



# The Ascent of Mineralocorticoid Receptor Antagonists in Diabetic Nephropathy



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**Abstract:** Diabetic nephropathy is defined as a decline in the renal function and an increase in the amount of albuminuria (>300 mg/day). The interruption of the renin-angiotensin-aldosterone system (RAAS) by well-established therapies such as angiotensin-converting enzyme inhibitor, angiotensin receptor blockers, calcium channel blockers or diuretics has been beneficial in reducing the progression of renal diseases; however, there is an increase in the levels of aldosterone due to the aldosterone escape phenomenon. Newer and novel approaches to counteract this aldosterone breakthrough while accentuating the anti-hypertensive and anti-proteinuric effects of these agents would be ideal and mineralocorticoid receptor antagonists fit in this slot perfectly. This review attempted to evaluate the safety and efficacy of mineralocorticoid receptor antagonists for diabetic nephropathy. Presently mineralocorticoid receptor antagonists such as spironolactone, eplerenone and finerenone are being investigated as both monotherapies and as additional therapies. Clinical studies have shown that these drugs have been effective in the reduction of blood pressure, urinary-albumin-excretion and estimated glomerular filtration rate. The commonly observed adverse effects are hyperkalemia, gynaecomastia and vaginal bleeding, that are bothersome with spironolactone seems to be avoidable if these patients are switched to non-steroidal and mineralocorticoid receptor antagonists such as finerenone and eplerenone. Most of the studies have only evaluated the short-term effects of mineralocorticoid receptor antagonists on diabetic nephropathy. Hard outcomes such as cardiovascular events, creatinine doubling, progression to end-stage renal disease, mortality and the need for temporary or permanent dialysis need to be studied with these molecules.

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## 1. INTRODUCTION

### 1.1. Diabetic Nephropathy

Diabetic nephropathy is one of the leading causes of end-stage renal disease and is associated with mortality and morbidity worldwide. Diabetic nephropathy is defined as a decline in the renal function and an increase in the amount of albuminuria (>300 mg/day). Recent evidences show that diabetic nephropathy comprises an intense inflammatory state triggered by metabolic, hemodynamic effects accompanied by heavy proteinuria and vascular injury resulting in myocardial and renal fibrosis [1]. Diabetic kidney disease is identified clinically by the persistently high urinary albumin-to-creatinine ratio  $\geq 30$  mg/g and/or sustained reduction in estimated glomerular filtration rate below 60 ml/min per 1.73 m<sup>2</sup> [2]. The risk of diabetic nephropathy is seen among

20-30% of diabetic patients, and the occurrence of the disease is observed to be homogeneous in both type I and II diabetic patients. The main risk factors of diabetic nephropathy include hypertension, uncontrolled blood glucose, dyslipidemia and increased levels of proteinuria [3]. The different stages of diabetic nephropathy include glomerular hypertrophy, microalbuminuria, overt albuminuria and a decrease in the glomerular filtration rate. The well-established first-line drug therapies for DN include angiotensin-converting enzyme inhibitor (ACEi) and angiotensin receptor blockers (ARBs) and the second line drug therapies include calcium channel blockers or diuretics. Once overt proteinase sets in, the progression is poor as the disease becomes irreversible. Hence, it is vital to make an early diagnosis and start treatment with ACEi or ARBs to significantly reduce proteinuria and hypertension, but the prevention of end-stage-renal-disease (ESRD) is suboptimal due to several factors including a paradoxical rise in aldosterone levels during long-term administration of ACEi/ARB called "aldosterone breakthrough" [4]. Moreover, hypertension in chronic kidney disease in general and diabetic nephropathy, in particular, re-

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quires the administration of two drugs, among the majority of the patients. Thus, newer and novel approaches to counteract this aldosterone breakthrough while accentuating the anti-hypertensive and antiproteinuric effects of these agents would be ideal and mineralocorticoid receptor antagonists appear to fit in this slot perfectly. This review attempts to evaluate the safety and efficacy of mineralocorticoid receptor antagonists for diabetic nephropathy.

## 2. MINERALOCORTICOID RECEPTOR ANTAGONISTS

Mineralocorticoid Receptor Antagonists such as spironolactone and eplerenone have been the main drugs for the treatment of patients with heart failure with reduced ejection fraction [5, 6]. However, the uses of these drugs are limited due to the occurrence of hyperkalemia. Therefore, in clinical practice, it is quite common to see these being discontinued even after a single dose [7, 8]. Although, treatment with ACEi and ARBs has shown a beneficial effect in reducing proteinuria and reducing the progression of diabetic nephropathy; the benefits were only observed at the beginning of the treatment, and the antiproteinuric effects were not observed in the later stages of the disease. The interruption of the renin-angiotensin-aldosterone system by ACEi and ARBs has been beneficial in reducing the progression of renal diseases; however, there is an increase in the levels of aldosterone due to the aldosterone escape phenomenon [9, 10]. Therefore, mineralocorticoid receptor antagonists might be effective in such a situation. The increase in the levels of aldosterone acts as a mediator for renal injury through inflammation induction, fibrosis, and necrosis occurring in the kidney tissue [11, 12].

## 3. MECHANISM OF ACTION

The administration of aldosterone blockade has an effect on the glomerular and tubular sclerosis and this effect was found to be independent of the angiotensin II. The addition of the aldosterone blocker can improve the renal function through the anti-hypertensive, anti-inflammatory and antioxidant mechanism. The addition of aldosterone antagonists inhibits the overexpression of transforming growth factor- $\beta$ 1 and plasminogen activator inhibitor-1, macrophage infiltration in the glomeruli and tubulointerstitium [13]. Treatment with mineralocorticoid receptor antagonists attenuates the inflammatory process by downregulating the overexpression of genes such as monocyte chemoattractant protein-1, the tumour necrosis factor receptor, and interleukin. The drug molecule reduces the activation of monocyte chemoattractant protein-1 and nuclear factor kappa light chain enhancer of activated B cells on the mesangial cells and proximal tubular cells that cause damage to the kidney function [14]. Mineralocorticoid receptor antagonists can restore the activity of glucose-6-phosphate dehydrogenase deficiency that would increase the production of glutathione and nicotinamide adenine dinucleotide phosphate, which is the primary intracellular reductant. This, in turn, will attenuate the production of reactive oxygen species, which would cause oxidative stress and lead to the progression of diabetic nephropathy. Therefore, mineralocorticoid receptor antagonists can prevent nephropathy by inhibiting oxidative stress and improving the antioxidant system [15]. Therefore, studies are being conducted to evaluate the beneficial effect of mineralocorticoid

receptor antagonists as an add-on therapy to the existing therapies such as ACEi, ARBs, and diuretics in reducing albuminuria and blood pressure among patients with diabetes. The mineralocorticoid receptor antagonists that are being investigated include spironolactone, eplerenone, and finerenone (Supplementary Table 1).

## 4. EFFICACY OF SPIRONOLACTONE IN DIABETIC NEPHROPATHY

Spironolactone, which is a potassium-sparing diuretic, is an aldosterone antagonist with a weak diuretic property effect. The drug molecule is currently used in clinical practice for the treatment of heart failure, secondary and primary hyperaldosteronism. The drug has been successful in the treatment of heart failure but comes with the price of an increased risk of hyperkalemia. Therefore, studies are being conducted to evaluate the beneficial effect of spironolactone as an add-on therapy to the existing therapies such as ACEi, ARBs, and diuretics.

In an open-label, parallel-group, single-center, randomized clinical trial, 136 diabetic patients with proteinuria who were already on treatment with enalapril and losartan were randomized to receive 25 mg of spironolactone after a two-week washout period. During the end of the 18-month follow-up, the spironolactone group showed a significant reduction in the blood pressure and urinary albumin excretion; however, the reduction in the estimated glomerular filtration rate and serum creatinine was found to be similar in both the groups [16]. In another multicenter randomized controlled trial, the levels of albuminuria were significantly reduced by 33% in the spironolactone group when compared to the conservative therapy group. The systolic blood pressure was lower and there was a significant decrease in the serum potassium, estimated glomerular filtration rate, and cystatin-C and high-sensitive C-reactive protein in the spironolactone group comparatively [17].

In another double-blind, placebo-controlled trial done in 81 diabetic nephropathy patients, the urine albumin-to-creatinine ratio was significantly reduced by 34.0% (95% CI, -51.0%, -11.2%,  $p=0.007$ ) in the spironolactone group and a reduction of 16.8% (95% CI, -37.3%, +10.5%,  $p=0.20$ ) was observed in the losartan group. However, the clinical and ambulatory blood pressure, creatinine clearance, sodium and protein intake did not differ between the treatment groups [18]. Trials have also compared the efficacy of spironolactone with the combination of drug molecules spironolactone and losartan. One of the double-blind randomized clinical trials demonstrated reductions in the levels of urinary albumin excretion, blood pressure, serum creatinine and potassium in both the groups. Therefore, monotherapy with spironolactone was found to be effective as the combination therapy of spironolactone and losartan [19].

Therefore, the drug molecule spironolactone can be used as an add-on therapy to the standard anti-diabetic/renoprotective/anti-hypertensive drugs. Patients receiving spironolactone as an add-on-therapy had significant short-term reductions in albuminuria and ambulatory blood pressure compared to patients receiving ARBs/ACEi. In one of the studies, the same effect was observed among patients with advanced proteinuria as well [20]. Moreover, monotherapy with spi-

ronolactone has resulted in albuminuria reduction among patients with diabetic nephropathy [19]. Therefore, spironolactone might become a new therapeutic option for the attenuation of aldosterone effects among diabetic nephropathy patients, who have shown the aldosterone escape during treatment with ACEi/ARBs. However, long-term studies are required to confirm the sustained effect of this medication and the use of spironolactone should also be weighed against the potential risks such as hyperkalemia.

## 5. EFFICACY OF FINERENONE IN DIABETIC KIDNEY DISEASE

Finerenone (BAY 94-8862), is an oral, next generation, non-steroidal mineralocorticoid receptor antagonist, with a high selectivity towards the mineralocorticoid receptor. *In vivo* studies demonstrated that finerenone was more effective than eplerenone in the reduction of cardiac and renal fibrosis, and the production of the B-type natriuretic peptide and proteinuria [21]. In a multicenter, randomized, double-blind, placebo-controlled, phase 2b study, oral doses of finerenone (1.25–20 mg) numerically reduced the urine albumin-to-creatinine ratio in the finerenone group than the placebo group. The study did not report any adverse events or mortality but there was a minute increase in the levels of serum potassium in the treatment group (0.025–0.167 mmol/L) than the placebo group (–0.075 mmol/L). Therefore, finerenone therapy could reduce the levels of albuminuria among patients with diabetic nephropathy [22].

In the mineralocorticoid receptor antagonists tolerability heart failure (ARTS-HF) study, 1066 patients with worsening heart failure, reduced ejection fraction and chronic kidney disease and/or diabetes mellitus were randomized to receive 2.5, 5, 7.5, 10, or 15 mg of finerenone orally and the dosage was further uptitrated to 5, 10, 15, 20, or 20 mg, respectively. The other group received 25 mg every other day of eplerenone and the dosage was increased to 25 mg once daily on day 30, and to 50 mg once daily on day 60. At the end of day 90, the percentage decrease of N-terminal pro-hormone of brain natriuretic peptide was not much different between the two groups. At day 90, the proportion of patients who had an N-terminal prohormone of brain natriuretic peptide level decrease of 30% compared to baseline was similar in both the groups. The exploratory endpoint was a composite clinical endpoint comprising all-cause mortality, cardiovascular hospitalizations, or emergency presentation for worsening heart failure until Day 90. The occurrence of the composite endpoint was lower in the finerenone group than the eplerenone group. However, the frequency of the composite endpoint was higher in the finerenone 2.5 mg group which was uptitrated to 5 mg group [23]. Therefore, the study revealed that therapeutic intervention with finerenone should be further evaluated in larger phase III trials. In another large randomized, double-blind, placebo-controlled, parallel-group study, a total of 1501 patients were screened and about 821 patients with diabetic nephropathy received the study drug finerenone. The patients were randomly allocated to receive (1.25mg/d, n = 96; 2.5mg/d, n = 92; 5mg/d, n = 100; 7.5mg/d, n = 97; 10mg/d, n = 98; 15mg/d, n = 125; and 25mg/d, n = 119) or matching placebo. The study showed a significant reduction in the urine albumin-to-creatinine ratio among the finerenone group than the placebo

group [24]. The adverse events such as hyperkalemia and gynecomastia which are associated with intake of spironolactone are likely to be avoidable if patients are swapped to finerenone [25]. However, larger trials are required to evaluate the efficacy of finerenone for diabetic nephropathy. Presently, a study evaluating the safety and efficacy of oral finerenone in subjects with type 2 diabetes mellitus and diabetic kidney disease (FIDELIO-DKD) is ongoing which is in the recruitment stage [26].

## 6. EFFICACY OF EPLERENONE IN DIABETIC KIDNEY DISEASE

Eplerenone, an aldosterone receptor antagonist, and potassium-sparing diuretic is a second oral aldosterone antagonist, approved by the US food and drug administration for the treatment of hypertension and heart failure secondary to myocardial infarction [27]. The binding of eplerenone to the mineralocorticoid receptor blocks the binding of aldosterone which in turn decreases the sodium resorption and increases the water outflow [28]. A phase II trial to determine if the study drug eplerenone is more effective than a double dose of ACE inhibitor, for the reduction of urinary protein (albumin) loss in diabetes mellitus has been completed. The study results have not yet been published [29]. The adverse events such as gynecomastia and vaginal bleeding that is bothersome with spironolactone seem to be avoidable if these patients are switched over to non-steroidal mineralocorticoid receptor antagonists such as eplerenone [27]. There are only a handful of studies evaluating eplerenone and more studies are required to establish eplerenone as a therapeutic option for diabetic nephropathy.

## 7. SAFETY OF MINERALOCORTICOID RECEPTOR ANTAGONISTS

The most commonly observed side-effects with the administration of mineralocorticoid receptor antagonists for diabetic nephropathy include hyperkalemia. The incidence of hyperkalemia was higher among patients receiving mineralocorticoid receptor antagonists plus ACEi/ARB therapy than that of a patient receiving ACEi/ARBs therapy [25, 30]. Under normal conditions, the excess intake of potassium will not lead to hyperkalemia, but during chronic kidney disease the kidneys will be unable to excrete a large amount of potassium. Therefore, this excess potassium accumulation will lead to the increased incidence of hyperkalemia. Aldosterone has the ability to stimulate the activity of sodium (Na<sup>+</sup>)-potassium (K<sup>+</sup>)-adenosine triphosphate (ATPase) and H<sup>+</sup>-K<sup>+</sup>-ATPase which in turn leads to the excessive absorption of Na<sup>+</sup> and secretion of K<sup>+</sup> in the distal nephron. Therefore, the risk of serious hyperkalemia can be reduced by routine monitoring of potassium and renal function along with the timely adjustment of dosage [25]. However, a recent meta-analysis revealed that the administration of mineralocorticoid receptor antagonists with ACEi and/or ARBs conferred a small and quantifiable risk of hyperkalemia [31]. The dose should be reduced to half or one-fourth of the usual dose, or given every other day if the estimated glomerular filtration rate is <60 ml min<sup>-1</sup> per 1.73 m<sup>2</sup>. The administration of spironolactone causes gynecomastia among male patients. Its administration alters the peripheral metabolism of testosterone causing changes in the ratio of testosterone-to-estradiol

resulting in gynaecomastia [32, 33]. Others effects include renal dysfunction, hypersensitivity and hematologic effects such as leukopenia and thrombocytopenia.

## 8. HOW TO PREVENT HYPERKALEMIA IN PATIENTS ON MINERALOCORTICOID RECEPTOR ANTAGONISTS

Hyperkalemia is one of the common side-effects observed among patients who are on mineralocorticoid receptor antagonists. Mineralocorticoid receptor antagonists and hyperkalemia are encountered often when the baseline estimated glomerular filtration rate is  $<45 \text{ ml min}^{-1} \text{ per } 1.73\text{m}^2$ , reduction in systolic blood pressure is greater than 15 mm Hg, the decline in estimated glomerular filtration rate is greater than  $30 \text{ ml min}^{-1} \text{ per } 1.73\text{m}^2$ , there is intake of diet rich in potassium and concomitant use of ACEi/ARBs [34]. This side-effect can be prevented by restricting the intake of potassium, administration of bicarbonates which are non-reabsorbable anions that facilitates potassium excretion, the concomitant use of potassium losing diuretics, avoiding mineralocorticoid receptor antagonists in patients with estimated glomerular filtration rate is  $<30 \text{ ml min}^{-1} \text{ per } 1.73\text{m}^2$ , administration of newer gut potassium sequestering agents like patiromer, dose adjustment and stopping of mineralocorticoid receptor antagonists if necessary and use of finerenone instead of steroidal mineralocorticoid receptor antagonists [35, 36].

## 9. FUTURE DIRECTIONS

Most of the studies have only evaluated the short-term effects of mineralocorticoid receptor antagonists on diabetic nephropathy [37-48]. Hard outcomes such as cardiovascular events, renal replacement therapy, creatinine doubling, progression to end-stage renal disease, mortality, and need for temporary or permanent dialysis needs to be studied. Furthermore, there is a paucity of evidence comparing the safety and efficacy of spironolactone, finerenone, and eplerenone for the treatment of diabetic nephropathy. Therefore, well-designed multicentric trials with long-term follow up and event-based outcomes need to be done to evaluate the effect of mineralocorticoid receptor antagonists on diabetic nephropathy.

## CONCLUSION

The safety and efficacy of mineralocorticoid receptor antagonists have been studied for the treatment of diabetic nephropathy. The addition of mineralocorticoid receptor antagonists to the existing ACEi/ARB therapy has been effective to prevent or slow diabetic nephropathy progression by reducing proteinuria and, for the reduction of blood pressure among patients with diabetic nephropathy and hypertension. The reduction of protein or albumin excretion which was observed was not entirely blood pressure-dependent; however, it is not easier to determine the independent effect of blood pressure lowering agents. The add-on therapy of mineralocorticoid receptor antagonists should be weighed against risks such as hyperkalemia. Mineralocorticoid receptor antagonists have pleiotropic effects apart from diuresis, like anti-fibrotic, anti-hypertensive, and antiproteinuric effect and these effects justify their use in diabetic nephropathy. Hence, ideally, the treatment should be started with the low-

est dose of steroidal mineralocorticoid receptor antagonists and the potassium levels should be monitored while increasing the dose. Alternatively a non-steroidal mineralocorticoid receptor antagonist, finerenone can be used which does not produce hyperkalemia, while retaining the anti-hypertensive and antiproteinuric effect.

## CONSENT FOR PUBLICATION

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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## SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article [37-48].

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