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REVIEW

The necessity and effectiveness of mineralocorticoid receptor antagonist in the treatment of diabetic nephropathy

Atsuhisa Sato

Diabetes mellitus is a major cause of chronic kidney disease (CKD), and diabetic nephropathy is the most common primary disease necessitating dialysis treatment in the world including Japan. Major guidelines for treatment of hypertension in Japan, the United States and Europe recommend the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers, which suppress the renin-angiotensin system (RAS), as the antihypertensive drugs of first choice in patients with coexisting diabetes. However, even with the administration of RAS inhibitors, failure to achieve adequate anti-albuminuric, renoprotective effects and a reduction in cardiovascular events has also been reported. Inadequate blockade of aldosterone may be one of the reasons why long-term administration of RAS inhibitors may not be sufficiently effective in patients with diabetic nephropathy. This review focuses on treatment in diabetic nephropathy and discusses the significance of aldosterone blockade. In pre-nephropathy without overt nephropathy, a mineralocorticoid receptor antagonist can be used to enhance the blood pressure-lowering effects of RAS inhibitors, improve insulin resistance and prevent clinical progression of nephropathy. In CKD categories A2 and A3, the addition of a mineralocorticoid receptor antagonist to an RAS inhibitor can help to maintain 'long-term' antiproteinuric and anti-albuminuric effects. However, in category G3a and higher, sufficient attention must be paid to hyperkalemia. Mineralocorticoid receptor antagonists are not currently recommended as standard treatment in diabetic nephropathy. However, many studies have shown promise of better renoprotective effects if mineralocorticoid receptor antagonists are appropriately used.
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Keywords: aldosterone; aldosterone breakthrough; diabetic nephropathy; mineralocorticoid receptor antagonists; renin–angiotensin system

INTRODUCTION

Diabetes mellitus is a major cause of chronic kidney disease (CKD), and diabetic nephropathy (DM nephropathy) is the most common primary disease necessitating dialysis treatment in the world including Japan.[1] In the management of DM nephropathy, particularly in preventing the onset and progression of early nephropathy, glycemic control is important. Comprehensive management also includes treatment of hypertension and hyperlipidemia. Hypertension is about twice as common in diabetics as in non-diabetics, and is an important risk factor for macroangiopathy and microangiopathy due to arteriosclerosis in diabetic patients. Therefore, strict 24-h control of hypertension is essential. Major guidelines for treatment of hypertension in Japan, the United States and Europe recommend the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs), which suppress the renin–angiotensin system (RAS), as the antihypertensive drugs of first choice in patients with coexisting diabetes.[2–4] Many large-scale clinical studies have shown that, in patients with DM nephropathy, ACEIs and ARBs decrease albuminuria and prevent nephropathy progression.[5–7] However, even with the administration of RAS inhibitors, failure to achieve adequate anti-albuminuric effects, renoprotective effects and a reduction in cardiovascular events has also been reported.[8–12]

To achieve more complete RAS inhibition in patients with type 2 diabetes, concomitant treatment with different types of RAS inhibitors has been promising. However, some clinical studies, including those in Japanese patients, have shown that concomitant treatment with an ACEI and ARB, or also including a direct renin inhibitor, may not provide a clinical synergistic effect in reducing cardiovascular events or preventing a decline in renal function, but conversely, may cause an increase in the incidence of adverse reactions such as hyperkalemia and acute renal insufficiency.[13–16] Although ACEIs and ARBs are cornerstone drugs for the treatment of DM nephropathy, new treatment strategies are necessary to achieve even better effectiveness. We have previously reported aldosterone breakthrough as a clinical phenomenon that can occur with an RAS inhibitor.[17] Aldosterone breakthrough is a phenomenon in which, after treatment with an RAS

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inhibitor, plasma aldosterone levels, once they have decreased, can again rise to higher than pretreatment levels during relatively long-term treatment. Aldosterone breakthrough usually does not influence the antihypertensive effects of RAS inhibitors, but breakthroughed aldosterone attenuates the organ-protective effects of RAS inhibitors through the actions of mineralocorticoid receptors (MRs).[18–23] With relatively long-term treatment with RAS inhibitors, regardless of dose or combination of drugs, aldosterone breakthrough may be impossible to prevent. Inadequate blockade of aldosterone may be one of the reasons why long-term administration of RAS inhibitors may not be sufficiently effective in patients with DM nephropathy. To achieve better treatment of DM nephropathy, in which RAS inhibitors are now the mainstay of treatment, investigation of aldosterone blockade is important.[24,25] In fact, in the field of cardiology, large-scale clinical studies in which a MR antagonist is added to an RAS inhibitor to inhibit the effects of aldosterone breakthrough have shown marked effects in patients with chronic heart failure who have decreased systolic function.[26–28]

This review focuses on treatment in DM nephropathy and discusses the significance of aldosterone blockade. MR antagonists used to treat refractory edema in patients with DM nephropathy as potassium-sparing diuretics, but are rarely used in advanced stages of DM nephropathy because of concern for hyperkalemia. Moreover, the current guidelines in Japan for the treatment of hypertension and CKD do not discuss the use of MR antagonists, but advise that extreme precautions when prescribing. However, early activation of the aldosterone/MR cascade, particularly in patients with diabetes, has been reported, including the need to add a MR antagonist in stage 1 (pre-nephropathy) with normoalbuminuria and a normal estimated glomerular filtration rate (eGFR). In the treatment of DM nephropathy, MR antagonists are effective and should be administered according to the stage of disease.

ALDOSTERONE AND HYPERGLYCEMIA: A VICIOUS CYCLE

A direct association between aldosterone and insulin resistance

One reason why aldosterone should be targeted in the treatment of diabetes before clinical diagnosis of DM nephropathy is because aldosterone is directly associated with insulin resistance. It has long been known that glucose intolerance is common in patients with primary aldosteronism (PA). This has been thought to be due to hypokalemia in PA, but, in addition, recent studies have shown a direct association with aldosterone. Plasma renin activity and plasma angiotensin II levels are decreased in PA, and this is due to the unique effects of aldosterone. Patients with PA, compared with those with essential hypertension or who are normotensive, have insulin resistance with decreased insulin sensitivity. Metabolic syndrome with insulin resistance due to visceral fat accumulation is also common in PA.[29,30] Moreover, improvement in insulin resistance with normalization of plasma aldosterone levels after surgery for an aldosterone-producing adenoma has also been reported. These reports suggest that plasma aldosterone levels alone may be the strongest determinant in insulin resistance.[31,32]

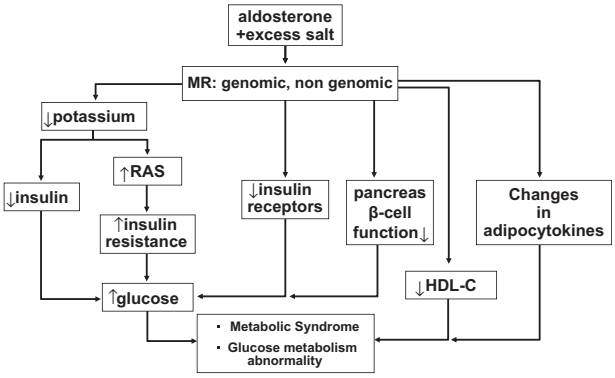

Figure 1 The influence of aldosterone on glucose metabolism and metabolic syndrome. Aldosterone is involved in metabolic abnormalities by direct effects other than just hypokalemia.

The association between aldosterone and insulin resistance has been reported not only in PA patients with autonomic hypersecretion of aldosterone, but also in hypertensive patients without PA.[33] In a Japanese study over a 10-year observation period, plasma aldosterone levels were a predictive factor for the development of insulin resistance.[34] As the number of risk factors for metabolic syndrome increases, plasma aldosterone levels rise in a non-renin-dependent manner, thus plasma aldosterone levels are independently associated with metabolic syndrome.[35] Plasma aldosterone levels have often been reported to correlate with waist circumference, plasma insulin levels and the homeostasis model assessment (HOMA) index. In addition, plasma aldosterone levels are significantly higher in patients with coexisting metabolic syndrome than without.[36] In Caucasian patients with essential hypertension, plasma aldosterone levels are significantly positively correlated with plasma glucose levels, C-peptide and the HOMA index, and, as plasma aldosterone levels increase, insulin sensitivity decreases.[37] The relationship between aldosterone with insulin resistance and metabolic syndrome has been shown in various conditions and ethnic groups.[38–41]

The mechanism of how aldosterone influences insulin sensitivity as seen in clinical studies has been reported in basic research studies. This is summarized in Figure 1. Aldosterone directly suppresses insulin signaling. These effects on insulin signaling are complex, including effects on insulin receptor expression as well as on insulin receptor substrate 1 (IRS-1) and IRS-2.[42–45] In addition, aldosterone is directly associated with gluconeogenesis in the human and mouse liver; aldosterone increases glucose by stimulating gene expression of enzymes involved in gluconeogenesis.[46,47] These actions of aldosterone cannot be fully suppressed by RAS inhibitors alone. This worsening of insulin resistance by aldosterone may have a direct role in increase of the risk for nephropathy progression and the development of cardiovascular events.

Furthermore, nighttime hypertension and treatment-resistant hypertension are more likely to occur with decreased insulin sensitivity,[48–50] and, when treatment with an RAS inhibitor is started, a good blood pressure-lowering response is often absent.[51,52] In diabetic patients, suppression of aldosterone/MR effects before the onset of DM nephropathy can improve insulin resistance, and this may also be promising for the management of hypertension that is difficult to control with RAS inhibitors alone.

Activation of the aldosterone/MR cascade before the onset of microalbuminuria in hyperglycemic states

Aldosterone directly contributes to insulin resistance, but conversely, the various actions of aldosterone in epithelial and non-epithelial tissues are enhanced in hyperglycemia. There is a vicious cycle between the effects of aldosterone and a hyperglycemic state. In epithelial tissue, MR selectivity for aldosterone is regulated by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), and this overcomes the 100-fold difference with plasma levels, aldosterone selectively binds to MRs, and appropriate water and electrolyte balance

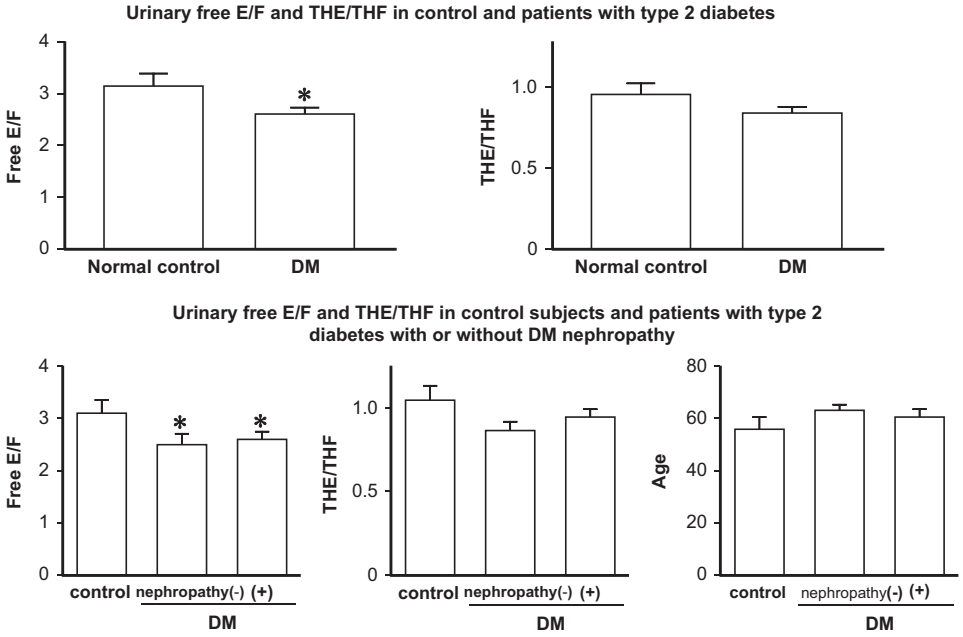

Figure 2 Changes in renal 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) activity in diabetic patients based on the free cortisone/cortisol (E/F) ratio as an index. In 40 patients with type 2 diabetes (DM) treated alone with diet or during oral antidiabetic drug therapy, 24-h urine was collected for measurement of free cortisone (E), free cortisol (F), total tetrahydrocortisone (THE) and total tetrahydrocortisol (THF) by gas chromatography-mass spectrometry/selective ion monitoring (GC-MS/SIM). The free E/F and THE/THF ratios were compared with normal controls. The free E/F ratio in diabetic patients significantly decreased regardless of the presence or absence of nephropathy, but the THE/THF ratio did not significantly differ. There was no significant difference in age between control group and DM patients. Data represent the mean ± s.d. (These data were presented at the 71st Annual Meeting of Japan Endocrine Society, 1998). $^*P<0.05$ *vs.* control value.

is maintained. However, in diabetic patients, renal tubular 11β-HSD2 activity is decreased before the onset of nephropathy; hence, cortisol can bind to MRs, sodium reabsorption is increased and salt-sensitive hypertension occurs.

In type 2 diabetic patients, including those with early nephropathy, our group has investigated the urinary free cortisone/cortisol ratio as an index of renal 11β-HSD2 activity. In diabetic patients, regardless of the presence or absence of nephropathy, this enzyme activity is decreased (Figure 2). A decreased intracellular NAD^+/NADH ratio has been reported in diabetic rats in basic experiments.[53,54] This suggests a decrease in activity of 11β-HSD2, for which NAD^+ is a cofactor. In fact, decreased renal 11β-HSD2 activity has been shown in diabetic rats, and this was reversed by treatment with insulin or a MR antagonist.[55] Therefore, one mechanism of salt-sensitive hypertension in diabetes is a decrease in renal 11β-HSD2 activity, and this occurs before the onset of nephropathy.

In contrast, in non-epithelial tissues, such as the brain, heart, blood vessels, adipose tissue and kidney tissue other than the renal tubules, because 11β-HSD2 activity is low or almost nonexistent, glucocorticoid cortisol binds to >90% of MRs. However, these MRs are in general thought to be transcriptionally inactive and not activated. In this respect, this is very different than that in epithelial tissue. However, by various mechanisms such as oxidative stress in hyperglycemia, MRs are activated without aldosterone and/or sensitivity of aldosterone for MRs increases, and organ injury by aldosterone occurs in non-epithelial tissues.[56–58] We previously reported that, in hyperglycemia, aldosterone increases protein synthesis via MRs in cultured cardiomyocytes from the heart, a non-epithelial tissue.[59] Therefore, early treatment with a MR antagonist in diabetic patients may prevent organ damage via MRs in non-epithelial tissue.

THE SIGNIFICANCE OF ALDOSTERONE/MRS BLOCKADE IN PRE-NEPHROPATHY

On the basis of the previous sections, we will now discuss the clinical use of MR antagonists in DM nephropathy. The Joint Committee on Diabetic Nephropathy in Japan classifies pre-nephropathy as normoalbuminuria ($<30\,mg\,g^{-1}$ creatinine (Cr)) and eGFR $\geqslant 30\,ml\,min^{-1}$ per $1.73\,m^2$, in general regarded as an eGFR $\geqslant 60\,ml\,min^{-1}$ per $1.73\,m^2$. When the eGFR is $<60\,ml\,min^{-1}$ per $1.73\,m^2$, this corresponds to CKD, a cause other than DM nephropathy may exist, and a differential diagnosis from other types of kidney disease is necessary. Therefore, pre-nephropathy is regarded in this review as a stage corresponding mainly to G1A1 and G2A1 in the CKD severity classification, with normoalbuminuria, and in which the eGFR is maintained.

The Japanese Society of Nephrology (Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012; Evidence-based Clinical Practice Guideline for CKD), Japanese Society of Hypertension (JSH 2014), and Japanese Diabetes Society (Evidence-based Practice Guideline for the Treatment of Diabetes in Japan 2013) all recommend an RAS inhibitor as the antihypertensive drug of first choice for the treatment of hypertension in diabetic patients. In patients with type 2 diabetes, ACEIs and ARBs have been reported to prevent progression from normoalbuminuria to microalbuminuria. This is one reason why RAS inhibitors are recommended as the drug of first choice for hypertension in type 2 diabetes patients irrespective of albuminuria status. However, in the ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention) trial, 24-h ambulatory monitoring of blood pressure showed a decrease of 3.5/1.2 mm Hg in the olmesartan group *vs.* placebo group, suggesting that the effectiveness in delaying microalbuminuria was due to a lowering of blood pressure.[60] The BENEDICT (Bergamo Nephrologic

Diabetes Complications Trial) also concluded that these effects were achieved because of blood pressure reduction in the trandolapril group, the blood pressure-lowering effect was significantly greater than that in the calcium channel blocker group.[61] In general, there is little evidence for the superiority of RAS inhibitors in the absence of proteinuria or albuminuria. A reduction in blood pressure is most important, regardless of the drug used. Therefore, in pre-nephropathy with normoalbuminuria, RAS inhibitors as a first-line drug should be used mainly for their antihypertensive effects. In fact, a meta-analysis of ACEIs and ARBs *vs.* other antihypertensive drugs in renal disease showed that when there were no differences in blood pressure, there were no additional renoprotective effects of either type of drugs.[62]

When RAS inhibitors are selected initially for blood pressure reduction in diabetic patients, actual clinical experience sometimes shows a diminished blood pressure-lowering effect. CKD patients, especially those with diabetes, typically have salt-sensitive hypertension, and RAS inhibitors may be less effective. Diabetic patients also often have treatment-resistant hypertension and nighttime hypertension. The vicious cycle between aldosterone actions and hyperglycemia at this stage leads to salt-sensitive hypertension and nighttime hypertension, and this may have a role in the clinical development of nephropathy. By adding a MR antagonist in the pre-nephropathy stage, these issues can be resolved. Reduced salt intake is very effective in salt-sensitive hypertension. However, even when the importance of low salt intake is recognized, continuing this dietary practice can be difficult. Greater blood pressure-reduction effects of MR antagonists with lower renin activity, and higher blood pressure normalization rates in low-renin hypertensive patients compared with hypertensive patients with high-renin have been reported.[63] In a study in Japanese patients, Saruta *et al.*[64] reported that most patients had low-renin hypertension, and that once-daily eplerenone significantly reduced 24-h blood pressure. However, many studies have also reported blood pressure reductions with MR antagonists in both low-renin and high-renin patients, and our results have been similar.[65] This property of MR antagonists in which blood pressure-lowering effects are not blunted, even in patients with salt-sensitive hypertension, can be greatly beneficial together with RAS inhibitors for treatment in pre-nephropathy.

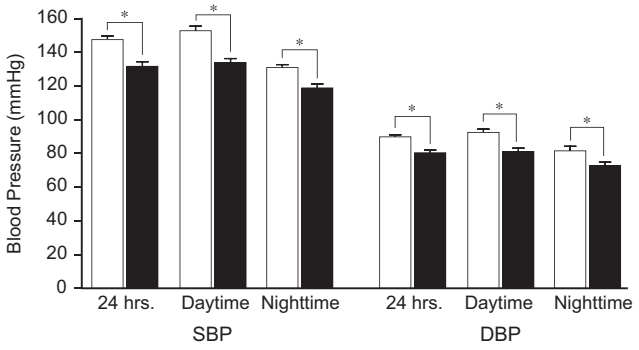

Figure 3 The effects of adding eplerenone to an angiotensin-converting enzyme (ACE) inhibitor in hypertensive patients. Effects of adding 50 mg of eplerenone to an ACE inhibitor on average systolic blood pressure (SBP) and diastolic blood pressure (DBP) for 24 h, daytime and nighttime in patients with essential hypertension. Open bars show blood pressure before eplerenone treatment, and closed bars show after adding eplerenone to an ACE inhibitor treatment for 12 weeks. Data represent the mean ± s.d. $*P<0.01$ *vs.* each baseline value. Eplerenone decreased the 24-h mean BP, daytime BP and nighttime BP in a similar manner (These data were presented at the 33rd Annual Meeting of Japan Society of Hypertension, 2010).

Diabetic patients often have a rise in nighttime blood pressure and have a non-dipper pattern of blood pressure variation.[66,67] In 30 patients, including those with diabetes, (13 men, 17 women, mean age: 61 ± 10 years), we reported that when 50 mg of eplerenone was added to an ACEI, 24-h mean blood pressure, daytime blood pressure and nighttime blood pressure decreased in a similar manner (Figure 3). Yano *et al.*[68] also reported that in 20 patients (including diabetics) with inadequately controlled blood pressure on an ACEI or ARB in whom eplerenone (mean dose: 37.5 mg) was then added, daytime blood pressure and nighttime blood pressure decreased in a similar manner.[68] Diuretics are useful in nighttime hypertension, and some of the effectiveness of MR antagonists is partly due to diuretic effects. However, eplerenone at doses of 37.5–50 mg does not in general have a potent diuretic effect. Nevertheless, these reports describe a significant reduction of nighttime blood pressure at these doses, with improvement from a non-dipper pattern to a dipper pattern. The detailed mechanism by which blockade of MRs is effective in nighttime hypertension remains unknown. One mechanism may be an indirect influence on obstructive sleep apnea syndrome (OSAS). By increasing sympathetic activity and active oxygen, OSAS may have a role in treatment-resistant hypertension and nighttime hypertension.[69] The role of aldosterone in OSAS has recently received attention. In patients with treatment-resistant hypertension and OSAS, plasma aldosterone levels are higher and correlate with OSAS severity.[70] In patients with treatment-resistant hypertension and OSAS, spironolactone has also been reported to reduce the severity of OSAS.[71] In future clinical studies, it would be desirable in diabetic patients with OSAS to investigate the effectiveness of MR antagonists on the severity of nighttime hypertension and OSAS.

In pre-nephropathy without overt nephropathy, a MR antagonist can be used to enhance the blood pressure-lowering effects of RAS inhibitors, improve insulin resistance and prevent clinical progression of nephropathy. Indeed, there are studies that clearly showed effectiveness of spironolactone on blood pressure control in the patients with type 2 diabetes and resistant hypertension.[72,73]

THE SIGNIFICANCE OF ALDOSTERONE/MRS BLOCKADE IN EARLY NEPHROPATHY AND LATER STAGES

The Joint Committee on Diabetic Nephropathy in Japan classifies these stages with clinical nephropathy as early nephropathy (microalbuminuria: 30–299 mg g^{-1} Cr and an eGFR $\geqslant$ 30 ml min^{-1} per 1.73 m^2) and later. These correspond to categories A2 and A3 in the CKD severity classification. In early nephropathy, the inadequacy of treatment with RAS inhibitors alone becomes more apparent than that in pre-nephropathy. When proteinuria and albuminuria occur in DM nephropathy, the superiority of RAS inhibitors increases, and they should be used aggressively. Most current CKD and hypertension treatment guidelines in Japan and overseas share this recommendation. Although the antiproteinuric effects of ACEIs and ARBs are seen soon after starting treatment, a clinical problem when expecting these early antiproteinuric effects to continue over a long period is that, contrary to expectation, this effectiveness may not continue.

In this so-called proteinuria/microalbuminuria breakthrough, the early antiproteinuric effects do not persist despite continued administration of an RAS inhibitor, and during treatment, proteinuria again increases. In the DETAIL (Diabetics Exposed to Telmisartan and Enalapril) Study in type 2 diabetic patients, after 5 years in both the enalapril group and telmisartan group, urinary albumin excretion returned to baseline pretreatment levels.[12] Cerezo *et al.*[9] also reported

that among 1433 hypertensive patients who received adequate doses of an ACEI or ARB for over 2 years, 16.1% had new-onset albuminuria despite continued treatment. In addition, in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) Study in type 2 diabetic patients, in whom most had received an ACEI or ARB, 43.4% had albuminuria at the end of the study, so the anti-albuminuric effects did not persist.[11]

Moreover, when an ACEI is combined with an ARB or direct renin inhibitor, absence of clinical efficacy, and conversely, an increase in adverse reactions have also been reported.[13–16] In CKD categories A2 and A3, the addition of a MR antagonist to an RAS inhibitor can help to maintain 'long-term' antiproteinuric and anti-albuminuric effects. However, in category G3a (mild-moderate decrease in GFR) and higher, sufficient attention must be paid to hyperkalemia.

Many studies in CKD patients showed that a MR antagonist is most effective in patients who have early stages of CKD with maintained eGFR. In the actual clinical setting, especially in large-scale clinical studies, hyperkalemia is still a concern, and it is therefore difficult to conduct studies in patients with advanced stages of CKD. For that reason, it is probably unlikely that such a study, especially on a large scale, will be reported in the future. In contrast, the outcome of an investigation on the effects of MR antagonists has been reported in stage G5D CKD patients undergoing dialysis treatment,[74,75] as potassium levels can be adjusted with dialysis. As these patients already have renal failure, the main treatment objective would be to prevent cardiovascular disease. Evidence in advanced stages (especially G3b to G4) of CKD is scarce, and we therefore anticipate the publication of clinical studies involving these patients with strict attention to side effects.

MR antagonists in basic researches

Endothelial nitric oxide bioavailability is decreased in patients with DM nephropathy,[76] and part of the renoprotective effects of RAS inhibitors is improvement in this bioavailability.[77,78] However, Kosugi *et al.*[79] reported that, in diabetic endothelial nitric oxide synthase (eNOS)-knockout mice, nephropathy progression occurred more readily, and that, despite treatment with an ACEI or ARB, the blood pressure-lowering response was less, and nephropathy progression could not be prevented. In these mice, the serum aldosterone level was high, and a MR antagonist significantly decreased blood pressure and prevented nephropathy progression. These results suggest one reason why an RAS inhibitor alone may be insufficient for diabetic patients, and a MR antagonist is also needed.

In a streptozotocin-induced type 1 diabetes model in rats, and in a type 2 diabetes model in db/db mice, MR antagonists have been reported to reduce renal injury. In these experimental models, renal MR expression is increased, and the aldosterone/MRs cascade is presumably stimulated. In addition, aldosterone blockade has renoprotective effects similar to glycemic control with insulin. MR antagonists inhibit upregulation of renal MRs, reduce local oxidative stress, prevent renal fibrosis and decrease transforming growth factor-beta 1 (TGF-β1), plasminogen activator inhibitor-1 (PAI-1), type 1 and type 4 collagen, and fibronectin.[80–82]

In both a streptozotocin-induced type 1 diabetes model in rats and a type 2 diabetes model in db/db mice, renal damage such as glomerular hypertrophy, mesangial expansion and tubulointerstitial injury was observed, and albuminuria developed. With a MR antagonist, the progression of renal injury was inhibited in a non-blood pressure and non-glucose-dependent manner, and renal cortex TGF-β and osteopontin mRNA levels were decreased.[83] That is, experimentally in both type 1 diabetes and type 2 diabetes, aldosterone has been observed to have an important role in the onset and progression of DM nephropathy, and aldosterone blockade can suppress the induction of proinflammatory cytokines, thus leading to renoprotective effects. Because of the complexity of aldosterone-induced renal dysfunction (Figure 4), the renoprotective effects of MR antagonists occur via a complex mechanism, and even if plasma aldosterone levels are not elevated, there is a possibility that MR-mediated actions are promoted locally.

MR antagonists in clinical studies

Many clinical studies have investigated the effects of MR antagonists in DM nephropathy. Most have shown additive effects with RAS inhibitors, with antiproteinuric and anti-albuminuric effects. A future area will be to investigate long-term renoprotective effects. Further, the effects of MR antagonists can be anticipated in preventing newly diagnosed diabetes in the future. It is highly probable that aldosterone directly affects insulin resistance, and insulin sensitivity may recover with early blockade of MR. However, there are no studies to date that have reported such results.

Chrysostomou *et al.*[84] were the first to report the effects of MR antagonists. They reported that with spironolactone 25 mg for over

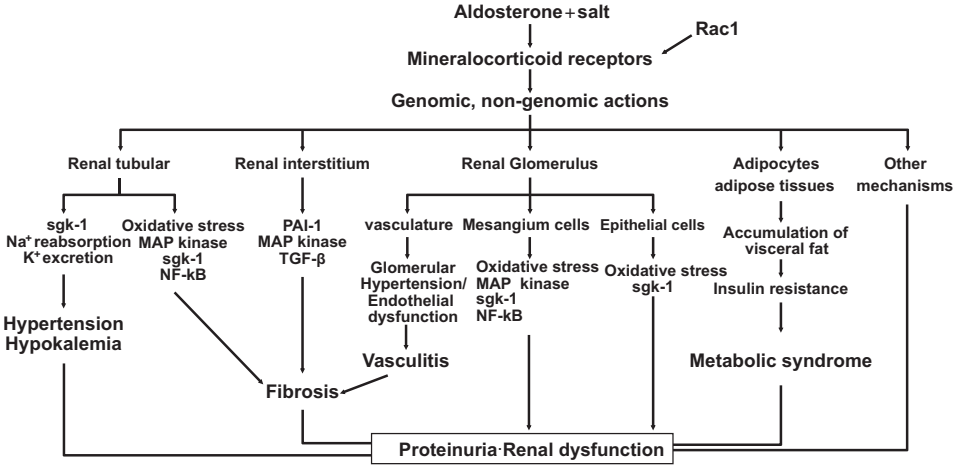

Figure 4 Aldosterone-induced renal dysfunction. Although not all of these actions are reported in diabetic patients or in studies using diabetic models, renoprotective effects of MR antagonists may be achieved by suppressing these actions in a comprehensive manner.

1 year in eight patients, including five patients with diabetes, daily proteinuria improved from 3.81 ± 2.50 g before treatment to 1.75 ± 1.02 g after treatment.[84] In another study in type 1 diabetic patients with overt nephropathy, the addition of spironolactone 25 mg to RAS blockade for 2 months reduced proteinuria by 30%, but there was no correlation between this reduction and blood pressure reduction.[85] The same group reported that, in type 1 diabetic patients with severe proteinuria ($\geqslant$2.5 g per day), treatment with spironolactone 25 mg for 2 months was also effective.[86] These antiproteinuric effects of MR antagonists in type 1 DM nephropathy are independent of BP.[87]

Our group has already reported that adding a MR antagonist to an RAS inhibitor has anti-albuminuric effects in type 2 DM nephropathy,[19,20] and several other studies in type 2 diabetic patients have shown similar results. In one such report, Rachmani *et al.*[88] compared spironolactone 100 mg with cilazapril 5 mg in female patients with type 2 diabetes and hypertension. Albuminuria declined more in the spironolactone group than in the cilazapril group, and, with a combination of both drugs, albuminuria declined even further. These effects were independent of blood pressure reduction.[88] In type 2 diabetic patients with albumin excretion $\geqslant 50\ \mathrm{mg\,g^{-1}}$ Cr, Epstein *et al.*[89] compared the addition of eplerenone 50 and 100 mg *vs.* placebo to 20 mg of the ACEI enalapril. After 12 weeks, albumin excretion decreased by 41% in the eplerenone 50 mg group, and by 48% in the 100 mg group, and no significant hyperkalemia was observed.[89]

In type 2 DM nephropathy patients with persistent overt proteinuria despite treatment with an ACEI or ARB, Van den Meiracker *et al.*[90] compared the effect of the addition of spironolactone 25–50 mg *vs.* placebo. These investigators found that proteinuria decreased by 40.6% after 1 year, and that this decrease correlated with a reduction in eGFR.[90] Takebayashi *et al.*[91] compared spironolactone 50 mg with a calcium channel blocker in type 2 DM nephropathy patients, and reported that, after 3 months with spironolactone alone, urinary albumin excretion, urinary monocyte chemoattractant protein-1 (MCP-1) and urinary 8-iso-prostaglandin F2 alpha (PGF2α) decreased. In addition, Mehdi *et al.*[92] compared the effects on urinary albumin excretion when spironolactone 25 mg, the ARB losartan 100 mg, or placebo was added to maximal ACE inhibitor (lisinopril 80 mg) in DM nephropathy patients. Although blood pressure did not significantly differ among the three groups, the spironolactone group had the greatest decline (34%) in albuminuria.[92]

The renoprotective effects of MR antagonists shown in common by these studies have mainly been antiproteinuric and anti-albuminuric effects, but long-term renoprotective effects have almost never been reported. The time until these antiproteinuric effects are seen is relatively fast, often within 1 month after starting treatment. At relatively low doses of spironolactone (12.5–25 mg) or eplerenone (25–50 mg), these effects are observed independently of blood pressure effects.

CAUTIONS REGARDING HYPERKALEMIA

The most serious concern during treatment with MR antagonists is the possibility of high potassium levels (hyperkalemia). Therefore, in patients with hyperkalemia before treatment, spironolactone and eplerenone are contraindicated. However, considering the beneficial effects of MR antagonists, it is important to take measures against hyperkalemia so that MR antagonist treatment can be continued, including education about dietary potassium restriction, and the combined use of diuretics and potassium absorption agents. If the GFR is $>60\ \mathrm{ml\,min^{-1}}$ per $1.73\ \mathrm{m^2}$, MR antagonists can be administered as needed. If the GFR is $<60\ \mathrm{ml\,min^{-1}}$ per $1.73\ \mathrm{m^2}$, the dose should be decreased to 1/2 to 1/4 of the usual dose, or given every other day. Although the RALES Study showed the effectiveness of alternate-day administration,[26] problems may occur with treatment adherence.

Because the antihypertensive effects of MR antagonists are dose dependent, up to maximum doses can be prescribed if GFR is maintained. However, because spironolactone is associated with dose-dependent endocrine adverse reactions, the dose used should be 25 (or 50) mg. For additional effects in patients with aldosterone breakthrough, eplerenone 50 mg or spironolactone 12.5–25 mg is usually sufficient even when GFR is maintained. Hyperkalemia is a possible concern when either drug is added to an RAS inhibitor. We have previously discussed the issue of potassium when using MR antagonists.[25]

Aside from hyperkalemia, possible adverse effect of spironolactone on endothelial function in patients with type 2 diabetes has been reported.[93,94] There are studies in type 2 diabetic patients demonstrating that glycemic control worsened with spironolactone treatment; consequently, vascular endothelial function decreased, contrary to what was expected. It is not very commonly known that the use of a MR antagonist exacerbates glycemic control, rather, there are many reports that show an improvement in vascular endothelial function with a MR antagonist treatment.

CONCLUSION

MR antagonists are not currently recommended as standard treatment in DM nephropathy. However, many studies have shown promise of better renoprotective effects if MR antagonists are appropriately used. The most serious concern is possible hyperkalemia. It is important to adjust the dose of a MR antagonist based on GFR as well as to take measures against hyperkalemia.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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