

Diabetic Nephropathy: Role of Aldosterone and Benefits of Therapy with Aldosterone Receptor Blocker

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1. Introduction

ACE-inhibitor and angiotensin receptor blocker (ARB) have been shown to reduce proteinuria and progression of renal dysfunction in both type 1 and type 2 diabetics (1-11). However, even with optimal use of ACE-Inhibitor or ARB, the progression of renal dysfunction is not completely stopped. Even in studies where ACEI or ARB therapy showed improved outcome, a very high percentage of patients still progress. This scenario is now highlighted in a recent study published in JAMA, which shows the incidence of diabetic nephropathy increasing in USA in excess of what can be accounted for by the increased incidence of type 2 DM in the population (12). The present treatment strategy is therefore not adequate and other additional effective treatment strategies are urgently needed.

Since the publication of the landmark RALES study (13) showing a significant survival benefit in patients with systolic heart failure when treated with aldosterone inhibition in addition to ACEI and beta-blockers, the interest in the vasculotoxic effect of aldosterone and the beneficial therapeutic effects of aldosterone receptor blocker drugs like spironolactone has been steadily increasing (14).

2. Aldosterone biology and lessons learnt from animal models

In addition to its classical action in the distal nephron, aldosterone is now known to exert many other effects on other areas of kidneys as well as in cardiovascular tissues. (14)

Aldosterone is now known to have a significant role in renal hemodynamics, independent of Angiotensin II. In a remnant kidney model in the rat Greene et al showed that there was >10-fold rise in aldosterone in the remnant kidney rats (REM) compared to sham operated ones (15). As expected, proteinuria, hypertension and glomerulosclerosis in the REM rats were attenuated with treatment using ACE-inhibitor or angiotensin receptor blockers. However, when these treated rats (REM AIIA) were given an aldosterone infusion the extent of proteinuria, hypertension and glomerulosclerosis were similar to untreated (REM) rats, suggesting deleterious renal hemodynamic effects of aldosterone independent of angiotensin II. Use of spironolactone in these rats transiently reduced proteinuria and lowered arterial pressure.

In rats with 5/6th nephrectomy, adrenalectomy and protein restriction independently ameliorated the ablative nephropathy independent of the corticosterone maintenance level (16). In stroke-prone spontaneously hypertensive rats (SHRSP), renal vascular injury causing proteinuria and malignant nephrosclerotic lesions were markedly reduced by treatment with spironolactone (17). The effect of spironolactone alone was comparable to the effect of treatment with captopril. In another study the ameliorating effect of ACE-inhibition in the SHRSP rats could be fully reversed by infusion of aldosterone, suggesting a major additive role for aldosterone in the vascular injury in these rats(18). Importantly, the deleterious effects of aldosterone and the protective effects of spironolactone against renal damage in SHRSP rats appeared to be independent of the blood pressure.

Renal damage, as evidenced by albuminuria and glomerulosclerosis, in response to 5/6 nephrectomy was markedly less in mineralocorticoid resistant Wistar-Furth rats compared to Wistar rats. Treatment of hypertension in the nephrectomized Wistar rats did not protect them from renal injury(19), suggesting again that mineralocorticoid mediated deleterious effect was independent of the blood pressure.

Hyperaldosteronism has been noted as a component of clinical chronic renal insufficiency of various etiologies including diabetic nephropathy (20-21). In a cross sectional study of patients with mild to moderate renal insufficiency, Hene et al observed that the level of serum aldosterone increased several fold as creatinine clearance fell below 50% of normal (22). The significance of this hyperaldosteronism to the progression of the renal insufficiency has not been studied systematically, but in one longitudinal study Walker noted a significant correlation between aldosterone level and rate of progression of renal failure (23). In this longitudinal cohort study of 131 diabetics, Walker noted that hypertension, plasma angiotensin II and aldosterone were independent predictors of accelerated loss of renal function.

In vitro studies of cultured mesangial cells revealed increased production of type IV collagen after incubation with aldosterone (24-25). In addition to the classical genomic action through the type 1 mineralocorticoid receptor, aldosterone is now known to have significant non-genomic actions in many different tissues including kidney tubules, mesangial cells, podocytes and vascular smooth muscle cells. Aldosterone also up-regulates angiotensin II membrane receptors thereby multiplying the vascular effect of Ang II. This up-regulation is inhibited by treatment with spironolactone (26-30).

The renoprotective effects of MR blockers have been demonstrated in a variety of animal models. While the benefits were seen in most of these models, mechanism of the beneficial actions were deemed different in different models, depending on the primary focus of the investigators. One area of interest was ACE2 generation. Angiotensin II (which comes from angiotensinogen released by the liver which is converted to inactive Ang I by ACE and then to biologically active Ang II) acts mainly through the AT1 receptor to mediate vasoconstriction/proliferation and the AT2 receptor which mediates vasodilatation and antiproliferation. Ang(1-7) is generated from Ang II by ACE2 and counteracts some of the biologic effects of Ang II. In the Dahl-sensitive hypertensive rat fed a high salt diet, treatment with epleronone normalized blood pressure and decreased the levels of type IV collagen mRNA, angiotensinogen and ACE mRNA, but did not affect ACE2mRNA expression and is possibly protective by decreasing the formation of angiotensin II but not vasodilatory Ang (1-7). On the other hand, candesartan increased ACE 2 mRNA expression, suggesting that aldosterone blockade and angiotensin receptor blockade may be complimentary (31). Treatment with epleronone also reduced urinary protein excretion,

renal injury scores and decreased (pro)renin receptor protein expression, angiotensinogen and AT1R mRNA levels and kidney Ang II content in the same rat model. (32)

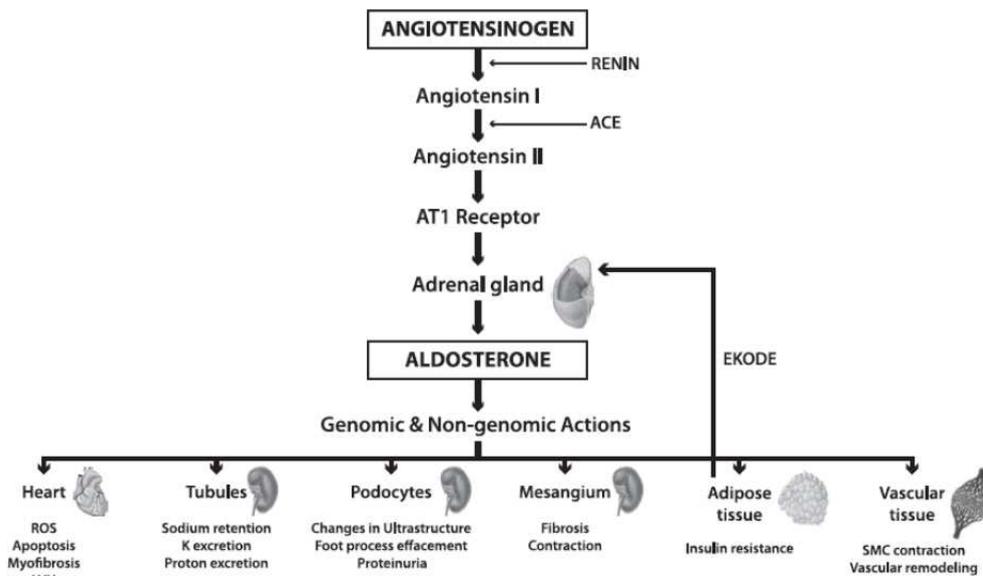


Fig. 1. Angiotensin-Aldosterone Axis and the Physiologic Effects of Aldosterone
 ROS Reactive Oxygen Species, AT1 Angiotensin I, EKODE epoxy-9keto-10trans-octadecenoic acid, SMC smooth muscle cell

In the diabetic rat model, spironolactone treatment was associated with a reduction in urinary albumin excretion and amelioration of glomerulosclerosis despite no change in blood pressure. In various organs including the kidney, there is a local system for aldosterone generation. High glucose stimulates the expression of CYP 11B2 and mineralocorticoid receptor. Spironolactone in addition to blockade of the aldosterone receptor, was also able to reduce intrinsic renal ACE and also aldosterone synthase gene (CYP 11B2) expression in the streptozotocin-induced diabetic mice without affecting blood sugar or blood pressure (33).

Monocyte chemotactic protein (MCP-1) synthesis and nuclear factor-kB are markers of inflammation increased in renal tissue and in urine of diabetic rats and patients. In the cultured mesangial and proximal tubular cells there was inhibition of urinary excretion of MCP-1 (MCP-1) and its upstream transcription factor NF-kB suggesting that aldosterone mediated activation of proinflammatory cytokines was blocked (34).

Transforming growth factor -B1 is a cytokine involved in ECM deposition, proliferation and fibrosis. Some of its tissue effects are mediated by connective tissue growth factor (CTGF). Aldosterone increases expression of TGF-1 and may directly induce CTGF. Spironolactone

reduced TGF-B1 expression and CTGF and renal collagen synthesis through a TGF-B1 independent pathway (not inhibited by prior TGF-B1 neutralization). (35)

Plasminogen Activator inhibitor (PAI-1) inhibits fibrinolysis and mediates ECM accumulation in mesangial and fibroblast cells and glomerulosclerosis. Its synthesis is induced by aldosterone and potentiated by the presence of TGF-B1. Spironolactone treatment reduced expression of PAI-1 and TGF-b in streptozotocin-induced diabetic rats and improves the antioxidant environment by reducing the fall in superoxide dismutase and glutathione peroxidase that accompanies diabetes induction resulting in reduced malondialdehyde levels (lipid oxidation byproduct) (36).

VEGF is a cytokine involved in the early development of diabetic nephropathy and its expression is increased by glucose, AGE, TGF-B1 and IGF-1. Aldosterone infusion increases renal VEGF synthesis. Spironolactone alone and in combination with losartan reduced VEGF, MCP-1 and malondialdehyde expression resulting in reduced mesangial expansion and sclerosis in an OLETF model. (37)

Aldosterone inhibition was also useful in reducing blood pressure and renal injury in diabetic mice which had impaired endothelial nitric oxide response induced by eNOS knockout. These mice did not have good response to ACE or ARB therapy. (38).

Recent studies have also investigated the effects of epleronone alone or in addition to ACE or ARB therapy in the diabetic rat. Mineralocorticoid receptor (MR) expression is increased in diabetic rats (OLETF) and epleronone reduced cortical levels of MR protein, MR RNA, TGF-b mRNA and osteopontin mRNA and improved various histological measures of renal injury along with albuminuria (39). The combination of epleronone and enalapril resulted in greatest decrease in TGF-b, Type IV collagen and TPA-1 expression both in the whole kidney and in cultured mesangial cells accompanied by an improvement in albuminuria, GFR and glomerulosclerosis compared to either agent alone. (40). In streptozotocin diabetic rats, the addition of epleronone with ramipril prevented glomerular hyperfiltration but did not have an additive effect on proteinuria or glomerular hypertrophy (41). Again in OLETF diabetic rats, epleronone added to telmisartan did not alter systolic blood pressure but resulted in greater reduction in proteinuria and podocyte injury and a greater increase in nephrin and podocin mRNA levels. Hydralazine decreased SBP but did not alter any of the renal parameters. (42)

Epleronone protected against podocyte damage in the hypertensive rat model as evidenced by reduced expression of podocyte injury markers desmin and B7-1. Mechanisms involved include inhibition of NADPH oxidase (p22phox and gp91phox), which is induced by aldosterone and generates reactive oxygen species, and reduced aldosterone effector kinase Sgk1, which is involved in diabetes stimulated matrix deposition. Unlike epleronone, hydralazine did not improve proteinuria or marker expression despite equivalent BP control. Local expression of apoptosis related molecules (caspase-3 and Bax) as well as reduction of BCL-2 (apoptosis regulatory protein) in podocytes of diabetic rats was prevented by treatment with spironolactone. Based on these studies, Shibata et al surmised that it is possible that Sgk1 plays a key role as the common effector molecule of the MR signaling in podocytes. (43-45)

During the progression of renal damage, aldosterone might be involved in injury to the glomerular podocytes, mesangium, tubulointerstitium and tubules through locally expressed Mineralocorticoid receptor (MR).(46-48) However, the precise molecular mechanisms responsible for aldosterone and MR-induced cell injury are unclear. In the kidney, aldosterone activates multiple intracellular mechanisms including reactive oxygen species, mitogen-activated protein kinases (MAPKs) and Rho-kinase etc. by activating MR(49-50). These molecular mechanisms have been reviewed recently(51-52).

The renoprotective effects of spironolactone or eplerenone had been seen in many other animal models of renal injury not limited to diabetic nephropathy, as noted in a recent review by Nishiyama et al. (46) These models included streptozotocin-induced and other forms of diabetic rats and mice, obese SHR rats, murine lupus nephritis, unilateral ureteral obstruction, ischemia reperfusion injury, 5/6th nephrectomised rats and rats treated with AngII infusion, NO synthase inhibitor or cyclosporine(53-66). In these animal models, treatment with aldosterone blockers had no effect on systemic blood pressure. Thus, these observations are consistent with the concept that aldosterone and MR-dependent renal injury is not dependent on blood pressure changes but on their local actions.

Metabolic syndrome with or without diabetes causes podocyte injury and progressive nephropathy. In type 2 diabetes, coexistent metabolic syndrome plays a synergistic role in progressive renal injury. Nagase et al investigated the role of aldosterone signaling in rats with metabolic syndrome(67). Proteinuria was prominent in SHR/NDmcr-cp compared with nonobese SHR, which was accompanied by podocyte injury as evidenced by foot process effacement, induction of desmin and attenuation of nephrin. Serum aldosterone level, renal and glomerular expression of aldosterone effector kinase Sgk1, and oxidative stress markers all were elevated in SHR/NDmcr-cp. Mineralocorticoid receptors were expressed in glomerular podocytes. Eplerenone treatment effectively reduced podocyte damage, proteinuria, Sgk1, and oxidant stress. Pretreatment with antioxidant tempol also alleviated podocyte impairment and proteinuria, along with inhibition of Sgk1.

When these investigators looked for the source of the excess aldosterone , it was found that visceral adipocytes, isolated from SHR/NDmcr-cp, secreted substances that stimulated aldosterone production in adrenocortical cells. The aldosterone-releasing activity of adipocytes was not inhibited by candesartan. Adipocytes from nonobese SHR did not show such activity. That visceral adipocytes may be the source of factors causing excess aldosterone was , however, first noted by Ehrhart-Bornstein et al (68) and later the secreted factor was further characterized as EKODE (12,13-epoxy-9keto-10(trans)-octadecenoic acid) by Goodfriend et al. (69) These are mainly oxidized polyunsaturated fatty acids produced by adipocytes. One of the most potent one is an oxidized product of linoleic acid (EKODE). EKODE stimulated aldosteronogenesis at concentrations from 0.5 to 5 micromol/L but inhibited it at higher dose. In samples from 24 adults levels of EKODE correlated directly with aldosterone level and in a subsample of 12 blacks in the cohort it correlated with body mass index and systolic blood pressure. The resistant hypertension seen in patients with abdominal obesity is partly due to these autacoids secreted by visceral adipocytes, and BP in these patients respond very well to the use of spironolactone. This may explain the observation in the Framingham study that plasma aldosterone concentration was significantly correlated with the risk of onset of the metabolic syndrome.

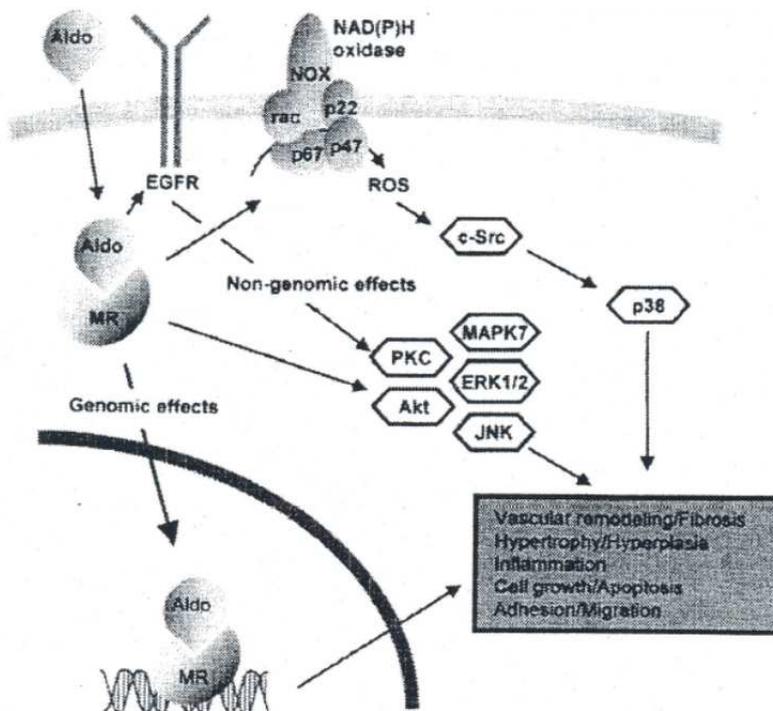


Fig. 2. Mechanisms of genomic (long term) and nongenomic (rapid) effects of aldosterone. Aldosterone activates the tyrosine kinase c-Src through the production of ROS, leading to the activation of p38MAPK and also various signalling molecules like PKC, Akt, ERK 1/2, ERK5, Mapk7, and JNK. Aldosterone also mediates the activation of EGFR. Genomic and rapid effects of aldosterone lead to vascular remodeling, hypertrophy, inflammation, cell growth, apoptosis, adhesion, and migration. *Aldo* aldosterone, *EGFR* epidermal growth factor, *MR* mineralocorticoid receptor, *ROS* reactive oxygen species. Other abbreviations as in Fig. 1. (Ref. 93)

2.1 Human studies using aldosterone receptor blockers

Within the past decade, several human studies have been conducted exploring the effects of spironolactone and epleronone on patients with chronic kidney disease with or without diabetes between which we shall be concentrating on the latter.

Since ACE-I/ARB therapy had been generally accepted as standard therapy for patients with diabetic nephropathy, most studies conducted with aldosterone receptor blocker drug like spironolactone involved the addition of this agent to either single agent ACE-I or ARB (referred hence to as single- drug add-on) (70-74) or to combined ACE-I/ARB therapy (dual-drug add-on) (75-76). Epleronone likewise has been tested as add-on therapy to enalapril (77-78).

In one study (79), albeit in non-diabetic patients, where spironolactone was compared head-to-head to the ACE-I drug cilazapril along with the combination, it was found that spironolactone was slightly better at reducing albuminuria than cilazapril, but the

combination resulted in a further reduction. The blood pressure reduction was the same among the three groups.

A review of the studies where spironolactone was used as single-drug or dual-drug add-on, the degree of albuminuria or proteinuria reduction was about 30-35% with a trend towards a further reduction in studies that had an extended period of observation of up to a year (76). The reduction in albuminuria was greater when spironolactone was used as single-drug add on compared to dual-drug add on (although one study (80) reported an impressive 58% reduction). The addition of spironolactone to baseline ACE-I (lisinopril) therapy resulted in greater reduction in albuminuria compared to the addition of an ARB agent (losartan) to baseline ACE-I (74). This was confirmed in another study that demonstrated that the addition of spironolactone to either single-drug (ramipril) or dual-drug (ramipril + irbesartan) baseline therapy resulted in further reduction in albuminuria but the addition of ARB alone to the ACE-I did not further reduce albuminuria. (75). Several studies correlated the degree of proteinuria reduction to a drop in GFR and to the preexisting serum aldosterone level. Urinary type IV collagen, which is stimulated by aldosterone and is a reflection of renal fibrosis, was also decreased. (73,80)

The efficacy of spironolactone as add-on agent in patients with uncontrolled hypertension specifically those with features of aldosterone excess, such as obesity and low serum potassium levels, has been demonstrated in several studies . The reduction of systolic BP in these studies exceeds 20 mmHg. In the studies we are reviewing on diabetic nephropathy, most of whom again, were already on preexisting ACE-I and ARB therapy, the focus of the aldosterone antagonist add-on was on proteinuria and renal function. The reduction in BP was more modest. When used as single-agent add-on, several studies show a drop of 6-8 mmHg in systolic BP or ABPM with an additional smaller reduction with longer followup. One study showed no further drop in blood pressure, but this group of patients had overall a very high GFR (73). Addition of epleronone to enalapril produced only a non-significant change in BP (22). Spironolactone used as dual-drug add-on generally did not further reduce BP (75). There has been controversy among researchers in the field as to whether the reduction in proteinuria with aldosterone antagonists is a result purely of further BP lowering, but these studies demonstrate that it is much easier to show a reduction of proteinuria that is statistically significant compared to a reduction in blood pressure.

The study results regarding the effects of aldosterone antagonists on renal function must be interpreted with caution. First of all, most of the studies followed renal function through measurement of serum creatinine or an estimation of GFR mathematically derived from creatinine levels, and it is well recognized that this is an insensitive marker to small changes in renal function. One exception are the studies from Denmark (26) which actually measured GFR directly. Secondly, the studies all excluded patients with Stage 4 and 5 CKD., and in fact the mean baseline GFR in most studies exceeded 60 ml/minute, and there are not enough patients in Stage 3 CKD to really draw any meaningful conclusions as to the effects of aldosterone antagonists on patients with more advanced CKD. With these caveats, the published studies indicate that the effect of spironolactone or epleronone on GFR is comparable to the effect of initiation of ACE-I or ARB agents . Single-drug add-on in most studies resulted in a 3-5 ml/min drop in GFR, while dual-agent add-on caused no further drop in GFR. The effects are most prominent in the first month or two after initiation, and drop in GFR is greater in those with baseline impaired function. One study in particular showed a sharp 13 ml/min decrease in GFR with spironolactone compared to baseline ACE-I or ARB therapy, but this decrease occurred early and eventually leveled off. Associated

with this was a sharp drop in albuminuria of 40%. Many studies confirm that the reduction in proteinuria correlates well with the degree in reduction of GFR.

Most of the adverse effects noted includes the known incidence of anti-androgenic effects of spironolactone and hyperkalemia which correlates with the dosage used. Epleronone is of course, free of the first set of side effects and generally results in less hyperkalemia, but this may be a function of the dosages currently being studied. Most studies excluded patients with baseline potassium exceeding 4.5 or 5.0 mmol/L. The trend of the results show that while dual-agent therapy had a greater tendency towards hyperkalemia when compared to single agent therapy, the addition of spironolactone to either ACE-I or ARB resulted in the highest risk of hyperkalemia. This complication may be more frequent among diabetics who tend to have hyporeninemic hypoaldosteronism and is definitely more prevalent in patients with lower baseline GFR, higher baseline potassium, and preexisting metabolic acidosis. With the background of the experience after publication of the RALES study, when practitioners promoted the use of spironolactone for heart failure in patients outside the inclusion criteria of the study, resulting in the appearance of several near fatal hyperkalemic episodes, it behooves us to follow the patients with more advanced CKD more closely and to check serum potassium agents earlier if we choose to use these agents for diabetic nephropathy. There was a suggestion that glucose tolerance worsened after spironolactone with a rise in HbA1c (70,81)), but this was not seen in other studies (78). Spironolactone may also decrease BNP over that achieved by ACE-I (84).

A small study conducted by these authors(82) using a randomized double-blind crossover design to study the effects of spironolactone when added to ACE-I or ARB shows similar results to the studies quoted above, in that spironolactone produced a 57% reduction in proteinuria along with a 7mmHg drop in systolic BP. This was accompanied by a rise in creatinine of about 0.2 mg/dl and serum potassium of 0.3 mEq/L.

The role of aldosterone antagonists in the treatment of diabetic nephropathy may lie in the group of patients whose blood pressure or proteinuria are uncontrolled despite ACE-I or ARB therapy, or who manifest so-called 'aldosterone escape' when aldosterone levels increase after long-term RAAS blockade. (83-84)). Table 1 lists all the clinical trials using Aldosterone receptor blockers in proteinuric patients. As shown in the table the range of proteinuria reduction with additional use of aldosterone receptor blocker was 19% to 58%.(70-87) Aldosterone antagonists seem to be more effective and more economical when added to ACE-I compared to ARBs at this time, albeit at the price of greater risk for acute GFR drop and hyperkalemia. Unfortunately, no long term studies are available at this time to demonstrate that renal function decline is slowed by this approach, and proteinuria is taken as a marker of disease progression, as was with ACE-I/ARB therapy at an earlier time point.

3. Future direction

The beneficial effects of mineralocorticoid/aldosterone receptor blockers in ameliorating or stopping the progression of diabetic nephropathy is impressive in in-vitro studies using mesangial, podocytes or endothelial cell culture system. These studies also help us understand the molecular mechanism by which these agents ameliorate the pathologic process. In-vivo animal model studies also showed encouraging results as elaborated in preceding pages. Similar benefits have been seen in human studies as summarized in the table 1. However most of the human studies were of relative short duration. Longest study

Author/Year	No. of Patients/ Design of Study	Drugs/Dose/ Duration (Weeks)	Reduction in Proteinuria (%)	Δ In Sys.BPmmHg/ GFRml/min/ Kmeq/L
Chrysostomou / 2001	8 / Uncontrolled	SP / 25 / 4	54%	
Epstein / 2002	141/(74 + 67) RCT-Parallel	EP / 200 / 12	19%	3/ - / -
Rachmani / 2004	60/RCT- Parallel	SP / 100 / 24	19%	--
Sato / 2005	32 / Uncontrolled	SP / 25 / 12	38%	- / - / \uparrow 0.1
Bianchi / 2005	42 / Uncontrolled	SP / 25 / 8	37%	- / - / \uparrow 0.4
Schjoedt / 2005	20 / RCT- Crossover	SP / 25 / 8	30%	\downarrow 8 / - / -
Rossing / 2005	21 / RCT- Crossover	SP / 25 / 8	33%	\downarrow 6 / \downarrow 3 / -
Van den Meiracker / 2006	59 (29 + 30) RCT-Parallel	SP / 25-50 / 8	41%	\downarrow 7 / \downarrow 8 / -
Schjoedt / 2006	20 / RCT- Crossover	SP / 25 / 8	32%	\downarrow 6 / \downarrow 3 / \uparrow 0.2
Chrysostomou /2006	41 / RCT- Parallel	SP / 25 / 12 (4 group)	14%	\downarrow 9 / - / \uparrow 0.2
Bianchi / 2006	165 (82 + 83) RCT-Parallel	SP / 25 / 52	58%	- / \uparrow \downarrow / \uparrow 0.8
Epstein/2006	268/RCT- Parallel	Ep/50-100/12	41% (high dose) 34% (low dose)	\downarrow 4 / \downarrow 6 / -
Ogawa 2006	30/RCT	SP / 25 / 52	47%	\downarrow 11 / - / -
Furumatsu 2008	25/RCT	SP / 25 / 52	58%	- / - / -
Saklayen 2008	24/RCT- Crossover	SP / 25 / 12	57%	\downarrow 12 / \downarrow 8 / \uparrow 0.3
Davidson 2008	24/Uncontrol	SP / 25 / 4	26%	\downarrow 9 / - / -
Mehdi 2009	81/ RCT	SP/ 25 / 52	52%	- / - / \uparrow

Legend: Table showing summaries of the clinical studies done with aldosterone receptor blocker in addition to ACE inhibitor or ARB use in proteinuric patients.

Table 1.

follow up was 1 year. And none of these studies examined the long term renal outcomes, especially progression to ESRD, need for dialysis or overall mortality. This paucity of clinical outcome studies is of major concern. Of note, when clinical studies of short duration showed additional lowering of microalbuminuria/proteinuria in diabetic nephropathy as well as in other proteinuric renal diseases, nephrologists became enthusiastic about dual use of ACEI and ARB in patients with diabetic nephropathy. When the large international

ONTARGET study showed that renal outcomes (GFR deterioration, incidence of ESRD, need for dialysis and incidence of hyperkalemia) in diabetic nephropathy of patients on dual therapy was worse than on single agent therapy (ACEI or ARB alone), that initial enthusiasm was checked. (88) Dual ACEI and ARB use is no longer recommended in patients with diabetic nephropathy except in extraordinary situations.

However, the long term outcomes of MR/aldo blocker therapy with ACEI or ARB in diabetic nephropathy need not be similarly detrimental or non-beneficial. Of note while ONTARGET failed to show cardiovascular benefits with dual ACEI and ARB use and other studies showed lack of mortality benefits in dual use of ACEI and ARB in systolic heart failure(89), RALES and other studies (90) showed significant mortality benefit of adding spironolactone or epleronone to ACE or ARB in systolic heart failure patients. However, unless large clinical outcome studies confirm that adding aldosterone blockade to ACEI or ARB actually results in reduction of ESRD incidence, such therapy cannot be recommended without some caution.

When we did our small cross over study in a single institute, we selected patients carefully. Those patients who had hyperkalemia, even remotely, were excluded from participation. Most of our patients also were using high dose thiazide or loop diuretics. Our study, like many other similar studies, were of few weeks duration. As shown in POST RALES study, the incidence of hyperkalemia in Ontario was much higher than seen in the RALES study itself, when spironolactone use became widespread for systolic heart failure. (91)

Questions often arise if one were to use an aldosterone receptor blocker, which one to choose. Spironolactone is the first mineralocorticoid receptor antagonist (MRA) which has been in clinical use for over half a century. Epleronone is a relatively new mineralocorticoid receptor blocker and is still under patent protection. Compared to the latter, spironolactone blocks the androgen and progesterone receptors in addition to its primary blocking effects on mineralocorticoid receptors. This leads to some unpleasant problem of gynecomastia in male patients, the incidence of which is about 10%. Epleronone is much less likely to cause gynecomastia. But binding affinity of epleronone for MR is much lower than that of spironolactone. Spironolactone also has 3 active metabolites all of which have prolonged half life. Epleronone has half life of 4-6 hours and its metabolites are not active. Because of these pharmacological and pharmacodynamic differences, spironolactone seems to be a clinically more effective MR blocking agent than epleronone. One recent comparison of treatment with spironolactone (75 to 225 mg daily) vs epleronone (100 to 300 mg daily) in patients with primary hyperaldosteronism showed better blood pressure lowering by spironolactone (diastolic BP reduction 12.5 mmHg in former vs 5.6 mmHg in later group). There has not been a head to head comparison of the two MR blockers in trials looking for a reduction of proteinuria or improvement in survival in patients with systolic dysfunction. (92)

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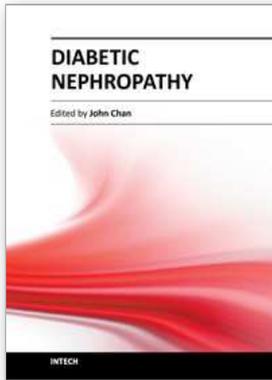
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Internationally renowned experts have provided data on their own studies, and discuss the relative usefulness of their work in relation to diabetic nephropathy. The first section describes the novel role of intrarenal renin-angiotensin-aldosterone system (RAAS) and oxidative stress in the development of diabetic nephropathy and discusses the current and novel pharmacological interventions in the treatment of diabetic nephropathy. The second section discusses other important contributors outside of the RAAS in the pathogenesis of diabetic nephropathy including AGE/RAGE, epithelial-mesenchymal-transition (EMT) and immune cytokines. Features: Provides novel information on various pathophysiological determinants in the development of diabetic nephropathy Provides novel information on various pharmacological interventions of diabetic nephropathy

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