 43 weeks [20]. In contrast, in another large trial (Val-HeFT) a sustained reduction of aldosterone in response to the ARB valsartan was reported for patients with chronic heart failure over a period of 24 months [21], but the interpretation of the data has been challenged [22]. There was indeed a decrease of aldosterone levels by 17.4% after 24 months compared with baseline, but the documented continuous increase in aldosterone levels between 4 and 24 months seems to indicate at least some degree of aldosterone escape. How can one explain aldosterone escape under AT1-receptor blockade? Apart from Ang II, several additional factors are known to stimulate adrenal aldosterone synthesis and release in vitro [23] for instance bradykinin, endothelin, noradrenaline and parathyroid hormone. A physiological role of these agonists is uncertain, however. In addition to Ang II, potassium (K\(^+\)) and corticotrophin (ACTH), have undoubted physiological significance and these stimuli may even synergize with Ang II. The increase in plasma potassium levels may be one reason for aldosterone escape during ARB treatment. Atrial natriuretic peptide inhibits adrenal aldosterone production [24]. Since at least in chronic heart failure aldosterone levels decrease during ARB therapy, release of aldosterone secretion from inhibition by ANP may be another potential interpretation. On the other hand experimental evidence in stroke-prone hypertensive rats suggests that aldosterone escape during ARB treatment is mediated by an AT2-receptor-dependent mechanism. Dexamethasone and the AT2-receptor antagonist PD123319, but not high doses of candesartan, reduced plasma aldosterone levels in these animals [25]. Another unresolved question is whether the aldosterone which is responsible for the deleterious effect on the kidney and other cardiovascular organs is derived from circulating blood or produced locally [26]. In adrenalectomized diabetic rat kidneys, Xue et al. [27] found evidence of local aldosterone production. In contrast, in transgenic rats over expressing both the human renin and angiotensinogen genes, Fiebeler et al. [28] were unable to show significant local aldosterone formation in cardiac tissue when these animals had been subjected to adrenalectomy.

Clinical considerations and outlook

When aldosterone receptor antagonists are administered on top of either ACE inhibitors or ARBs, a further decrease of proteinuria is commonly observed. This was first shown by Chrysostomou et al. [29] for the combination enalapril plus spironolactone. After 1 year of enalapril treatment, eight patients with various chronic kidney diseases still had an average proteinuria of 3.81 g/24 h which was reduced to 1.75 g/24 h after 4 weeks of add-on 25 mg spironolactone [29]. Similar results were obtained subsequently by other investigators. A causal role of aldosterone is suggested by the observation in patients with diabetic nephropathy that those with aldosterone escape have more pronounced proteinuria than those without [30]. In addition the higher the plasma aldosterone level, the greater the anti-proteinuric response to aldosterone antagonists [31]. Moreover, patients with aldosterone escape have a faster decline of renal function. Schjoedt and coworkers [32] treated 63 hypertensive type 1 diabetics for 35 months with 100 mg losartan. The rate of loss of GFR was 5 ml/min/year in patients with aldosterone escape (n = 26) and 2.4 ml/min/year in those without (n = 37). Taken together, the presented evidence favours the idea that aldosterone escape during treatment with either ACE inhibitors or ARBs results in a secondary rise of glomerular proteinuria. There remain open questions: in view of potential adverse events, e.g. hyperkalaemia, which patients can safely be treated with aldosterone antagonists? Bianchi et al. [31] demonstrated that patients with a GFR < 60 ml/min are more likely than those with a GFR > 60 ml/min to develop hyperkalaemia. Is it justified to use ‘prophylactically’ a combination of RAS blockade with low dose aldosterone antagonists in all patients with proteinuria > 0.5 g/day as suggested [33] or only in patients with documented aldosterone escape? Is there a cut-off for aldosterone levels justifying combination therapy? The author believes that at present neither prophylactic use of aldosterone antagonists nor definite cut-off levels of plasma aldosterone for initiating aldosterone antagonist therapy can be recommended. It is the author’s opinion that any patient with increasing aldosterone levels during ARB or ACE inhibitor therapy has aldosterone escape to an extent which might legitimate add-on of an aldosterone receptor blocker. However, online monitoring of aldosterone levels before and after initiating ARB or ACE inhibitor therapy appears inappropriate in daily practice. Therefore, the following recommendation seems feasible. In compliant patients with a GFR > 30 ml/min and proteinuria > 1 g/day after 6 months of treatment with an ARB or ACE inhibitor add-on of 25 mg spironolactone should be considered. In a recent study by Chrysostomou et al. [34], the combination of 5 mg ramipril with 25 mg spironolactone was more effective in reducing proteinuria than the combination of 5 mg ramipril with 150 mg irbesartan. Nevertheless, a careful eye on serum potassium and creatinine is mandatory! Finally, it will be interesting to see whether renin inhibition by aliskiren will overcome the problem of aldosterone escape in the future.
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