Published in final edited form as:

Curr Opin Nephrol Hypertens. 2016 January ; 25(1): 16–21. doi:10.1097/MNH.0000000000000189.

Aldosterone in vascular and metabolic dysfunction

James M. Luther, MD, MSCI

Divisions of Clinical Pharmacology and Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Abstract

Purpose of review—This review will highlight recent developments in mineralocorticoid receptor research which impact aldosterone-associated vascular and cardio-metabolic dysfunction.

Recent findings—The mineralocorticoid receptor is also expressed in vascular smooth muscle and vascular endothelium, and contribute to vascular function and remodeling. Adipocyte-derived leptin stimulates aldosterone secretion, which may explain the observed link between obesity and hyperaldosteronism. Adipocyte mineralocorticoid receptor overexpression produces systemic changes consistent with metabolic syndrome. Ongoing studies with novel nonsteroidal mineralocorticoid receptor antagonists may provide a novel treatment for diabetic nephropathy and heart failure in subjects with chronic kidney disease with reduced risk of hyperkalemia.

Summary—Ongoing research continues to demonstrate novel roles of the vascular and adipocyte mineralocorticoid receptor function, which may explain the beneficial metabolic and vascular benefits of mineralocorticoid receptor antagonists.

Keywords

Aldosterone; Mineralocorticoid receptor; diabetes; inflammation

INTRODUCTION

Blockade of the renin-angiotensin-aldosterone system (RAAS) is the most effective strategy for prevention of renal disease progression, heart failure, and cardiovascular death. A portion of these beneficial effects can be attributed to aldosterone reduction or mineralocorticoid receptor (MR) antagonism, with beneficial effects beyond hypertension control, such as improvements in glucose metabolism, fibrosis, and inflammation. Although the extra-renal effects of aldosterone and the MR have been well demonstrated within cardiac tissues, specific actions within the vascular endothelium and smooth muscle have recently been demonstrated. The purpose of this review is to summarize developments in the literature pertaining to aldosterone and vascular and metabolic dysfunction.

Author of correspondence: James M. Luther, 2200 Pierce Avenue, 560C RRB, Vanderbilt University Medical Center, Nashville, TN 37232-6602, Phone: (615) 936-3420, James.Luther@Vanderbilt.edu.

CONFLICTS OF INTEREST: No conflict of interest declared

TEXT

Adipocytes secrete aldosterone-stimulating factors

The association between adipose mass and increased plasma aldosterone concentration has been demonstrated in diverse populations, leading to the hypothesis that circulating adipocyte-derived factors stimulate aldosterone secretion [1]. This is supported by *in vitro* studies, where transfer of culture media from adipocyte to adrenal cell culture stimulates aldosterone secretion to the same magnitude as angiotensin II, but is not prevented by angiotensin receptor blockade [2]. Recently in the Multi-Ethnic Study of Atherosclerosis study, plasma adiponectin associated negatively and leptin associated positively with plasma aldosterone concentration in 1,970 subjects free of cardiovascular disease, suggesting that these adipokines could also alter aldosterone secretion [3]. Functional leptin receptors are present on zona glomerulosa cells, and leptin stimulates aldosterone production *in vitro* in human adrenocortical cells and *in vivo* in mice, demonstrating that leptin may be a significant mediator of obesity-associated hyperaldosteronism. These effects are mediated via the leptin receptor and are independent of angiotensin II or adrenergic activation [4]. Leptin-stimulated aldosterone secretion may also explain the elevated aldosterone concentration in subjects with obesity and metabolic syndrome [5] and the decreased concentration after weight loss [6] (see Figure 1). Because leptin increases in direct proportion to fat mass, it may be an additional link between obesity, hypertension, and metabolic syndrome.

MR overexpression in adipocytes interrupts glycemic and blood pressure control

Conversely, aldosterone directly stimulates adipocyte expansion, increases leptin expression, and impairs adipocyte function in culture systems [7,8]. Decreased circulating adiponectin concentration is associated with insulin resistance, obesity, and endothelial dysfunction [9]. Aldosterone decreases adiponectin expression in adipocyte culture, and MR antagonism normalizes adiponectin and decreases adipocyte macrophage infiltration and inflammatory cytokines in obese diabetic *db/db* mice [10]. Multiple studies have also demonstrated that aldosterone impairs insulin sensitivity via MR activation in adipocytes *in vitro* [11,12]. Nevertheless, obesity and insulin resistance develop during high fat feeding in aldosterone synthase deficient mice, although diet-induced changes in glycemia, hepatic steatosis, adipocyte macrophage inflammation, and plasma high-molecular weight adiponectin are attenuated [13]. Obesity is also associated with increased MR expression in subcutaneous and visceral fat and in mature adipose fractions in humans and in mice [8]. In the same investigation, doxycycline-induced adipocyte MR-overexpression (adipo-MROE mice) for 12 weeks causes metabolic syndrome-like alterations in visceral fat, glucose tolerance, triglyceridemia, and cholesterolemia without altering circulating aldosterone or blood pressure. Furthermore, lipocalcin-like prostaglandin D2 synthase (PTGDS) increases during MR activation by overexpression *in vivo* or by aldosterone or glucocorticoid incubation *in vitro*. PTGDS inhibition with AT56 prevents aldosterone-induced adipogenesis and insulin resistance *in vitro*, demonstrating a novel MR-dependent pathway which may impair systemic metabolism [8]. These studies demonstrate that adipocyte-derived factors can stimulate aldosterone secretion, and in turn aldosterone may cause adipocyte dysfunction and adverse metabolic consequences.

Effects of aldosterone on vascular inflammation and function

Obesity, metabolic syndrome, and diabetes are associated with markedly increased cardiovascular risk, and aldosterone has been linking as a potential mediator. Experimental aldosterone administration causes perivascular inflammation and fibrosis, whereas MR antagonism prevents this injury. Angiotensin II administration produces a similar pattern of injury, which is prevented in part by adrenalectomy, MR antagonism, or aldosterone synthase inhibition or deficiency [14–17]. During high fat/high-carbohydrate diet (Western diet), mice develop obesity and vascular remodeling with vascular endothelial and smooth muscle cell stiffness, aortic medial hypertrophy, peri-aortic inflammation, and impaired vasodilation. In this model, spironolactone prevents Western diet-induced vascular remodeling and vascular dysfunction, even though it does not prevent obesity, systemic insulin resistance or hyperglycemia [18]. This study significantly expands the literature by demonstrating that spironolactone also prevents pro-inflammatory M1 macrophage infiltration in aorta, shifting the balance towards an anti-inflammatory M2 phenotype with increased interleukin-10 production [18].

Since the initial demonstration that targeted MR deletion within vascular smooth muscle attenuates age-related hypertension [19], additional studies have continued to dissect the role of the MR within the vascular endothelium and vascular smooth muscle *in vivo* [20,21]. After a short period of aldosterone (8 days) endothelial cell MR deletion (EC-MRKO) preserves acetylcholine-stimulated NO-dependent vasodilation in aorta but not mesenteric vessels, suggesting a specific role in conduit arteries. After deoxycorticosterone/salt treatment for 8 weeks, EC-MRKO were similarly protected against increased cardiac intercellular adhesion molecule 1 (ICAM-1), macrophage infiltration, inducible nitric oxide synthase, and collagen deposition even though the blood pressure response was not significantly altered [21]. In contrast, MR overexpression in vascular endothelial cells (MR-EC) confers protection against ferric-chloride-induced carotid artery thrombosis, which is mediated in part via increased von Willebrand factor (vWF) release and endothelial protein C receptor expression [22]. Systemic blood pressure and pressor response to multiple vasoconstrictors are also increased in these MR-EC mice [23]. The authors hypothesize that a healthy vascular endothelium is essential for the anti-thrombotic effects of vascular endothelial MR activation, whereas aldosterone exerts prothrombotic effects in the presence of endothelial injury [22].

The vascular smooth muscle MR has complementary but independent effects on vasculature function which have been recently delineated. Inducible, targeted MR deletion from smooth muscle cells (SMC-MR, derived from SMA-Cre-ER^{T2} line) reduces vascular myogenic tone and systemic blood pressure with ageing and reduces oxidative stress and hypertension during angiotensin II infusion [19]. After wire-induced carotid injury, MR deletion also prevents aldosterone-augmented vascular smooth muscle proliferation and vascular fibrosis [24]. Vascular endothelial growth factor receptor1 (VEGFR1) expression increases in vascular smooth muscle after vessel injury, and VEGFR1 blockade prevents fibrosis and vascular smooth muscle proliferation in a blood pressure independent manner [24]. Placental growth factor (PIGF) likely contributes to this injury because it increases in response to aldosterone and it binds specifically to VEGFR1 [24,25]. Other investigators have created a

constitutive vascular smooth muscle MR knockout (MR^{SMKO}, derived by crossing with the SM22-Cre line) which develops no alterations in renal sodium handling [26]. After 4 weeks of nephrectomy/aldosterone/salt, blood pressure increases similarly in MR^{SMKO} mice, but MR deletion preserves carotid artery distensibility, reduces $\alpha 5$ -integrins, and increases $\alpha 1$ -integrin expression.

These studies demonstrate that aldosterone and the vascular MR contribute to vascular dysfunction and remodeling independent of blood pressure and renal sodium handling, but the endothelial MR may also have protective anti-thrombotic effects. These studies also highlight the specific endothelial (e.g., ICAM-1, EPCR, vWF) and vascular smooth muscle MR-dependent genes (PIGF, TNF- α).

Effect of MR antagonism on coronary flow reserve

The vascular effects of MR antagonists have been most prominently demonstrated in patients with atherosclerotic heart disease and heart failure, including those with T2DM. Coronary flow reserve reflects cardiac microvascular function, and has been associated with increased cardiovascular risk in T2DM patients even in the absence of obstructive coronary artery disease. Two studies recently examined the effect of spironolactone on coronary flow reserve. Garg et al. performed a randomized, double-blind study of 64 subjects with T2DM and no evidence of cardiac ischemia by positron emission tomography imaging. After washout of other anti-hypertensive medications and a run-in period on enalapril therapy, subjects were treated with either spironolactone 25 mg, hydrochlorothiazide 12.5 mg, or placebo daily for 6 months. Spironolactone 25 mg daily significantly increased coronary flow reserve compared to the other groups [27], despite a similar reduction in blood pressure between the spironolactone and HCTZ groups. No significant differences in resting echocardiographic measures were observed during the course of treatment, however.

Bavry *et al.* performed a randomized double-blind placebo controlled trial in 41 patients with nonobstructive coronary artery disease. After a baseline coronary angiogram, subjects were randomized to eplerenone 25 mg for 4 weeks and then 50 mg for 12 weeks before returning for a repeat coronary angiogram. Coronary vascular response was measured after adenosine, acetylcholine, and nitroglycerin. As opposed to the previous study, there was no significant difference between eplerenone and placebo. In a *post-hoc* analysis, however, eplerenone tended to improve coronary vasodilation in subjects with the most severe dysfunction at baseline. These two studies differ in study population, standardized treatment, treatment duration, and method of assessment of coronary endothelial function which could explain the differing results.

Effects of MR on cardiovascular inflammation

Vascular inflammation and fibrosis are prominent features of mineralocorticoid-induced hypertension. Deletion of the macrophage/monocyte MR (Mac-MRKO) has been shown to ameliorate vascular inflammation hypertension, plasminogen activator inhibitor-1 expression, and fibrosis in MR-dependent and MR-independent models [28,29]. As noted above, the EC-MRKO mice are protected against cardiovascular inflammatory cell infiltration and fibrosis. In contrast, macrophage infiltration in response to mineralocorticoid

hypertension is intact in Mac-MRKO but inflammatory and fibrotic responses (e.g., PAI-1) are attenuated [29]. In myeloid-specific MR knockout mice (MyMRKO), macrophage polarization is alternatively activated by PPAR γ or glucocorticoids [30]. The finding that spironolactone shifts the Western diet-induced M1 macrophage towards an M2 phenotype demonstrates that this response may be altered using conventional pharmacologic means [18]. This mechanism could contribute to the observed reduction in cardiovascular complications during spironolactone treatment.

Role of MR antagonism in prevention of diabetic nephropathy

Although RAAS blockade reduces the risk of diabetic nephropathy (DN) progression, the number of patients who progress to renal failure remains unacceptable. Annual Medicare costs for end-stage renal disease are approximately \$30 billion, accounting for 5.6% of the total Medicare budget [31]. Therefore, new approaches are urgently needed not only to improve clinical outcomes but to reduce annual Medicare costs. One potentially beneficial approach is the use of MRAs, which prevent renal injury in multiple renal injury models and reduce proteinuria in small clinical studies [32–34]. However, their effect on long-term outcomes has not been proven, and the risk of hyperkalemia with spironolactone and eplerenone has limited the enthusiasm for use in high risk conditions, such as diabetic nephropathy [34].

Recently, a new class of nonsteroidal MRAs was discovered. Their development and early clinical studies have been reviewed previously, and several drugs have advanced into clinical trials [35,36]. As opposed to most diuretic agents, MRAs do not require filtration to reach their renal epithelial target, and therefore would not be anticipated to lose effectiveness in renal insufficiency. This potential benefit must be weighed against the increased risk of hyperkalemia, however. Nonsteroidal MRAs, including finerenone, reduce proteinuria in rodents with a lower incidence of hyperkalemia compared to steroidal MRAs [35,36]. Finerenone has advanced the furthest in clinical trials for treatment of diabetic nephropathy and for heart failure with diabetes or chronic kidney disease [37–39].

The MinerAlocorticoid Receptor Antagonist Tolerability Study-Diabetic Nephropathy (ARTS-DN; NCT01874431) recently reported on the results of this randomized, double-blind, placebo-controlled, parallel-group study. The primary outcome is effect of finerenone on the risk of hyperkalemia and the biomarker outcome of albuminuria reduction (urine albumin/creatinine ratio, UACR). Finerenone treatment was given as 1.25, 2.5, 5, 7.5, 10, 15, or 20 mg daily of finerenone added onto standard RAAS blockade with either ACE-I or ARB for 3 months. A total of 823 total subjects were randomized, and 764 completed the treatment.

Finerenone demonstrated a dose-dependent reduction of albuminuria after 3 months, without reaching a clear plateau at the maximum dose of 20 mg daily (0.62 ratio of day 90 versus baseline UACR). A greater proportion of subjects treated with finerenone 20 mg daily had a 50% reduction of UACR compared to placebo (40.2% versus 13.6%; $p < 0.001$). This degree of albuminuria reduction is comparable to the reduction of 34% during spironolactone 25 mg daily added to lisinopril 80 mg daily [34]. Statistical significance for albuminuria reduction was reached for doses of 7.5, 10, 15, and 20 mg once daily, and future studies will

likely use doses in this range to test long-term benefit. These doses are consistent with early analyses of the ARTS-Heart Failure (HF) study which demonstrate an optimal dose of 10–20 mg daily.

The main concern regarding these agents is hyperkalemia, especially in patients at high risk due to diabetes and chronic kidney disease who are already receiving maximal ACEI or ARB treatment. In the ARTS-DN study, 1.8% of subjects receiving an effective finerenone dose (7.5–20 mg) had documented serum K⁺ 5.6 mmol/L, and one subject in this group had a serum K⁺ 6.0 mmol/L. On average, finerenone 20 mg increased serum potassium by 0.17 ± 0.46 mmol/L at 90 days, whereas no change was observed in the placebo group. In the subgroup with a baseline eGFR of 30–60 mL/min/1.73m², potassium increased by 0.30 ± 0.44 during finerenone 20 mg daily versus 0.04 ± 0.44 mEq/L during placebo. Although the risk for hyperkalemia in ARTS-DN was minimized by discontinuing potassium supplements and other drugs which may increase potassium, subjects were not provided specific dietary potassium recommendations at study entry. The majority of subjects in the study, including 86% of those on high dose finerenone, received loop or thiazide diuretics which should reduce the hyperkalemia risk. In addition, RAAS blockade was maximized in 40.8% of subjects, with 24.8% of subjects receiving the minimum recommended dose. The effects of finerenone on colonic potassium handling are also unknown, whereas this mechanism assumes a significant importance in patients with advanced renal disease. Future phase III studies will hopefully better define the hyperkalemia risk of finerenone, in addition to testing effectiveness for definitive renal endpoints when combined with protocolized, full-dose ACE-I or ARB therapy. Additional studies are ongoing to investigate the benefit of spironolactone on cardiovascular outcomes in patients with CKD [40].

CONCLUSIONS

New investigations in the past year have significantly advanced our understanding of the extra-renal effects of aldosterone within the vascular endothelium, vascular smooth muscle, adipocytes, and macrophages. These findings suggest that the benefits of MR antagonists in clinical trials could be mediated by these extra-renal MR effects. Additional studies are ongoing to determine if the beneficial effects of MR antagonists can be dissociated from the hyperkalemia risk, with novel nonsteroidal MR providing some promising results for prevention of diabetic nephropathy.

Acknowledgments

FINANCIAL SUPPORT AND SPONSORSHIP: supported in part by NIH grants DK081662 and DK096994.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Goodfriend TL, Egan BM, Kelley DE. Plasma aldosterone, plasma lipoproteins, obesity and insulin resistance in humans. *Prostaglandins Leukot Essent Fatty Acids*. 1999; 60:401–405. [PubMed: 10471129]
2. Ehrhart-Bornstein M, Lamounier-Zepter V, Schraven A, et al. Human adipocytes secrete mineralocorticoid-releasing factors. *Proc Natl Acad Sci USA*. 2003; 100:14211–14216. [PubMed: 14614137]
3. Allison MA, Jenny NS, McClelland RL, et al. The associations of adipokines with selected markers of the renin-angiotensinogen-aldosterone system: The multi-ethnic study of atherosclerosis. *J Hum Hypertens*. 2015; 29:127–133. [PubMed: 24919752]
4. Huby AC, Antonova G, Groenendyk J, et al. The adipocyte-derived hormone leptin is a direct regulator of aldosterone secretion, which promotes endothelial dysfunction and cardiac fibrosis. *Circulation*. 2015 Epub ahead of print. 10.1161/CIRCULATIONAHA.115.018226
5. Ingelsson E, Pencina MJ, Tofler GH, et al. Multimarker approach to evaluate the incidence of the metabolic syndrome and longitudinal changes in metabolic risk factors: The framingham offspring study. *Circulation*. 2007; 116:984–992. [PubMed: 17698726]
6. Tuck ML, Sowers J, Dornfeld L, et al. The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. *N Engl J Med*. 1981; 304:930–933. [PubMed: 7010165]
7. Marzolla V, Armani A, Feraco A, et al. Mineralocorticoid receptor in adipocytes and macrophages: A promising target to fight metabolic syndrome. *Steroids*. 2014; 91:46–53. [PubMed: 24819992]
- 8**. Urbanet R, Nguyen Dinh Cat A, Feraco A, et al. Adipocyte mineralocorticoid receptor activation leads to metabolic syndrome and induction of prostaglandin d2 synthase. *Hypertension*. 2015; 66:149–157. This manuscript demonstrates that overexpression of the MR within adipocytes is sufficient to produce systemic metabolic effects consistent with the metabolic syndrome, likely mediated via prostaglandin D2 synthase. PGD2 was also increased in human adipose tissue from obese individuals. [PubMed: 25966493]
9. Wang ZV, Scherer PE. Adiponectin, cardiovascular function, and hypertension. *Hypertension*. 2008; 51:8–14. [PubMed: 17998473]
10. Guo C, Ricchiuti V, Lian BQ, et al. Mineralocorticoid receptor blockade reverses obesity-related changes in expression of adiponectin, peroxisome proliferator-activated receptor-gamma, and proinflammatory adipokines. *Circulation*. 2008; 117:2253–2261. [PubMed: 18427128]
11. Wada T, Ohshima S, Fujisawa E, et al. Aldosterone inhibits insulin-induced glucose uptake by degradation of insulin receptor substrate (irs) 1 and irs2 via a reactive oxygen species-mediated pathway in 3t3-l1 adipocytes. *Endocrinology*. 2009; 150:1662–1669. [PubMed: 19095745]
12. Hirata A, Maeda N, Nakatsuji H, et al. Contribution of glucocorticoid-mineralocorticoid receptor pathway on the obesity-related adipocyte dysfunction. *Biochem Biophys Res Commun*. 2012; 419:182–187. [PubMed: 22326264]
13. Luo P, Dematteo A, Wang Z, et al. Aldosterone deficiency prevents high-fat-feeding-induced hyperglycaemia and adipocyte dysfunction in mice. *Diabetologia*. 2013; 56:901–910. [PubMed: 23314847]
14. Luther JM, Luo P, Wang Z, et al. Aldosterone deficiency and mineralocorticoid receptor antagonism prevent angiotensin ii-induced cardiac, renal, and vascular injury. *Kidney Int*. 2012; 82:643–651. [PubMed: 22622494]
15. Lea WB, Kwak ES, Luther JM, et al. Aldosterone antagonism or synthase inhibition reduces end-organ damage induced by treatment with angiotensin and high salt. *Kidney Int*. 2009; 75:936–944. [PubMed: 19225557]
16. Fiebeler A, Nussberger J, Shagdarsuren E, et al. Aldosterone synthase inhibitor ameliorates angiotensin ii-induced organ damage. *Circulation*. 2005; 111:3087–3094. [PubMed: 15939810]
17. Rocha R, Martin-Berger CL, Yang P, et al. Selective aldosterone blockade prevents angiotensin ii/salt-induced vascular inflammation in the rat heart. *Endocrinology*. 2002; 143:4828–4836. [PubMed: 12446610]
18. DeMarco VG, Habibi J, Jia G, et al. Low-dose mineralocorticoid receptor blockade prevents western diet-induced arterial stiffening in female mice. *Hypertension*. 2015; 66:99–107. [PubMed: 26015449]

19. McCurley A, Pires PW, Bender SB, et al. Direct regulation of blood pressure by smooth muscle cell mineralocorticoid receptors. *Nat Med.* 2012; 18:1429–1433. [PubMed: 22922412]
20. Schafer N, Lohmann C, Winnik S, et al. Endothelial mineralocorticoid receptor activation mediates endothelial dysfunction in diet-induced obesity. *Eur Heart J.* 2013; 34:3515–3524. [PubMed: 23594590]
21. Rickard AJ, Morgan J, Chrissobolis S, et al. Endothelial cell mineralocorticoid receptors regulate deoxycorticosterone/salt-mediated cardiac remodeling and vascular reactivity but not blood pressure. *Hypertension.* 2014; 63:1033–1040. [PubMed: 24566081]
- 22*. Lagrange J, Li Z, Fassot C, et al. Endothelial mineralocorticoid receptor activation enhances endothelial protein c receptor and decreases vascular thrombosis in mice. *FASEB J.* 2014; 28:2062–2072. This study demonstrates that MR overexpression protects against ferric chloride-induced thrombosis in vascular endothelium. The authors hypothesize that aldosterone exerts anti-thrombotic effects in healthy activated endothelium, but may promote thrombotic events in the setting of endothelial damage. [PubMed: 24451386]
23. Nguyen Dinh Cat A, Griol-Charhbil V, Loufrani L, et al. The endothelial mineralocorticoid receptor regulates vasoconstrictor tone and blood pressure. *FASEB J.* 2010; 24:2454–2463. [PubMed: 20299606]
- 24**. Pruthi D, McCurley A, Aronovitz M, et al. Aldosterone promotes vascular remodeling by direct effects on smooth muscle cell mineralocorticoid receptors. *Arterioscler Thromb Vasc Biol.* 2014; 34:355–364. This manuscript demonstrates that vascular smooth muscle MR contributes to aldosterone- and endothelial injury-induced vascular smooth muscle proliferation and fibrosis via placental growth factor and VEGFR1. [PubMed: 24311380]
25. Jaffe IZ, Newfell BG, Aronovitz M, et al. Placental growth factor mediates aldosterone-dependent vascular injury in mice. *J Clin Invest.* 2010; 120:3891–3900. [PubMed: 20921624]
26. Galmiche G, Pizard A, Gueret A, et al. Smooth muscle cell mineralocorticoid receptors are mandatory for aldosterone-salt to induce vascular stiffness. *Hypertension.* 2014; 63:520–526. [PubMed: 24296280]
27. Garg R, Rao AD, Baimas-George M, et al. Mineralocorticoid receptor blockade improves coronary microvascular function in individuals with type 2 diabetes. *Diabetes.* 2015; 64:236–242. [PubMed: 25125488]
28. Bienvenu LA, Morgan J, Rickard AJ, et al. Macrophage mineralocorticoid receptor signaling plays a key role in aldosterone-independent cardiac fibrosis. *Endocrinology.* 2012; 153:3416–3425. [PubMed: 22653557]
29. Rickard AJ, Morgan J, Tesch G, et al. Deletion of mineralocorticoid receptors from macrophages protects against deoxycorticosterone/salt-induced cardiac fibrosis and increased blood pressure. *Hypertension.* 2009; 54:537–543. [PubMed: 19635989]
30. Usher MG, Duan SZ, Ivaschenko CY, et al. Myeloid mineralocorticoid receptor controls macrophage polarization and cardiovascular hypertrophy and remodeling in mice. *J Clin Invest.* 2010; 120:3350–3364. [PubMed: 20697155]
31. Chapter 9: Costs of esrd. *Am J Kidney Dis.* 66:S183–S186.
32. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. *Kidney Int.* 2006; 70:2116–2123. [PubMed: 17035949]
33. van den Meiracker AH, Baggen RG, Pauli S, et al. Spironolactone in type 2 diabetic nephropathy: Effects on proteinuria, blood pressure and renal function. *J Hypertens.* 2006; 24:2285–2292. [PubMed: 17053552]
34. Mehdi UF, Adams-Huet B, Raskin P, et al. Addition of angiotensin receptor blockade or mineralocorticoid antagonism to maximal angiotensin-converting enzyme inhibition in diabetic nephropathy. *J Am Soc Nephrol.* 2009; 20:2641–2650. [PubMed: 19926893]
35. Kolkhof P, Nowack C, Eitner F. Nonsteroidal antagonists of the mineralocorticoid receptor. *Curr Opin Nephrol Hypertens.* 2015; 24:417–424. [PubMed: 26083526]
36. Luther JM. Is there a new dawn for selective mineralocorticoid receptor antagonism? *Curr Opin Nephrol Hypertens.* 2014; 23:456–461. [PubMed: 24992570]

- 37**. Bakris GL, Agarwal R, Chan JC, et al. Effect of finerenone on albuminuria in patients with diabetic nephropathy: A randomized clinical trial. *JAMA*. 2015; 314:884–894. This randomized, double blind placebo controlled trial of a new nonsteroidal MR antagonist convincingly demonstrates the anti-albuminuric effect of MR antagonism in patients with diabetic nephropathy. The safety profile due to hyperkalemia appears to be attenuated at lower doses which requires more rigorous study in additional trials. [PubMed: 26325557]
38. Ruilope LM, Agarwal R, Chan JC, et al. Rationale, design, and baseline characteristics of arts-dn: A randomized study to assess the safety and efficacy of finerenone in patients with type 2 diabetes mellitus and a clinical diagnosis of diabetic nephropathy. *Am J Nephrol*. 2014; 40:572–581. [PubMed: 25591469]
39. Pitt B, Filippatos G, Gheorghiade M, et al. Rationale and design of arts: A randomized, double-blind study of bay 94-8862 in patients with chronic heart failure and mild or moderate chronic kidney disease. *Eur J Heart Fail*. 2012; 14:668–675. [PubMed: 22562554]
40. Hill NR, Lasserson D, Thompson B, et al. Benefits of aldosterone receptor antagonism in chronic kidney disease (barack d) trial-a multi-centre, prospective, randomised, open, blinded end-point, 36-month study of 2,616 patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg once daily in addition to routine care on mortality and cardiovascular outcomes versus routine care alone: Study protocol for a randomized controlled trial. *Trials*. 2014; 15:160. [PubMed: 24886488]

KEY POINTS

- Vascular endothelial MR prevents vascular thrombosis, whereas vascular smooth muscle MR contributes to hypertension and smooth muscle hypertrophy
- Adipocyte-derived leptin stimulates aldosterone secretion, and adipocyte MR activation produces metabolic syndrome phenotype.
- Novel nonsteroidal MR antagonists demonstrate promising effects in diabetic nephropathy and may reduce hyperkalemia risk.

Figure 1.

Interaction between adipocytes and aldosterone production in zona glomerulosa cells. Ang, Angiotensin; AT₁, angiotensin II type I receptor; LR, leptin receptor; MR, mineralocorticoid receptor; PTGDS, prostaglandin D synthase; ZG, zona glomerulosa.