

# Aldosterone: Role in Edematous Disorders, Hypertension, Chronic Renal Failure, and Metabolic Syndrome

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The role of aldosterone has expanded from the hormone's genomic effects that involve renal sodium transport to nongenomic effects that are independent of the effect of aldosterone on sodium transport. The nongenomic effects of aldosterone to increase fibrosis, collagen deposition, inflammation, and remodeling of the heart and blood vessels, however, are markedly increased in the presence of high sodium intake. The genomic effect of aldosterone increases renal sodium transport, but the administration of large doses of aldosterone to normal individuals does not cause edema, relating to the phenomenon of "aldosterone escape"; however, in edematous disorders including cardiac failure, cirrhosis, and nephrotic syndrome, impaired aldosterone escape leads to renal sodium retention and edema formation. There is now considerable evidence for the nongenomic effects of aldosterone in several important diseases. Thus, low dosages of mineralocorticoid antagonists, with little or no effect on urinary sodium excretion, have been shown to afford a beneficial effect on morbidity and mortality in patients with advanced cardiac failure and after acute myocardial infarction. Three-drug-resistant hypertension has also been found to respond to spironolactone in modest dosages. The combination of an angiotensin converting enzyme inhibitor (ACEI) with spironolactone to treat such resistant hypertension may be more effective than adding an angiotensin receptor blocker to an ACEI. The role of spironolactone has also been shown to decrease albuminuria in chronic kidney disease including diabetic nephropathy in the presence of maximal dosages of ACEI. The effect of aldosterone in metabolic syndrome is also discussed in this review.

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**A**ldosterone is secreted by the zona glomerulosa under the influence of angiotensin II, potassium, and ACTH (1). The genomic pathway for aldosterone regulates the transport of sodium and potassium in epithelial cells. In the kidney, aldosterone binds to mineralocorticoid receptors in the cytoplasm of the principal cells of the collecting duct with resultant stimulation of nuclear protein synthesis. This results in an increase in (1) apical epithelial sodium channels for sodium entry into the cell, (2) basolateral sodium/potassium ATPase for cellular sodium extrusion and potassium entry, and (3) the apical ROMK channel for passive movement of cellular potassium into the lumen (Figure 1). Because this genomic effect of aldosterone involves new protein synthesis, the process takes hours to generate the epithelial effect and can be blocked by an inhibitor of protein synthesis (*e.g.*, actinomycin).

In recent years, nongenomic effects of aldosterone have been demonstrated (2). These effects presumably involve plasma membrane receptors, and the effects can be observed within minutes. The cell-signaling pathways of these nongenomic effects have not been completely defined. Of importance, with the nongenomic effects of aldosterone is the pivotal role of sodium intake in modulating the results (3). Specifically, increased sodium chloride intake enhances the nongenomic effects of aldosterone. Renal

epithelial sodium transport does not seem to be necessary for the nongenomic effects of aldosterone. For example, mineralocorticoid antagonists (*e.g.*, spironolactone) have been shown to decrease BP significantly in patients with anuria and ESRD (4). Conversely, the Yanomama Indians in Venezuela live a sodium-free culture as exhibited by a mean daily urinary sodium excretion of 1 mEq (5). These primitive Indians with virtually no sodium chloride intake have very high plasma aldosterone concentrations in the range of 80 ng/dl yet have no evidence of hypertension or metabolic abnormalities.

Many organs seem to have mineralocorticoid receptors that respond to the nongenomic effects of aldosterone (6). These include the heart, blood vessels, liver,  $\beta$  cells of the pancreas, and glomerular mesangial cells. The NF- $\kappa$ B transcription factor may be involved in the effects of aldosterone, which lead to inflammation, oxidative stress, apoptosis, and fibrosis (Figure 2) (7). Aldosterone synthase has also been identified in various organs other than the adrenal glands; these include heart, blood vessels, glomerular podocytes, and retina (8,9). As is discussed, mineralocorticoid antagonists have been shown to afford beneficial effects on many of these organs independent of any genomic effect on sodium transport. For example, a recent study demonstrated a beneficial effect of spironolactone on diabetic retinopathy (9).

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## Aldosterone and Cardiovascular Disease

It is hypothesized that when species moved from salt water to fresh water, there emerged the need for a sodium-retaining hormone. Aldosterone is known to be such a sodium-retaining

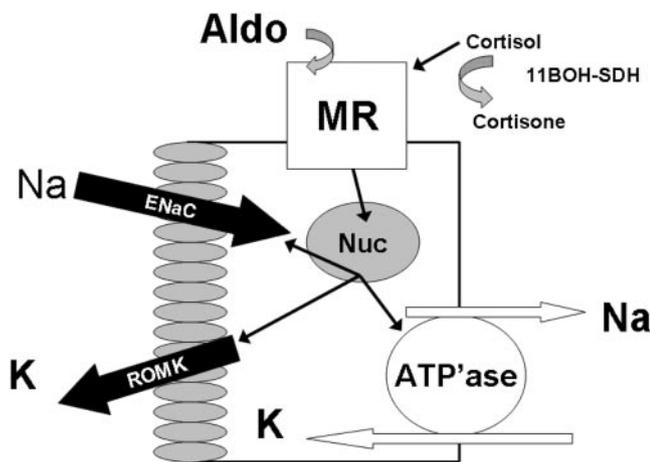


Figure 1. Genomic mechanisms of aldosterone action. Aldo, aldosterone; MR, mineralocorticoid receptor; ENaC, epithelial sodium channel; Nuc, nucleus; ROMK, potassium channel; 11βOH-SDH, β-hydroxysteroid dehydrogenase.

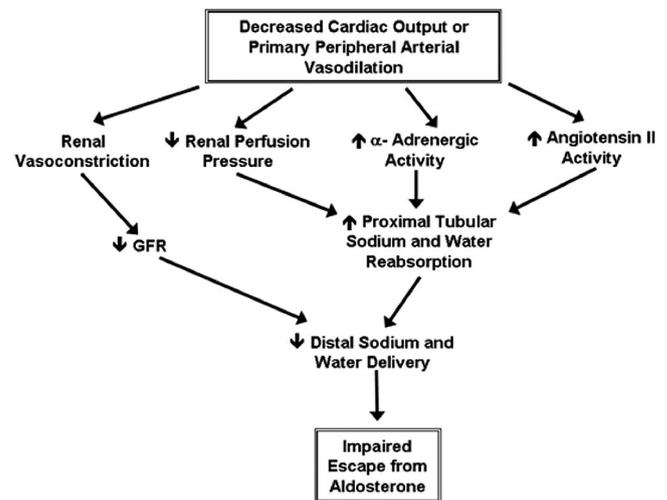


Figure 3. Role of diminished distal sodium delivery to impair aldosterone escape in states of arterial underfilling including cardiac failure and cirrhosis. Reprinted from reference (11), with permission.

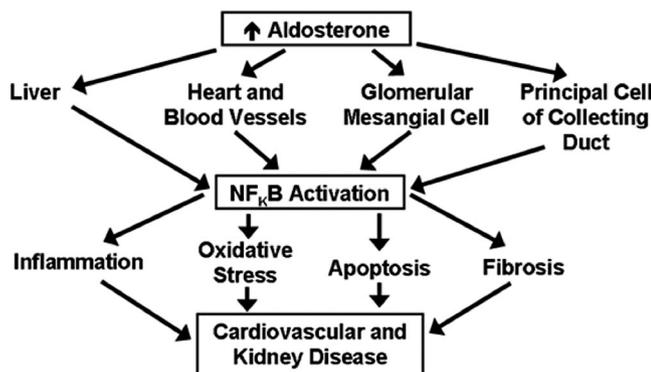


Figure 2. Role of NF-κB in mediating the nongenomic effects of aldosterone in cardiovascular and kidney disease.

hormone that is very important in circumstances with losses of total body sodium (*e.g.*, diarrhea, vomiting, hemorrhage, excessive sweating, glucosuria, diuretics). Primary hyperaldosteronism secondary to an adrenal adenoma or hyperplasia is known to be a cause of sodium retention and hypertension. Paradoxically, however, administration of large exogenous amounts of aldosterone to normal individuals does not cause edema. After the initial sodium-retaining effect of aldosterone, urinary sodium excretion increases to balance intake before any edema formation (the so-called “aldosterone escape” mechanism) (10). The dilemma, however, is the edematous patient with cardiac failure who has an increase not only in extracellular fluid but also in total plasma volume yet the kidney continues to retain sodium. The cause seems to be the failure of the aldosterone escape mechanism. The normal escape mechanism involves increased sodium delivery to the distal collecting duct site of mineralocorticoid site of action. The aldosterone escape, however, does not occur in heart failure and cirrhosis because of the neurohumoral effects that decrease distal sodium delivery (Figure 3) (11). Of importance, blockade of the genomic effect of aldosterone necessitates dosages of mineralocorticoid antago-

nists that are sufficient to block competitively the elevated endogenous aldosterone concentrations in patients with heart failure. Figure 4 shows the effect of large dosages of the mineralocorticoid antagonist spironolactone in advanced heart failure to reverse the avid sodium retention (12).

Some important studies, however, have demonstrated potential nongenomic effects of aldosterone. The dosage-finding Randomized Aldosterone Evaluation Study (RALES) in patients with severe cardiac failure demonstrated that low daily dosages of spironolactone (25 mg) did not increase urinary sodium excretion (13). In the later randomized mortality RALES of 1663 patients with severe heart failure that demonstrated a 30% decrease in all-cause and cardiac mortality, the mean spironolactone dosage was 26 mg/d (14). Although the authors proposed that this dosage of spironolactone to decrease mortality was due to inhibition of nonrenal effects of aldosterone such as cardiac and vascular fibrosis, they stated a minor effect on sodium excretion could not be excluded (14). In the Eplerenone post-AMI Heart Failure Efficacy and Survival Study (EPHESUS), the mineralocorticoid antagonist eplerenone (mean 43 mg/d) reduced mortality after acute myocardial infarction (15). Although no effects on body weight or sodium excretion were reported in the EPHESUS, the natriuretic effect of 50 mg/d eplerenone is considered comparable to 25 mg/d spironolactone.

It thus seems reasonable to suggest that at least some of the results of the mortality RALES and EPHESUS are due to inhibition of nongenomic effects of aldosterone. Low-dosage mineralocorticoid antagonists are now standard of clinical care in advanced heart failure and acute myocardial infarction; however, inhibition of the genomic effects of aldosterone on sodium and potassium transport with larger dosages of mineralocorticoid antagonists is virtually not used clinically in patients with cardiac failure (16). One reason is the danger of hyperkalemia secondary to mineralocorticoid antagonist. An article published

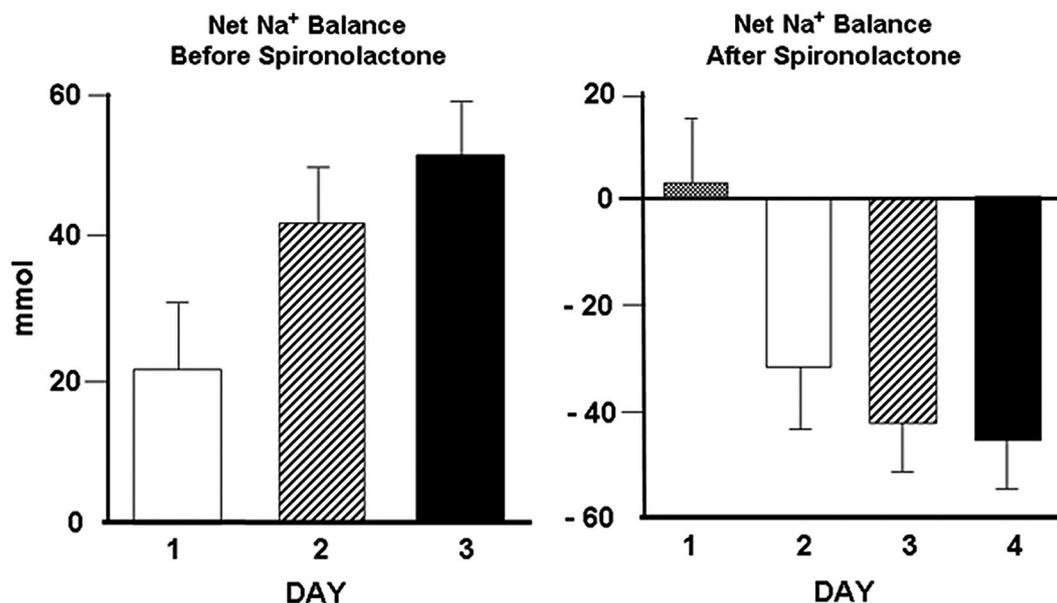


Figure 4. Reversal of sodium retention with aldosterone antagonism in patients with heart failure. (Left) Positive sodium balance without spironolactone. (Right) Negative sodium balance with spironolactone. Reprinted from reference (12), with permission.

in the *New England Journal of Medicine* by Juurlink *et al.* (17) reported an observational study that analyzed *International Classification of Diseases, Ninth Revision* codes of hospitalized patients relative to hyperkalemia in Ontario, Canada, and made comparisons before and after the publication of the RALES (Figure 5). The study used the *International Classification of Diseases, Ninth Revision*, which is generally defined as an elevated level of potassium in the blood  $>5$  mmol/L. The authors concluded that after the RALES was published, the rate of spironolactone prescriptions increased, a finding that was not unexpected; however, they also reported that hospitalizations for hyperkalemia and hospital deaths associated with hyperkalemia increased. No renal function data were reported, however—an important factor because hyperkalemia increases with spironolactone as renal function decreases. The patient populations were different in the RALES and observational study, and mean plasma potassium rose by only 0.3 mEq/L in the RALES. In the observational study, there were 16 other diagnoses, in addition to hyperkalemia, at the time of hospitalization. Moreover, the association of hyperkalemia with deaths in-hospital does not establish cause and effect.

The question, therefore, remains whether mineralocorticoid antagonists in genomic dosages that decrease sodium transport can be used in edematous patients with advanced heart failure. This is an important question, because the results of the Acute Decompensated Heart Failure Registry (ADHERE) in 105,388 hospitalized patients indicated the need for better treatment for acute cardiac decompensation (18). Ninety percent of such patients were on intravenous loop diuretics, and 30% were considered to have diuretic resistance. The ADHERE study also reported that 48% of patients were discharged from the hospital with continued symptoms. Moreover, 33% were discharged with  $\leq 5$  lb loss of body weight and 16% actually were discharged with increased body weight. The proposed role of the

renin-angiotensin-aldosterone system (RAAS) in diuretic resistance in cardiac failure is shown in Figure 6. A small study reported that diuretic-resistant patients who were on angiotensin-converting enzyme inhibitor (ACEI) treatment for cardiac failure demonstrated an important natriuresis with 100 mg/d spironolactone without any clinically important rise in plasma potassium concentration (19). Braunwald *et al.* (20) also demonstrated a natriuresis in three patients who had heart disease and received 100 mg/d spironolactone. Given the ADHERE results, genomic dosages of mineralocorticoid antagonists are in need of study in patients who have decompensated heart failure and are receiving a low-potassium diet and no potassium supplements. The diuretic resistance of loop diuretics may be reversed with mineralocorticoid antagonists, and the resultant increased urinary potassium losses may also protect against any clinically relevant hyperkalemia in patients who have cardiac failure and receive the combination of ACEI and spironolactone.

### Aldosterone and Cirrhosis

The pathophysiology of cirrhosis is very similar to that of cardiac failure (16), but blocking the genomic effects of aldosterone as practiced clinically is dissimilar. Arterial underfilling, as sensed by arterial baroreceptors, occurs with decreased cardiac output in heart failure and primary systemic arterial vasodilation in cirrhosis. With this unloading of the arterial baroreceptors in cardiac failure and cirrhosis, the neurohumoral axis is activated, including the RAAS, sympathetic nervous system, and vasopressin release. In both clinical circumstances, aldosterone is pivotal in the sodium retention, and edema formation occurs secondary to impaired aldosterone escape (11). In cirrhosis, the initial diuretic therapy for cirrhotic ascites is spironolactone and diuretic resistance in cirrhosis is defined as failure to respond to a daily dose of 400 mg of

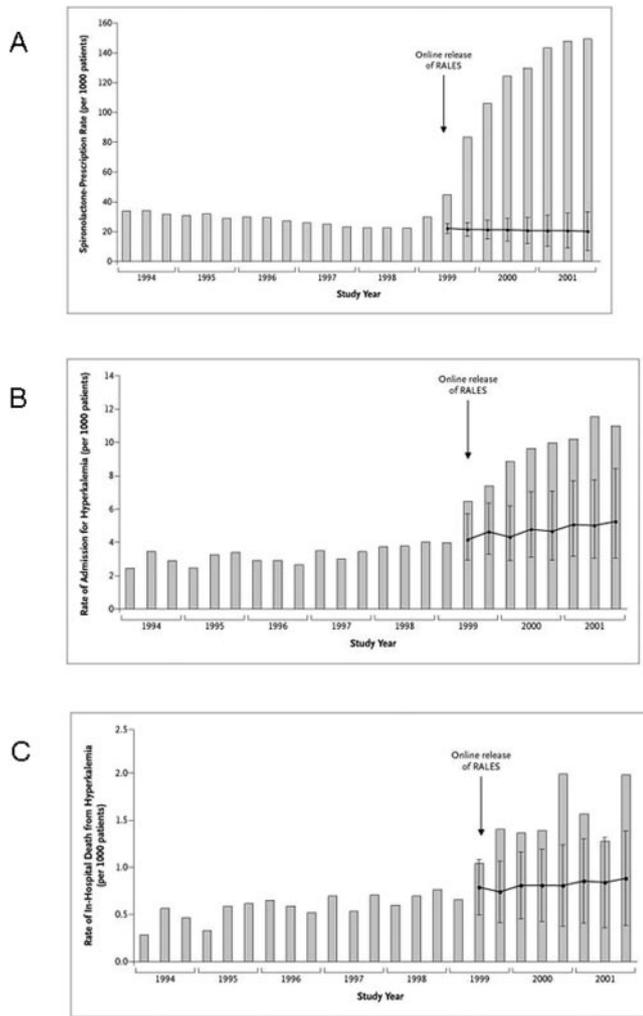


Figure 5. (A) Rate of prescriptions for spironolactone in hospitalized patients with heart failure. (B) Rate of hospital admissions associated with hyperkalemia in hospitalized patients with heart failure. (C) Rate of hospital deaths associated with hyperkalemia in hospitalized patients with heart failure. Reprinted from reference (17), with permission.

spironolactone and 160 mg of furosemide. This is in contrast to the nongenomic, non-natriuretic dosages of spironolactone in the RALES and eplerenone in EPHEBUS on cardiovascular morbidity and mortality.

Experimental prehepatic portal hypertension causes primary systemic vasodilation and sodium retention (21). A study of compensated patients who had cirrhosis without detectable ascites provided evidence for the pivotal role of primary systemic arterial vasodilation in ascites formation (22). These patients were administered large dosages of mineralocorticoid hormones to examine which patients would escape and not develop ascites and which patients would develop ascites. As shown in Figure 7, the patients who developed ascites exhibited more arterial underfilling with lower systemic vascular resistance and higher compensatory rises in cardiac output. In contrast, patients who had cirrhosis and less arterial underfilling (*i.e.*, higher systemic vascular resistance) escaped from the so-

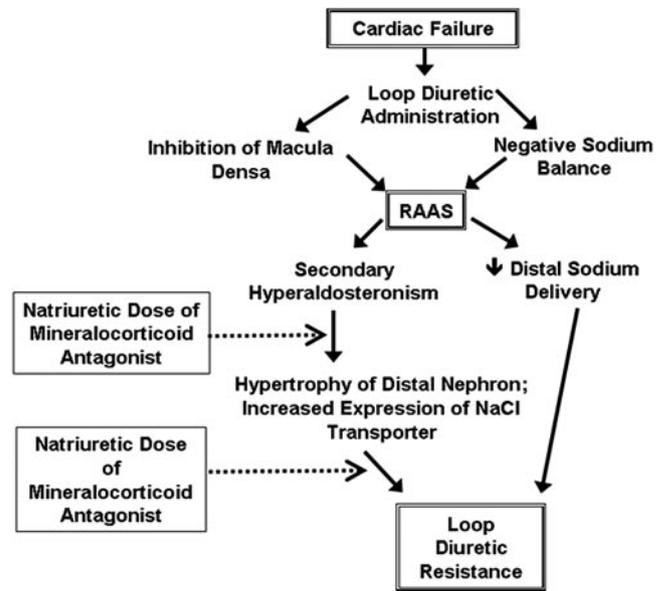


Figure 6. Diuretic resistance in cardiac failure: proposed reversal with mineralocorticoid antagonists. Solid lines, mechanism of diuretic resistance in cardiac failure; dashed lines, proposed reversal of diuretic resistance with mineralocorticoid antagonist. Published with permission from ref. 16.

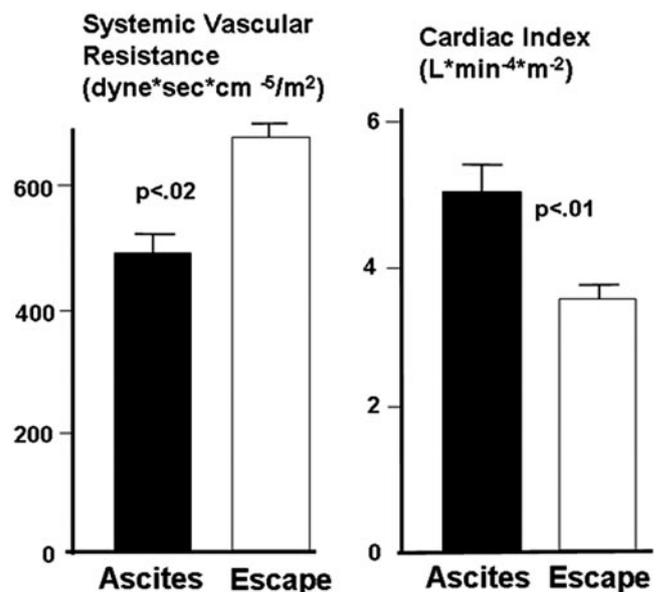


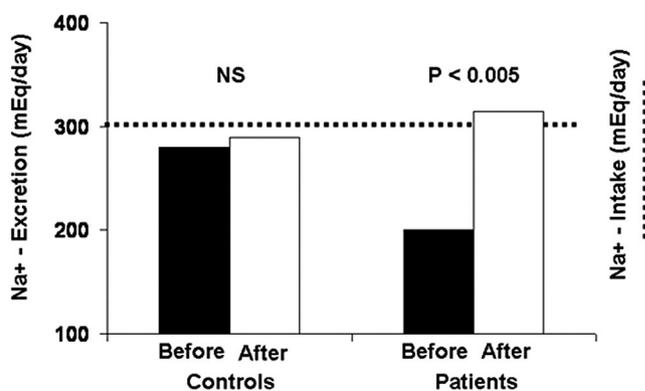
Figure 7. Patients who had cirrhosis and did not escape from the sodium-retaining effect of mineralocorticoid hormone and developed ascites (■) exhibited lower mean systemic vascular resistance and higher compensatory cardiac outputs (*i.e.*, more arterial underfilling) than patients who had cirrhosis and escaped from the sodium-retaining effect of mineralocorticoid hormone and did not develop ascites (□). Reprinted from reference (22), with permission.

dium-retaining effect of the mineralocorticoid antagonist and did not develop ascites (22). The earlier study by Gregory *et al.* (23) demonstrated that spironolactone in natriuretic dosages

over time led to disappearance of ascites in 16 or 21 patients with cirrhosis, whereas in the untreated control group of patients with cirrhosis, only four of 22 had disappearance of ascites during the same period. Thus, in contrast to cardiac failure, inhibition of the genomic, sodium-retaining effect of aldosterone with a mineralocorticoid antagonist is the standard of care in cirrhosis.

### Aldosterone and Nephrotic Syndrome

Studies were undertaken of patients with nephrotic syndrome secondary to various glomerular causes to examine the role of aldosterone in the renal sodium retention (24). The ACEI captopril was shown to decrease significantly plasma aldosterone, yet there was no increase in urinary sodium excretion as the positive sodium balance and increase in body weight continued (Figure 8). These results led to the conclusion that aldosterone was not involved in the sodium retention and edema formation in nephrotic syndrome. There was, however, a caveat. The ACEI blocked angiotensin generation and was associated with a fall in BP, which could have obscured the renal effect of the decline in plasma aldosterone on urinary sodium excretion. Balance studies were therefore performed with the mineralocorticoid antagonist spironolactone 200 mg twice daily to compare the response of patients who had nephrosis with normal control subjects (25). Both patients with nephrosis and control subjects were placed on a constant sodium intake ( $285 \pm 6$  mEq/d) for 4 days and then placed on the same dosage of spironolactone for 4 days. The results are shown in Figure 9. There was no difference in the control subjects, indicating that the high sodium intake had suppressed plasma aldosterone. In contrast, the patients with nephrosis demonstrated a marked



Data illustrate means of days 3 and 4 before spironolactone (“before”) and on days 3 and 4 after spironolactone (“after”), respectively.

Figure 9. Sodium excretion of patients with nephrosis and control subjects on a constant sodium intake. Reprinted from reference (25), with permission.

increase in urinary sodium excretion with spironolactone such that urinary sodium excretion equaled sodium intake. These results indicated that the genomic effect of aldosterone to enhance sodium transport in the renal collecting duct was important in the sodium retention in nephrotic syndrome.

### Aldosterone and Drug-Resistant Hypertension

Recent studies have suggested that increased aldosterone is an important factor in three-drug-resistant hypertension. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) of 1141

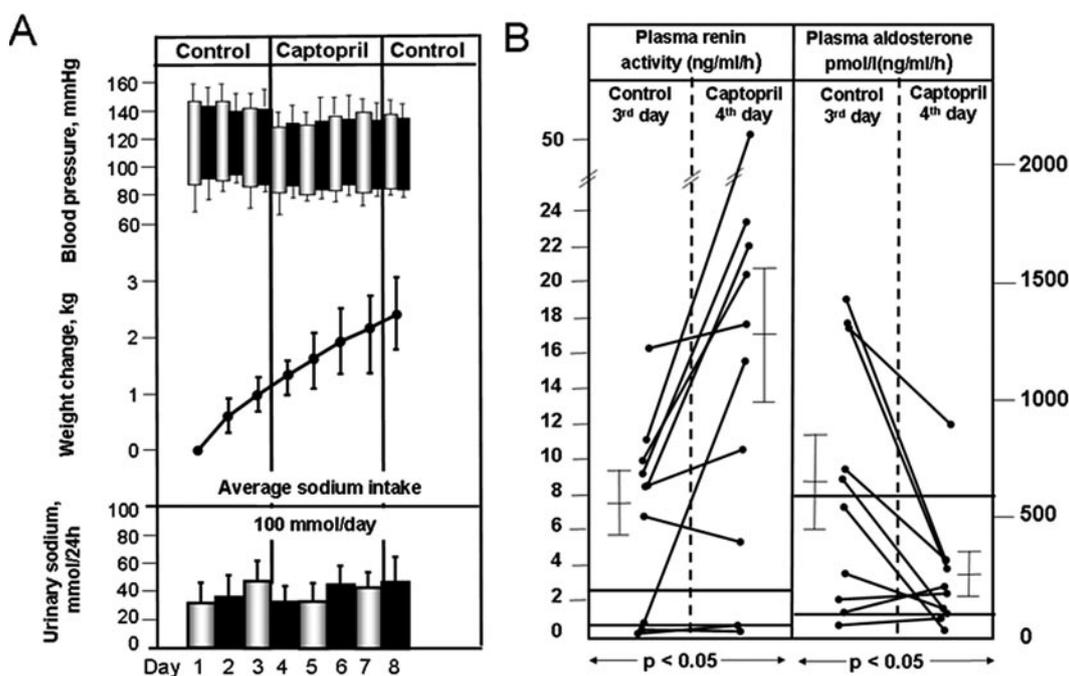


Figure 8. (A) Effect of captopril to decrease mean 24-hour BP but not prevent weight gain or increase urinary sodium excretion when given to patients who had nephrotic syndrome who were retaining sodium ( $n = 10$ ). (B) Effect of captopril to increase plasma renin activity and decrease plasma aldosterone concentration. Reprinted from reference (24), with permission.

patients with three-drug-resistant hypertension, 25 mg/d spironolactone during 1.3 years decreased mean systolic BP by 21.8 mmHg and diastolic BP by 9.5 mmHg (26). Adverse effects included gynecomastia or breast tenderness (6%) and hyperkalemia (2%). In another study of patients with three-drug-resistant hypertension (mean baseline BP 163/91 mmHg), spironolactone decreased BP to a similar amount as the aforementioned investigation. The same authors demonstrated that the decrements in systolic and diastolic BP at 6 weeks, 3 months, and 6 months were the same in three-drug-resistant hypertension in patients with and without primary hyperaldosteronism (Figure 10) (27). The effect of spironolactone in three-drug-resistant hypertension was also shown to be comparable in black and white patients. Although some of the antihypertensive effect is undoubtedly secondary to causing a natriuresis, there is also the possibility of a nongenomic effect. Evidence for this possibility is the previously cited report of the fall in BP with spironolactone (50-mg dose) in patients who had ESRD and anuria (4). Moreover, there is evidence of a nongenomic effect of aldosterone to injure the endothelium, which could contribute to elevated BP and be prevented by a mineralocorticoid antagonist (28). Three-drug-resistant hypertension may also be associated, particularly in obese patients, with obstructive sleep apnea. The role of aldosterone in this setting is in need of study.

### Aldosterone and Chronic Kidney Disease

There are several pathogenetic factors in which aldosterone, *via* the hormone’s nongenomic pathway, may contribute to chronic kidney disease (CKD; Figure 11). In this respect, the degree of tubulointerstitial disease is a better index of progression of renal disease than glomerular disease (29). As with blood vessels and the heart and the kidney, aldosterone increases inflammation and fibrosis secondary to TGF- $\beta$ , plasminogen activation inhibitor 1, and reactive oxygen species (30). Glomerular injury, particularly of the podocytes, can also occur secondary to the nongenomic effect of aldosterone. In this

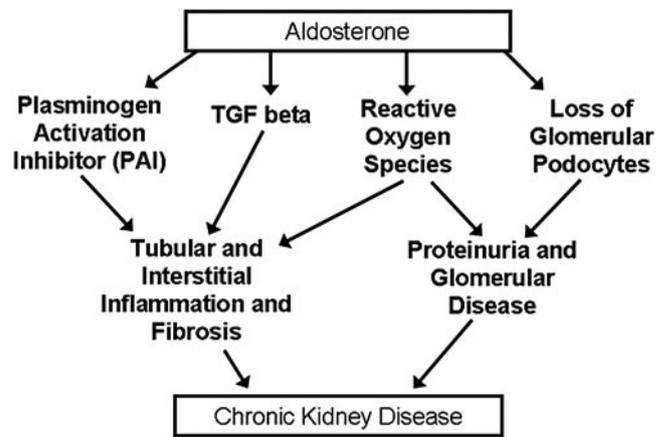


Figure 11. Proposed mechanisms whereby aldosterone causes CKD,

regard, a correlation between proteinuria and plasma aldosterone has been shown to occur in patients with CKD (Figure 12) (31). Moreover, spironolactone (25 mg/d) has been shown to reduce proteinuria in patients who had CKD and were already receiving an ACEI or angiotensin receptor blocker (ARB). There are studies of patients with CKD and proteinuria >1.5 g/24 h in which addition of spironolactone (25 mg/d) to an ACEI decreased the proteinuria more than addition of an ARB to an ACEI (32). What is less well established is the effect of spironolactone on slowing the loss of GFR. There is, however, a report that the monthly rate of decrease in estimated GFR at 1 year was significantly less in the spironolactone-treated group than in the placebo group (31).

### Aldosterone and Metabolic Syndrome/ Diabetes

There is a growing worldwide epidemic of obesity and type 2 diabetes. Results have shown that adipocytes have secretagogues that stimulate aldosterone (33). In this regard, a recent

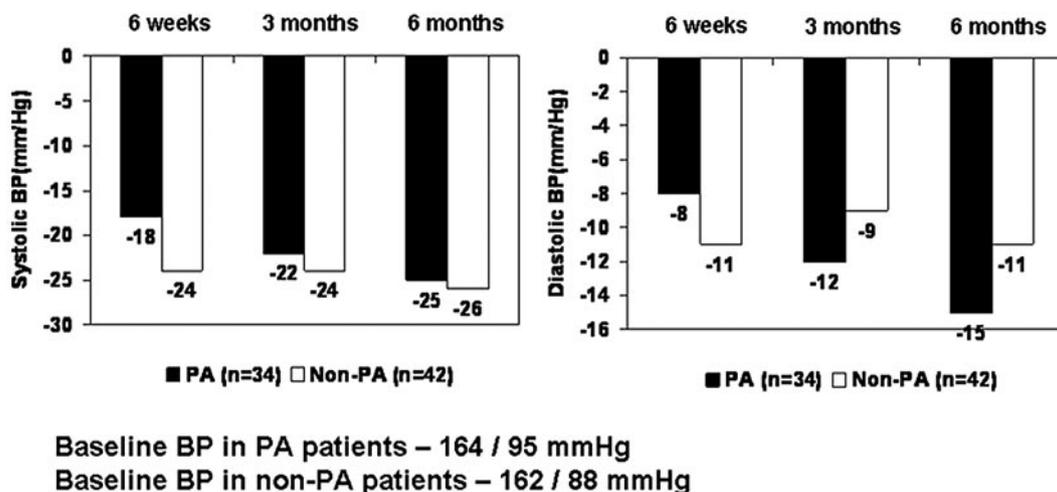


Figure 10. Effect of spironolactone in three-drug-resistant hypertension with (■) and without (□) primary hyperaldosteronism (PA). Reprinted from reference (27), with permission.

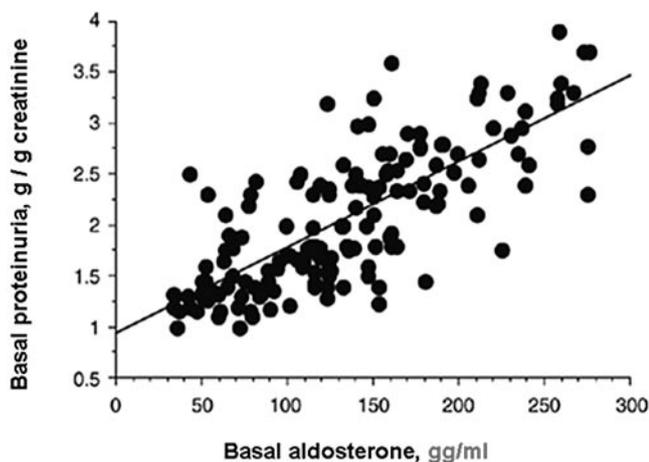


Figure 12. Correlation between basal proteinuria and plasma aldosterone in CKD. Reprinted from reference (31), with permission.

study compared black patients with and without metabolic syndrome with respect to plasma renin activity and plasma aldosterone in the supine and standing positions (Figure 13) (34). The results demonstrated no difference in plasma renin activity between the two groups, but plasma aldosterone concentrations were significantly higher in the group with metabolic syndrome. These results are, therefore, compatible with the occurrence of aldosterone secretion independent of increased RAAS but as a result of adipocyte secretagogues. Figure 14 shows the aldosterone-mediated factors that may contribute to the development of metabolic syndrome and diabetes. These include impaired insulin sensitivity and  $\beta$  cell insulin release as well as increased hepatic gluconeogenesis (35). Studies in type 2 diabetes have demonstrated that spironolactone decreases systolic and diastolic BP as well as urinary protein and albumin excretion as compared with placebo (36).

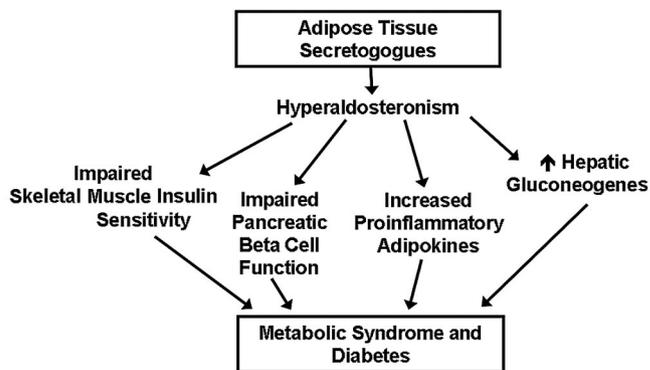


Figure 14. Proposed mechanism whereby secretagogues from adipose tissue stimulate aldosterone and cause metabolic syndrome and diabetes.

Initially, estimated GFR decreased more in the spironolactone group, but, after 9 to 12 months, a stable state occurred with less of a monthly decrease compared with the placebo group. A recent double-blind, randomized 48-week study of patients who had type 2 diabetic nephropathy and were on an ACEI compared the effect of addition of an ARB, losartan (100 g/d), with spironolactone (25 mg/d) to decrease urinary albumin-to-creatinine ratio (37). There was no difference between the two groups in dosage of ACEI (80 mg/d lisinopril), BP <130/80 mmHg, creatinine clearance, glycemic control, or sodium and protein intake. The decrease in urinary albumin-to-creatinine ratio from baseline did not reach significance with losartan (16.8%;  $P \leq 0.20$ ) but did with spironolactone (34.0%;  $P = 0.007$ ). Thus, the combination of an ACEI with a mineralocorticoid antagonist decreased albuminuria, an indicator of renal disease progression, more than the combination of an ACEI and an ARB. An explanation for this difference may relate to the phenomenon of aldosterone breakthrough (10,38). With either an ACEI or an ARB, the initial fall in plasma aldosterone may

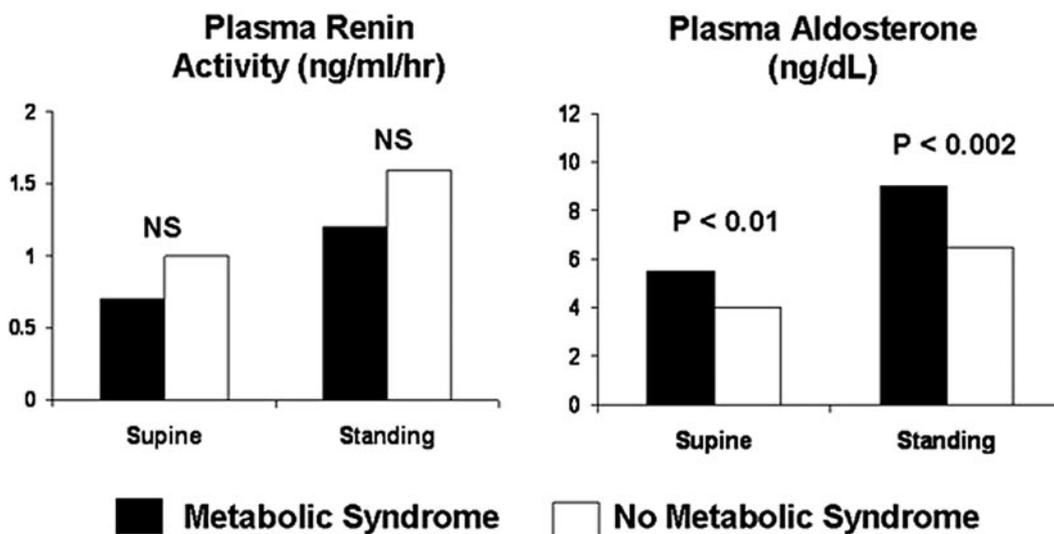


Figure 13. Supine and standing plasma renin activity (left) and plasma aldosterone (right) in black patients with (■) and without (□) metabolic syndrome. Reprinted from reference (34), with permission.

be followed over weeks by a return of plasma aldosterone concentration to baseline or even above. Patients with aldosterone breakthrough seem to have worse outcomes than patients who do not demonstrate the aldosterone breakthrough phenomenon while on an ACEI or an ARB. The addition of a mineralocorticoid antagonist may block the effects of aldosterone breakthrough and thus potentially improve clinical outcomes.

In patients with diabetic nephropathy, the addition of a daily mineralocorticoid antagonist, either 25 mg of spironolactone or 50 mg of eplerenone, will be expected to raise serum potassium by approximately 0.4 mEq/L. A recent study demonstrated that the predictors of hyperkalemia (*i.e.*, serum potassium >5.5 mEq/L) in patients who had diabetic nephropathy, were on acceptable dosages of a diuretic and a renin-angiotensin blocker, and were treated with a mineralocorticoid antagonist had a baseline serum potassium level  $\geq 4.5$  Eq/L and a GFR  $\leq$  of 45 ml/min per 1.73 m<sup>2</sup> (39).

## Conclusions

The clinical importance of aldosterone involves genomic and nongenomic effects, both of which may be blocked by mineralocorticoid antagonists. This review discussed some of these effects in patients with edematous disorders, drug-resistant hypertension, CKD, and metabolic syndrome/diabetes.

## Disclosures

None.

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