Aldosterone and Metabolic Syndrome
Is Increased Aldosterone in Metabolic Syndrome Patients an Additional Risk Factor?

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The classic role of aldosterone is to regulate water and electrolyte balance and, therefore, blood pressure homeostasis. Apart from that, experimental studies have demonstrated that aldosterone induces structural and functional alterations in the heart, kidneys, and vessels with effects such as myocardial fibrosis, nephrosclerosis, vascular inflammation and remodeling, and disturbed fibrinolysis. This damage seems to be aldosterone mediated, and aldosterone blockade with mineralocorticoid receptor (MR) antagonists, such as spironolactone, may prevent the onset of these effects. On the other hand, it cannot completely be ruled out that potassium and high blood pressure also play additional key roles in this damage. This evidence has impressively been supported by clinical studies, such as the Randomized Aldactone Evaluation Study and the Eplerenone Post-Acute Myocardial Infarction Survival and Efficacy Study. For example, increased mortality in patients with chronic heart failure has been associated with elevated aldosterone plasma levels, and high circulating plasma aldosterone levels predict the clinical outcome in patients after myocardial infarction. Furthermore, primary aldosteronism (PA) has been demonstrated to enhance the risk of cardiovascular events and kidney disease. In summary, aldosterone is considered a cardiovascular risk factor, promoting disease processes such as cardiac fibrosis, nephrosclerosis, and arteriosclerosis, all of which are increased in patients with obesity and the metabolic syndrome.

What Role Does Aldosterone Play in the Metabolic Syndrome?
The term “metabolic syndrome” (MSyn) has evolved various definitions in recent times; most of the studies introduced here use slight modifications. Nevertheless, all of the definitions used have a common denominator, which is reflected in a definition by the American Heart Association/National Heart, Lung, and Blood Institute. According to this definition, the MSyn is considered as a constellation of interrelated risk factors of metabolic origin, including arterial hypertension, dyslipidemias, alterations in glucose homeostasis with type 2 diabetes mellitus, and abdominal obesity. Importantly, these risk factors seem to promote the pathogenesis of arteriosclerosis directly. The clinical importance of a possible relationship between the MSyn and aldosterone is crucial: first, we are currently witnessing a dramatic increase in MSyn patients worldwide, and, second, aldosterone and the MSyn are both associated with increased cardiovascular morbidity and mortality. (Figure 1).

Aldosterone Causes Arterial Hypertension
The implication of mineralocorticoids in the pathogenesis of arterial hypertension is supported by a vast body of evidence from experimental and clinical studies. PA is the most common form of endocrine hypertension. The extent to which PA is the true cause for elevated blood pressure in overall hypertensive patients is subject to debate, with estimates ranging from 2% to 20%. Other than this vital discussion, the crucial importance of aldosterone in the incidence of arterial hypertension is supported by follow-up subanalyses from the Framingham Offspring Study. Serum aldosterone levels were significantly associated with an elevation of blood pressure in 1688 normotensive participants, indicating that increased plasma aldosterone levels within the physiological range predispose toward the development of arterial hypertension. In a more recent investigation on this group, the aldosterone:renin ratio was shown to be a heritable trait influenced by clinical and genetic factors that, even more than plasma aldosterone levels, predispose for the risk of hypertension development in nonhypertensive individuals.

Aldosterone Plasma Levels in Obesity and in Patients With MSyn
The renin-angiotensin system (RAS) has been implicated in the stimulation of aldosterone secretion in obesity. In particular, weight loss studies demonstrated a significant reduction in aldosterone levels together with renin and angiotensin II (Ang II), following even moderate weight loss, suggesting the involvement of an increased RAS activity in the development of obesity hypertension.
this context, a contribution of the adipose-tissue RAS, in addition to the classic RAS, is discussed in the development of insulin resistance and hypertension. Studies showing an increase in renin and aldosterone in patients with the MSyn are supported by studies in different animal models showing that obesity-induced hypertension increases both renin and aldosterone. However, clinical and experimental data suggest the involvement of other mechanisms in addition to the RAS in the stimulation of aldosterone secretion in obesity.

Only recently, a posthoc study examined the influence of body weight on aldosterone plasma levels in normotensive overweight subjects (n=120). Importantly, participants in this study were subjected to a high-sodium diet, an important modulator of aldosterone secretion. Twenty-four-hour urinary aldosterone secretion, but not cortisol, was elevated in overweight (body mass index [BMI]: >25 kg/m²) compared with lean normotensive subjects. In addition, aldosterone was higher in overweight subjects after Ang II infusion. Total supine plasma renin activity (PRA), serum aldosterone, and potassium levels were not different. Comparison between aldosterone levels in a small group (n=34) of obese hypertensive and normotensive women revealed significantly elevated aldosterone:PRA ratios in the hypertensive group. Plasma aldosterone was not different in the 2 groups, whereas PRA was decreased in the hypertensive patients, also indicating inappropriate aldosterone secretion, possibly because of an increased adrenocortical sensitivity to Ang II. These studies indicate inappropriately increased aldosterone secretion in overweight subjects.

In 2292 participants from the Framingham Offspring Study a panel of 8 biomarkers reflecting hemostasis, inflammation, endothelial dysfunction, and neurohumoral activity was correlated to incidence of MSyn; in the next step, related biomarkers of incident MSyn were correlated with longitudinal changes in its components. After adjustment, plasminogen activator inhibitor-1 (PAI-1) and aldosterone were the only parameters tested that remained associated with MSyn incidence. Note that PAI-1 is considered an important regulator in cardiac repair after myocardial infarction and a contributor to tissue fibrosis. Aldosterone increases PAI-1 expression, and MR blockade may attenuate PAI-1 expression and, therefore, also tissue remodeling. PAI-1 was positively and significantly associated with longitudinal changes in systolic blood pressure, fasting blood glucose, and triglycerides. Aldosterone correlated positively with an increase in systolic blood pressure, supporting the view that aldosterone levels can predict the onset of arterial hypertension and the MSyn.

A recent cross-sectional study evaluated the influence of aldosterone on the pathogenesis of hypertension and the MSyn in 397 black subjects. Blood pressure correlated positively with plasma aldosterone levels, and the latter correlated significantly with waist circumference, insulin, the insulin resistance index, and unfavorable lipid profiles. MSyn patients had higher plasma aldosterone levels and higher aldosterone:PRA ratios compared with those without MSyn. Interestingly, plasma aldosterone levels were elevated in MSyn patients, but PRA was not. These observations suggest that aldosterone may contribute to obesity hypertension, at least in people of African origin. Another cross-sectional study on an East-African population examined the association between plasma aldosterone and PRA on the one hand and the MSyn and its components on the other. The authors demonstrated that aldosterone was positively associated with waist circumference in men and with blood pressure in older participants of the study. Plasma aldosterone was ~20% higher in subjects with MSyn compared with those without. Similar to the study mentioned above, plasma aldosterone, but not PRA, was positively associated with ambulatory blood pressure. Both studies report similar results on similar genetic backgrounds. However, this reflects a limitation of these studies with regard to generalizing to the entire population. In contrast to the studies mentioned above, no correlation of serum aldosterone levels with BMI was found in 2891 participants of predominantly Caucasian background from the Framingham Offspring Study, with ages ranging from 29 to 86 years and BMI ranging from 16 to 56 kg/m². Similarly, in a Trial of Preventing Hypertension substudy focusing on congruity of MSyn and insulin resistance, no differences in aldosterone levels between subjects with the MSyn and those without were found. However, this study did not look into correlations between aldosterone plasma levels and single MSyn risk factors such as obesity or arterial hypertension apart from insulin resistance.

Therefore, the correlation of aldosterone levels with BMI seems to be different in different racial groups. Grim et al aimed at clarifying possible differences between MSyn patients of African origin and white French Canadians regarding the association of aldosterone plasma levels and arterial hypertension, representing 2 genetically distinct populations. Blood pressure directly correlated with aldosterone levels and the aldosterone:PRA ratio in blacks, whereas PRA itself remained unaffected. On the other hand, blood pressures only pointed toward a positive correlation with aldosterone levels in European Canadians, demonstrating a stronger and more
consistent correlation between aldosterone and arterial blood pressure in those of African origin.\textsuperscript{41}

In summary, an increasing body of evidence suggests a direct correlation between aldosterone levels and the MSyn, especially abdominal obesity and arterial hypertension. However, the correlation is more constant in subjects from African origin compared with white subjects. The importance of aldosterone in the pathogenesis of obesity hypertension is supported by studies on chronically instrumented dogs with dietary-induced obesity, where the administration of an aldosterone antagonist, eplerenone, markedly attenuated hypertension.\textsuperscript{32}

**What Actually Stimulates Elevated Aldosterone Secretion in Obese Patients?**

Under physiological conditions, the main stimulus for adrenal cortex–derived aldosterone secretion is the RAS, and a hyperactivity of this system has been implicated in the stimulation of aldosterone secretion in obesity.\textsuperscript{24} However, RAS-independent stimuli, such as K\textsuperscript+ and adrenocorticotrophic hormone, are also known to be involved in adrenal aldosterone secretion, although the latter are less potent than Ang II.\textsuperscript{1} In obesity, additional mechanisms in the stimulation of aldosterone secretion are discussed.

A correlation between plasma aldosterone levels and markers of insulin resistance and hyperinsulinemia has consistently been observed in obesity. Because insulin was shown to directly stimulate aldosterone secretion and to attenuate Ang II–mediated aldosterone secretion,\textsuperscript{42} hyperinsulinemia is discussed as one cause for increased adrenocortical aldosterone production in obese patients.\textsuperscript{43,44} Furthermore, there is increasing evidence indicating the amount of fat tissue, especially abdominal fat, as a major cause of increased aldosterone production in obese subjects. One mechanistic link discussed in this context is the oxidation of endogenous fatty acids released from visceral fat depots. Although non-esterified fatty acids inhibit aldosterone secretion,\textsuperscript{45} they form stimuli for adrenal aldosterone secretion after being oxidized in the liver.\textsuperscript{46} The most prevalent polymunsaturated fatty acid in humans is linoleic acid, and one of its oxidized derivatives (12,13-epoxy-9-keto-10[trans]-octadecanoic acid) had a particularly potent aldosterone-stimulating activity. Interestingly, its levels correlated with aldosterone levels, and in black subjects also with measures of the MSyn,\textsuperscript{47,48} suggesting its involvement in the stimulation of aldosterone secretion in obese patients.

As mentioned above, studies by Kidambi et al\textsuperscript{37} and Bochud et al\textsuperscript{38} demonstrated plasma aldosterone levels, but not PRA, to be elevated in patients carrying all of the components of the MSyn. In addition, urine and plasma potassium levels were not significantly different between hypertensive and normotensive patients.\textsuperscript{57} On the one hand, genetic variations in pathways responsible for aldosterone secretion may be partly responsible for these observations. However, aldosterone plasma levels correlated not only with high blood pressure but also with waist circumference. In addition, abdominal obesity is a known predictor for insulin resistance and dyslipidemia. Thus, the findings from these studies are in agreement with the hypothesis that insulin and/or fat-derived factors (adipocytokines) constitute a major stimulus for aldosterone secretion in obese subjects with hypertension and the MSyn.\textsuperscript{37} Support for this view comes from a recent study using a rat model for MSyn.\textsuperscript{49} Plasma aldosterone levels were elevated in animals with the MSyn, whereas PRA remained unchanged. Accordingly, the study found increased renal expression of aldosterone effector proteins, as well as markers of renal damage, such as oxidative stress and proteinuria, an effect that was prevented by aldosterone blockade. Interestingly, visceral adipocytes from obese MSyn animals secreted factors that enhanced aldosterone secretion from adrenocortical cells in vitro, an effect not observed in lean control animals.\textsuperscript{49} This supports earlier studies, where we demonstrated that also human adipocytes secret factors that directly stimulate steroid secretion, with a predominant effect on aldosterone, from human adrenocortical cells in vitro.\textsuperscript{50,51} Therefore, the direct stimulation of aldosterone secretion by adipokines (“adipotensins”) has to be considered as an additional mechanism leading to increased aldosterone levels in obesity. Chemical characterization revealed that the mineralocorticoid-stimulating effect was mediated by $\approx 2$ factors, a heat-sensitive fraction (molecular mass $>$ 50 kD) representing 60\% of total activity and an inactive fraction (molecular mass $<$ 50 kD) that interacts in the stimulation of steroidogenesis.\textsuperscript{50} Recently, our group demonstrated that adipocytes not only secrete mineralocorticoid-stimulating factors but can also sensitize adrenocortical cells to Ang II,\textsuperscript{52} via a mitogen-activated protein kinase–dependent upregulation of steroidogenic enzymes. These findings are supported by a recent clinical study that demonstrated enhanced Ang II–mediated aldosterone secretion in overweight and obese patients compared with lean subjects,\textsuperscript{53} reflecting an increased adrenal sensitivity among overweight individuals.

Adipose tissue is now considered a highly active endocrine organ involved in many physiological and pathological processes.\textsuperscript{53,54} The evidence reviewed here supports the hypothesis of factors released from fat cells directly or indirectly stimulating aldosterone secretion from the adrenal cortex and of fat cell–mediated sensitization of adrenocortical cells to Ang II. Alongside the known mechanisms, such as activation of peroxisome proliferator-activated receptor-\(\gamma\), leptin, insulin, insulin resistance, and activation of the sympathetic nervous system,\textsuperscript{55} these as-yet-unidentified humoral factors may contribute to the pathogenesis of obesity hypertension (Figure 2).

**Does Elevated Plasma Aldosterone Negatively Influence MSyn Risk Factors?**

Observational studies have suggested direct associations between aldosterone levels and parameters of impaired glucose homeostasis, such as fasting plasma glucose, insulin resistance, and insulin levels in patients with\textsuperscript{37,40} and without the MSyn.\textsuperscript{43} In an early report, Conn\textsuperscript{56} noted that $>50$\% of a small number of patients with PA showed impaired glucose tolerance. For example, a higher rate of disturbed glucose homeostasis in a small number of patients with PA was monitored as compared with control subjects.\textsuperscript{57,58} and surgical removal of the aldosterone-producing adenoma signifi-
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Figure 2. Abdominal obesity and the MSyn are associated with elevated plasma aldosterone levels. This figure summarizes factors involved in the pathogenesis of obesity hypertension. Other than known mechanisms (please refer to the text), adipose tissue may secrete factors that directly stimulate aldosterone secretion from adrenocortical cells and sensitize the cells to Ang II.

Does Aldosterone Interact With the Lipid Metabolism?

In summary, no conclusions can be drawn from these studies as to whether aldosterone, per se, on the one hand or elevated blood pressure on the other hand, as a concomitant component of the MSyn and a possible consequence of elevated aldosterone levels, is the causative factor for impaired glucose homeostasis. The causal relationship between aldosterone and insulin resistance/hyperinsulinemia remains unclear. There is evidence that aldosterone may worsen preexisting alterations in glucose homeostasis, such as insulin resistance, and hypertension in high-risk patients, such as MSyn patients. However, there is still no conclusive evidence that establishes aldosterone as an independent risk factor for the development of diabetes mellitus or hypertension. Arterial hypertension, because it is prevalent in patients with the MSyn, may reflect another major factor in the pathogenesis of insulin resistance. This may, therefore, positively influence aldosterone secretion.

Significantly improved insulin sensitivity and other parameters of disturbed glucose homeostasis.69–61 In a large prospective study, Fallo et al62 demonstrated a higher prevalence of the MSyn in patients with PA compared with essential hypertension (41% versus 29%). The prevalence of the MSyn in a respective general control population without arterial hypertension was ∼23%, an estimation that correlates well with earlier reports. Alterations in glucose homeostasis, alone or as a component of the MSyn, especially represented by an increased rate of hyperglycemia, a higher prevalence in diabetes mellitus (8.2% versus 3.4%), and patients taking glucose-lowering drugs, were present in patients with PA compared with those with essential hypertension. These findings contrast with another study that excluded diabetic patients. Patients with idiopathic or tumoral PA were more insulin resistant than matched healthy controls. However, severity of insulin resistance seemed to be less pronounced in the PA patients compared with patients with essential hypertension. Insulin sensitivity was restored by surgical intervention or MR blockade in the PA group, but no improvement in long-term glucose metabolism parameters could be observed.63 These findings tally with an earlier report that showed no differences with respect to plasma glucose and insulin response to glucose challenge in patients with PA compared with essential hypertensive subjects.64 This supports the view that essential hypertension is associated with increased insulin resistance and hyperinsulinemia and accounts for enhanced cardiovascular risk in these patients.65 In contrast, an earlier study even reported increased insulin sensitivity in a small sample of patients with PA.66 Little is known about interactions between aldosterone and insulin signaling at the molecular level. Low K7 has been discussed as a pathogenetic factor for disturbed glucose homeostasis in patients with PA, possibly interfering with insulin receptor function, insulin secretion, or gluconeogenesis.67–69 Only recent evidence suggests that aldosterone may impair insulin signaling by downregulating insulin receptor substrate-1 in vascular smooth muscle cells.70

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could be observed regarding the triglyceride or HDL cholesterol levels in PA patients compared with those with essential hypertension, indicating that not aldosterone but hypertension may affect blood lipids. According to this view, in 2891 subjects from the Framingham Heart Study, no direct correlation between low HDL cholesterol with higher plasma aldosterone could be observed.39

In summary, some studies suggest a correlation between plasma aldosterone levels and lipid metabolism in MSyn patients, where aldosterone might lower HDL levels, thereby increasing cardiovascular risk in these patients. However, a Framingham Heart Study subanalysis with higher subject numbers did not show a direct correlation between aldosterone and low HDL cholesterol, and evidence suggests that hypertension and not aldosterone, per se, might affect blood lipid homeostasis. Therefore, a possible causative relation between aldosterone and lipid metabolism needs to be investigated further.

Does Aldosterone Antagonism Benefit MSyn Patients?

MR blockade was found to provide substantial benefit in animal models, as well as in patients with arterial hypertension,71 chronic kidney disease,72,73 heart failure, and after myocardial infarction.8,9 and it has been suggested as treatment of resistant hypertension in obese patients.74 As yet, no reliable studies have tested MR blockade specifically to treat the MSyn and its complications. In an animal rodent model of diabetic nephropathy, MR expression was upregulated, and MR blockade effectively reduced diabetic renal injury.75 Similarly, eplerenone administration exerted renoprotective effects in an MSyn model with elevated plasma aldosterone levels.49 This demonstrates the need for future clinical studies addressing MR blockade to treat the MSyn and its components.

Summary and Conclusions

Aldosterone and the MSyn are known cardiovascular risk factors associated with increased mortality and morbidity. The causal relationship between aldosterone and arterial hypertension is unquestioned. There is an increasing body of evidence linking elevated plasma aldosterone levels to the MSyn and its single components, especially abdominal obesity. Aldosterone plasma levels are elevated in obese and in MSyn patients, and increasing evidence from clinical and experimental studies points to renin-independent stimulation of elevated aldosterone secretion in obese hypertensive patients. In addition, evidence suggests that Ang II–stimulated aldosterone secretion is enhanced in obese subjects. Adipocytokines and/or fatty acids released from fat cells might be the link between elevated aldosterone levels and hypertension in obese patients with and without the MSyn.

Some evidence suggests a direct effect of aldosterone on alterations of glucose homeostasis, possibly worsening pre-existing altered glucose homeostasis in MSyn patients. However, whether aldosterone, per se, causes type 2 diabetes mellitus is still unclear. Aldosterone may lower cardioprotective HDL cholesterol, but the exact effect on lipid homeostasis remains to be elucidated. It is important to address the possible beneficial effects of aldosterone blockade in MSyn patients in future studies.

Acknowledgment

Figures were produced using SERVIER Medical Art.

Sources of Funding

Work done in our laboratory was supported by grants from the University of Dresden (MedDrive to A.W.K.), Robert Pfleger Stiftung (to A.W.K.), and the Deutsche Forschungsgemeinschaft (EH161/4-1 to M.E.B. and KR3337/2-1 to A.W.K.).

Disclosures

None.

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Krug and Ehrhart-Bornstein: Aldosterone and Metabolic Syndrome


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Hypertension. 2008;51:1252-1258; originally published online March 17, 2008;
doi: 10.1161/HYPERTENSIONAHA.107.109439
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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