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The Role of Aldosteronism in Causing Obesity-Related Cardiovascular Risk

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Synopsis

A large body of evidence strongly links aldosterone to development and progression of cardiovascular disease, including vascular stiffness, left ventricular hypertrophy, congestive heart failure, chronic kidney disease, and especially, hypertension. Emerging data suggests that adipocytes may serve as a source of aldosterone, either directly, or indirectly, through release of aldosterone-stimulating factors. If adipocytes are confirmed to contribute importantly to hyperaldosteronism, it would have significant clinical implications in linking aldosterone to obesity-related increases in cardiovascular risk. Such a cause-and-effect would then provide the opportunity to reverse that risk with preferential use of aldosterone antagonists in obese patients.

Keywords

aldosterone; obesity; hypertension; adipocyte; spironolactone; eplerenone

Introduction

Obesity is strongly associated with an increased risk of cardiorenal disease, including hypertension, coronary artery disease, congestive heart failure, and chronic kidney disease (CKD). Recent studies indicate that hyperaldosteronism is a much more common cause of hypertension than had been thought historically. This observed increase in hyperaldosteronism has coincided with worldwide increases in obesity, suggesting that the 2 disease processes may be mechanistically related. In this review, we highlight the role that aldosterone plays in mediating cardiovascular and renal disease risk and then explore data linking adiposity to excess release of aldosterone. Such data suggests that visceral adipose tissue serves as a source of potent stimuli of aldosteronogenesis, thereby implicating aldosterone as a potentially important mediator of obesity-related cardiovascular risk.

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Obesity and Hypertension

There is a direct correlation between increasing body weight and risk of hypertension. Data from the National Health and Nutrition Examination Survey 1999-2004 indicate that the prevalence of hypertension increases progressively with increasing body mass index (BMI) from about 15% among people with a BMI less than 25 kg/m² to approximately 40% among those with a BMI of 30 kg/m² or greater (1). Analyses from the Framingham Heart Study suggest that approximately 78% of the risk of hypertension in men and 65% in women are directly related to excess body weight (2). In some populations, there is an almost linear relation between increasing body weight and increasing severity of systolic and diastolic blood pressure (3,4). The strong association between obesity and hypertension demonstrated in these and other studies suggests that obesity may be the most common cause of hypertension worldwide.

Aldosterone and Hypertension

Cross-sectional and prospective studies indicate that aldosterone, independent of renin-angiotensin II, contributes importantly both to the development and severity of hypertension. In a prospective analysis done as part of the ongoing Framingham Offspring Study, serum aldosterone, plasma renin concentration, and the aldosterone/plasma renin ratio (ARR) were prospectively related to development of hypertension or to blood pressure progression (increase in severity) (5). In this evaluation of over 3,000 normotensive subjects that were followed for an average of 3 years, rates of incident hypertension and blood pressure progression rose across tertiles of increasing aldosterone levels, while the relation to renin was the opposite, with incident hypertension and blood pressure progression rising across tertiles of decreasing renin concentration (Figure 1). The ARR was a stronger predictor of increasing blood pressure than aldosterone or renin alone, with the highest ARR quartile associated with a more than 2-fold risk of incident hypertension or blood pressure progression compared to the lowest quartile. These results strongly suggest that increasing aldosterone levels contribute importantly to development of hypertension. This is particularly true when aldosterone is in physiologic excess as suggested by suppressed renin levels.

Cross-sectional studies demonstrate a significant correlation between plasma aldosterone levels and untreated 24-hour ambulatory blood pressure levels. In an evaluation of black American and white French Canadian subjects, supine and standing plasma aldosterone levels were significantly related to daytime and nighttime systolic and diastolic blood pressure levels in the African-American subjects (6,7). In the white Canadian subjects, standing aldosterone levels correlated with both daytime and nighttime blood pressure while supine aldosterone levels significantly related to nighttime systolic blood pressure. In both ethnic groups, blood pressure levels were unrelated to plasma renin activity (PRA) suggesting that aldosterone, more so than the renin-angiotensin II axis, contributed to the severity of hypertension.

In a recent cross-sectional evaluation of 283 older, adult subjects with and without a history of hypertension, there were significant correlations between systolic blood pressure and levels of plasma aldosterone following suppression with dexamethasone and after stimulation with corticotropin (8). Diastolic blood pressure levels was significantly correlated with plasma aldosterone after dexamethasone administration. The associations were stronger in men than in women and remained after adjustment for potential confounding factors and after excluding subjects taking antihypertensive medications. In this analysis there was an approximate 10 mm Hg difference in systolic pressure when subjects in the lowest and highest tertile of aldosterone were compared.

These results of the above observational studies and the prospective findings of the Framingham Offspring Study provide compelling evidence of a broad role of aldosterone in contributing to both the onset and severity of hypertension in both men and women.

Aldosterone as an important mediator of hypertension is further supported by the general antihypertensive benefit of aldosterone blockade. For example, studies leading to the approval of eplerenone, a selective mineralocorticoid receptor antagonist, for the treatment of hypertension demonstrated broad efficacy in general hypertensive cohorts. In a prospective evaluation of 417 patients with mild-moderate hypertension, found that eplerenone reduced clinic blood pressure by up to 15/9 mm Hg (9). Importantly, these patients represented a generalized hypertensive cohort that was otherwise unselected, that is, patients were not screened based on aldosterone levels, renin activity, or aldosterone/renin ratios. These results support the role of aldosterone in contributing importantly to the development of hypertension in a general population.

Historically, primary aldosteronism was reported to be an uncommon cause of hypertension with a prevalence of <1% among general hypertensive patients. However, beginning in the early 1990's with reports from investigators in Brisbane, Australia, the prevalence of primary aldosteronism has been described by clinics worldwide to be considerably higher, occurring in perhaps 5-10% of hypertensive patients (10,11). Perhaps the most compelling of these is the PA Prevalence in Hypertensives or PAPY study (12). The study is particularly impressive in its prospective design, its large sample size, and its rigorous assessment of aldosterone status including adrenal vein sampling of most patients with confirmed primary aldosteronism and adrenalectomy when appropriate, thus allowing for definitive discrimination of idiopathic bilateral hyperplasia from an aldosterone-producing-adenoma.

In the PAPY study 1,125 Italians newly diagnosed with hypertension agreed to be screened for primary aldosteronism including, if biochemical primary aldosteronism was confirmed, lateralization studies (either adrenal vein sampling or adrenocortical scintigraphy) and adrenalectomy. Primary hyperaldosteronism was confirmed based on a high baseline ARR and high ARR after captopril suppression testing or with application of a previously validated logistic function. Aldosterone-producing adenomas were then confirmed by positive lateralization, surgical resection, pathological examination, and clinical outcome following adrenalectomy. Subjects with confirmed primary hyperaldosteronism but without confirmed adrenal adenomas were diagnosed as having idiopathic primary aldosteronism.

Overall, the prevalence of biochemical primary aldosteronism was 11.2%. Approximately 43% of these cases could be attributed to an aldosterone-producing-adenoma with the remaining 57% considered idiopathic in etiology. Accordingly, in this cohort of newly diagnosed hypertensive patients, the overall prevalence of primary aldosteronism secondary to an adrenal adenoma was 4.8% and the prevalence of idiopathic primary aldosteronism was 6.4%. These results confirmed in a prospective, scientifically rigorous evaluation a now large body of evidence indicating a high prevalence of primary aldosteronism in general hypertensive cohorts.

Primary aldosteronism is especially common in patients with resistant hypertension. In an evaluation conducted at the University of Alabama at Birmingham, PA was diagnosed in 20% of consecutive patients referred for resistant hypertension (13). A similarly high occurrence of primary aldosteronism in patients with resistant or poorly controlled hypertension was observed in separate prospective investigations by investigators in Seattle, Washington (14); Oslo, Norway (15); and Prague, Czech Republic (16) suggesting that aldosterone excess commonly underlies resistance to antihypertensive treatment.

Recent study results suggest, at least in patients with resistant hypertension, that aldosterone also contributes to underlying hypertension beyond the approximately 20% of patients with classical primary aldosteronism. In a prospective evaluation of over 250 patients with resistant hypertension, we found that even the subgroup of patients with normal or low aldosterone

levels had evidence of greater intravascular fluid retention as evidenced by higher levels of both brain and atrial natriuretic peptide levels (Figure 2) (17). The role of aldosterone in contributing broadly to resistance to antihypertensive treatment is further supported by the antihypertensive benefit of spironolactone in treating resistant hypertension. We and others have found that spironolactone is widely effective in treating resistant hypertension and that the degree of antihypertensive benefit is similar in patients with and without demonstrable hyperaldosteronism (18). This broad benefit of spironolactone suggests that the role of aldosterone in causing hypertension in this group of patients is not limited to patients with obvious aldosterone excess.

Aldosterone and Cardiorenal Disease

A growing body of evidence links aldosterone excess to the development and progression of several cardiovascular disease processes separate from hypertension, including congestive heart failure, CKD, coronary artery disease, and stroke. In congestive heart failure, higher plasma aldosterone and angiotensin II levels predict increased mortality. Cross-sectional studies implicate aldosterone excess as a probable contributor to the development of CKD. In an evaluation of 2,700 participants in the Framingham Cohort Study, urinary sodium excretion was a strong positive predictor of urinary albumin excretion (19). In addition, the top quintile of serum aldosterone levels was associated with a 21% higher urinary albumin excretion than the lowest quintile. In a separate study, patients with confirmed primary aldosteronism had significantly higher urinary albumin excretion compared to subjects with primary hypertension (20). Other clinical studies have shown that chronic aldosterone excess is associated with increased left ventricular hypertrophy, greater diastolic dysfunction, exacerbation of endothelial dysfunction, and recently, increased risk of various components of the metabolic syndrome (21).

Consistent with these negative effects on cardiovascular risk factors, observational studies suggest that primary aldosteronism is associated with a rate of cardiovascular complications that seems to exceed that of primary hypertension. In one such comparison, patients diagnosed with primary aldosteronism were more than 4 times as likely to have had a stroke, 6.5 times as likely to have had a myocardial infarction, and more than 12 times as likely to have developed atrial fibrillation compared to general hypertensive patients matched as much as possible for duration and severity of hypertension (22).

Prospective studies likewise link aldosterone to worse outcomes while studies of aldosterone blockade demonstrate improvement in cardiovascular risk. Beygui and colleagues reported that plasma aldosterone levels drawn soon after admission predict cardiovascular morbidity and mortality and in patients presenting with acute ST elevation myocardial infarction (23). Patients in the highest quartile of plasma aldosterone level had a more than 2-fold increase in 6-month mortality compared to patients with lower aldosterone levels as well as significantly more post-infarction cardiovascular complications including ventricular fibrillation, resuscitated cardiac arrest, and new or worsening congestive heart failure.

Aldosterone antagonists, even when added to renin-angiotensin blockers, reduce proteinuria in patients with CKD (24). In heart failure, the RALES study indicated that addition of low-dose spironolactone to regimens that included in most patients an angiotensin converting enzyme (ACE) inhibitor significantly improved survival by 30% (25). In the EPHESUS trial, eplerenone added to an ACE inhibitor or angiotensin receptor blocker and beta-blocker improved survival by 31% in patients with left ventricular dysfunction following acute myocardial infarction (26). In showing benefit by directly blocking the mineralocorticoid receptor, these intervention studies lend support to the role of aldosterone in directly contributing to development and/or progression of cardiorenal disease.

Potential Mechanisms of Aldosterone-Induced End-Organ Damage

A large body of experimental evidence has demonstrated that aldosterone excess in combination with high dietary salt intake induces perivascular inflammation and fibrosis (27). These effects occur in multiple organs including the heart, kidney and brain. In addition, human studies suggest a variety of other effects presumed to negatively affect cardiovascular risk including suppression of nitric oxide activity, impairment of endothelial function and stimulation of thrombogenic pathways (28).

Aldosterone receptors are classically localized to the principal cells of the cortical collecting duct, colonic epithelia, and salivary glands (29). Aldosterone stimulates sodium reabsorption and potassium secretion via its binding to the intracellular mineralocorticoid receptor (MR). Aldosterone utilizes both short-term and delayed transcriptional effects to stimulate the activity and synthesis of the epithelial sodium channel (ENaC) and Na-K ATPase. The delayed stimulation of ENaC and the Na-K-ATPase is primarily due to nuclear translocation of the ligand-receptor complex and binding to co-regulators that stimulate gene transcription of ENaC (α subunit) and the Na-K ATPase. The MR may form homodimers with itself and heterodimers with the glucocorticoid receptor. Importantly, cortisol may also bind the MR with great avidity, however in “protected” sites, the presence of the cortisol degrading enzyme 11βHSD2 prevents cortisol activation of the MR. A variety of co-activators that bind to the MR in the presence of aldosterone have been identified, including p160 family coactivators, steroid receptor coactivator-1 (SRC-1), SRC-2, and SRC-3, activating signal cointegrator 2 (ASC2) and PPARγ coactivator-1α (PGC-1α) (30).

Aldosterone also stimulates ENaC activity via indirect effects, which occur before the direct transcriptional stimulation of ENaC (31). Aldosterone can stimulate rapid transcription of the serum- and glucocorticoid-induced kinase (SGK-1). SGK1 phosphorylates the ubiquitin-protein ligase Nedd4-2 at Serine 328 and Ser212. In the absence of serine phosphorylation by SGK1, Nedd4-2 interacts with ENaC and induced ubiquitination and degradation of ENaC. When SGK1 phosphorylates ENaC, Nedd4-2 binds to 14-3-3 proteins which interferes with its interaction with ENaC (32). Thus ENaC is then active for sodium transport. The increased sodium transport activity will lead to a net electronegative luminal voltage that drives H⁺ secretion or K⁺ secretion. Thus the classic pattern of hypertension (associated with increased sodium uptake), metabolic alkalosis (increased H⁺ secretion) and hypokalemia (increased K⁺ secretion) will result in patients with primary aldosteronism. Aldosterone in combination with salt loading can induce proteinuria, mesangial matrix accumulation and tubulointerstitial fibrosis (33). As noted above increased sodium reabsorption could exacerbate proteinuria. Chronic hypokalemia may also result in interstitial fibrosis, possibly due to stimulation of renin release and TGF-β production (34).

The MR has now been identified in a variety of other cell types such as cardiac and vascular smooth muscle cells, and has been shown to mediate other functions of the MR leading to inflammation, fibrosis and metabolic regulation in cardiac and vascular tissue (29). Recently, it has been found that glucocorticoids may regulate adipocyte differentiation via the MR in adipocytes. As adipocytes have low levels of 11βHSD2, the high levels of intracellular cortisol will not be degraded in adipocytes and can bind and activate the MR. Thus potentially, MR blockade may be beneficial in inhibiting adipocyte growth. The MR may mediate inflammation in multiple cell types via activation of NADPH oxidase (35).

Aldosterone receptors have also been found in podocyte, mesangial cells and fibroblasts (36). Via the MR, aldosterone has been found to stimulate reactive oxygen species production, TGF-β production and matrix synthesis in renal cells leading to direct effects to stimulate inflammation and fibrosis. Interestingly, a recent study suggests that there may be local

aldosterone production in the kidney itself as adrenalectomized rats may have low levels of circulating aldosterone that appears to be produced from the kidney and possibly other sites (37).

In recent studies, there appears to be a link between ENaC and the sodium retention noted with proteinuric and nephrotic states (38). Increased filtration of circulating plasminogen will enter the urine in states of heavy proteinuria. The plasminogen can be cleaved to plasmin in the urinary lumen via tubular urokinase-type plasminogen activator. The active plasmin is then free to cleave the luminal facing ENaC, thus activating it and allowing for excess sodium reabsorption. Although a luminal diuretic such as amiloride or triamterene may be the preferred way to block the enhanced ENaC activity, presumably aldosterone receptor blockade may also limit the degree of ENaC channels entering the lumen and be useful in proteinuric states.

Obesity and Aldosterone

The etiology of the apparent increase in aldosterone excess and its role in contributing to the development of hypertension over the last several decades remains unexplained.

Demonstration of this growing role of aldosterone in mediating hypertension and other cardiovascular complications has coincided with progressive increases in worldwide rates in obesity, suggesting a possible causative relation between increasing body weight and stimulation of aldosterone release. Population-based, observational studies suggest a correlation between obesity and aldosterone levels while experimental studies implicate adipocyte-related factors as possible stimuli of aldosterone release. If adiposity is confirmed to either directly or indirectly stimulate aldosterone release it would serve to mechanistically link obesity-related hypertension to excess aldosterone. This would represent an important clinical advance in explaining underlying mechanisms of obesity-induced hypertension and support preferential use of aldosterone antagonists to treat prehypertension and hypertension in obese patients.

A number of cross-sectional studies have demonstrated a significant relation between aldosterone levels and indices of obesity, including BMI and waist circumference. In one of the earliest studies linking aldosterone to obesity, Rocchini et al. evaluated 30 obese and 10 non-obese adolescents before and after weight-loss (39). The obese adolescents had significantly higher supine and 2-hour upright plasma aldosterone concentrations. Compared with an obese control group who had maintained their body weight, weight loss resulted in a significant decrease in plasma aldosterone without a decrease in PRA. In addition to weight loss being associated with a significant decrease in blood pressure, there was a significant correlation between the change in plasma aldosterone and the change in mean blood pressure. Although a small study, these findings were significant in demonstrating that obese adolescents have higher plasma aldosterone levels than non-obese, that the aldosterone decreased with weight loss seemingly independent of renin activity, and the decrease in aldosterone levels correlated with decreases in blood pressure. This supports obesity-related increases in blood pressure being attributable, at least in part, to excess aldosterone independent of renin-angiotensin stimulation.

In another early study, Goodfriend et al. measured visceral adipose tissue by CT scanning, total fat mass by dual energy X-ray absorptiometry, and plasma aldosterone levels in 28 normotensive women and 27 normotensive men (40). Plasma aldosterone in women correlated directly with visceral adipose tissue independent of PRA. There were no corresponding correlations in men. Seventeen women and 15 men completed a weight-reduction regimen, losing an average of 15.1±1.2 kg. After weight loss, plasma aldosterone was significantly lower; however, the correlations of aldosterone with visceral adipose tissue in women persisted. In the female subjects, blood pressure correlated with plasma aldosterone both before and after

weight loss. In a separate analysis of a largely male cohort, similar correlations were observed between aldosterone levels and measurements of visceral adipose tissue (41). These results link adiposity, particularly visceral adiposity, to aldosterone release which then relates to blood pressure levels.

In a cross-sectional analysis, Andronico et al. found that 39 severely obese subjects (mean BMI $47.8 \pm 1.4 \text{ kg/m}^2$) being screened for bariatric surgery had significantly higher plasma aldosterone levels and a higher mean aldosterone/PRA ratio than lean (mean BMI 24.1 ± 0.4) and mildly obese (mean BMI 31.5 ± 0.9) control subjects (42). PRA values were higher in the severely obese compared to mildly obese controls but not the lean controls, suggesting that the greater aldosterone levels were not attributable solely to renin-angiotensin activation.

As observed initially by Goodfriend et al., the positive relation between adiposity and aldosterone may be most consistent in women. In an evaluation of 109 hypertensive African-American subjects and 73 hypertensive white French Canadians, El-Gharbawy et al. found significant associations between aldosterone and obesity in women but not men (43). Specifically, among African-American women, supine plasma aldosterone was significantly correlated with BMI, body surface area, and hip circumference, but not with waist-to-hip ratio or percent body fat as determined from measurements of skinfold thickness. There were no significant correlations of plasma aldosterone with any of the anthropomorphic measurements in African-American men or in either French Canadian women or men.

A subsequent analysis was done by this same laboratory of 466 African-Americans that included an equal proportion of normotensive and hypertensive subjects (44). Overall, systolic blood pressure positively correlated with BMI and plasma aldosterone and inversely with PRA. Plasma aldosterone was significantly correlated with waist circumference but not BMI. Among hypertensive subjects, plasma aldosterone levels were significantly higher and PRA was significantly lower with increasing BMI strata. The authors concluded that their findings suggest that in African-Americans hypertension related to visceral obesity may be mediated by aldosterone.

Evaluation of 2 large, Italian cohorts have also reported that plasma aldosterone levels correlate with indices of adiposity. Mulè et al. prospectively evaluated 450 subjects referred to their hypertension center (45). Antihypertensive medications, if present, were withdrawn for 2 weeks prior to evaluation. By univariate analysis, plasma aldosterone was significantly correlated with both BMI and waist circumference. The correlations remained significant even after multivariate adjustments. In this same evaluation, plasma aldosterone levels were also positively correlated with 24-hr ambulatory systolic and diastolic blood pressure as well as indices of left ventricular mass as measured by echocardiography. Overall, these results suggest that obesity is associated with increased aldosterone levels, which may then independently contribute to higher blood pressure levels and greater left ventricular mass. These results are important in linking aldosterone to cardiovascular complications of obesity, specifically high blood pressure and left ventricular hypertrophy.

Evaluation of the PAPY cohort by Rossi et al. also indicated a significant correlation between plasma aldosterone and BMI (46). The analysis included the 1,125 subjects prospectively enrolled into the PAPY study, 999 of whom were diagnosed with primary hypertension and 126 with primary aldosteronism. Plasma aldosterone was positively correlated with BMI in the cohort of patients with primary hypertension, with the correlation being strongest in the most overweight subjects. Interestingly, in subjects with confirmed primary aldosteronism, plasma aldosterone levels were not correlated with BMI. These results suggest that in the absence of primary aldosteronism, that is in patients with presumed primary hypertension, obesity appears to be an important mediator of aldosterone secretion consistent with a

pathophysiological link between fat disposition and the synthesis and/or secretion of aldosterone. In patients with classical primary aldosteronism, this link is not evident, suggesting an autonomous release of aldosteronism independent of adiposity.

Consistent with observational studies linking aldosterone to obesity, weight loss studies support a mechanistic link between adipocytes and aldosterone release. In both the Rocchini (39) and Goodfriend (40) studies discussed above, weight loss was associated with significant decreases in plasma aldosterone levels. In the former study, the decrease in aldosterone was reported to occur independent of changes in PRA. Tuck et al. had likewise reported in an earlier study that successful weight loss by obese subjects is associated with significant decreases in plasma aldosterone levels (47). In this study, the decrease in aldosterone was also accompanied by significant decreases in PRA, suggesting that obesity may be associated with a generalized stimulation of the renin-angiotensin-aldosterone system. These results are consistent with 2 recent studies relating weight loss to reductions in renin-angiotensin-aldosterone activation. In the first, Engeli et al reported that an approximately 5% weight loss in obese women was associated with significant reductions in circulating angiotensinogen, renin, and aldosterone levels as well as significant reduction in angiotensinogen expression in adipose tissue biopsy samples (48). In the second study, Dall'Asta et al. found that weight loss following laparoscopic banding in severely obese subjects is associated with decreases in both plasma aldosterone levels and PRA (49). Overall, these studies, although individually small, provide interventional confirmation that obesity contributes to increased aldosterone release.

Recent studies of HIV-infected patients provide intriguing support that visceral adiposity contributes to hyperaldosteronism. HIV infection is sometimes associated with abnormal deposition of visceral fat. In one recent analysis, approximately 22% of HIV-infected subjects had significant abdominal lipohypertrophy (50). In a separate evaluation, Lo et al. found that HIV-infected women with increased visceral abdominal tissue had higher aldosterone levels compared to age- and BMI-matched healthy controls and HIV-infected women without visceral fat accumulation (51). In the HIV-infected patients with increased visceral fat accumulation, the 24-hr aldosterone secretion was positively correlated with BMI and the amount of visceral fat tissue. These results provide further support that excess abdominal adiposity contributes importantly to inappropriate secretion of aldosterone.

A positive correlation between aldosterone and adiposity has not been universally observed. In a very large and rigorous evaluation of 1,172 subjects in the United Kingdom, Alvarez-Madrado did not find that plasma aldosterone levels correlated with BMI (52). This was true of the entire cohort and also a smaller subgroup of subjects who were not receiving any antihypertensive medications. In fact, the aldosterone-renin ratio was negatively correlated with BMI, while the plasma renin concentration was positively correlated. Unlike the other studies discussed above, the authors did not find evidence that obesity was associated with increased aldosterone levels. At this point there is no obvious explanation for these negative results and the multiple positive results discussed above.

Obesity and Blood Pressure Response to Aldosterone Blockade

If obesity contributes to aldosterone excess, it would be anticipated that aldosterone antagonists would be more effective in lowering blood pressure in obese subjects than non-obese subjects. While there is little if any direct data assessing this possibility, preliminary data is emerging suggestive of a preferential benefit of aldosterone blockade in relation to adiposity. In a retrospective analysis of the blood pressure response of spironolactone in patients with CKD, Khosla et al. found that, the largest blood pressure response was observed in obese, African-American women (53). In a recent prospective assessment of the antihypertensive efficacy of

spironolactone in patients with resistant hypertension, de Souza et al., found that a higher waist circumference predicted a more favorable blood pressure response (54).

While these studies are provocative, well-designed clinical trials specifically evaluating the antihypertensive efficacy of aldosterone antagonists in obese patients are clearly needed to test for enhanced benefit. If such studies confirm that aldosterone antagonists are more effective in obese than non-obese patients, it would provide important supporting data for the role of adipose tissue in causing hyperaldosteronism and would provide rationale for preferential use of aldosterone antagonists in obese hypertensive and, perhaps, prehypertensive patients.

Potential Mechanisms of Adipocyte-Derived Hyperaldosteronism

Potential mechanisms by which adipocytes may contribute to excess aldosterone secretion include both generalized stimulation of the renin-angiotensin-aldosterone system and, separately, release from adipocytes of secretagogues specific for aldosterone. Adipocytes appear to have all the components of the renin-angiotensin system and thus may produce locally generated angiotensin II (55-57). As noted above, adipocytes may also produce aldosterone and thus may directly contribute to systemic aldosterone levels. A generalized stimulation of the renin-angiotensin-aldosterone system is supported by weight loss studies that demonstrate reductions in components of the pathway, including aldosterone (58). In addition to this generalized effect, a growing body of evidence suggests that adipocytes release factors, adipokines, may stimulate aldosterone release independent of renin-angiotensin (59).

Obesity is associated with increased oxidative stress and circulating levels of free fatty acids, of which, the most readily oxidized are the polyunsaturated acids, and in particular, linoleic acid, which may be the most abundant. Goodfriend et al. have shown that oxidized derivatives of linoleic acid stimulate release of aldosterone from isolated rat adrenal cells, with one specific derivative, 12,13-epoxy-9-keto-10(*trans*)-octadecenoic acid, being particularly potent (60). These studies suggest that in adipocytes release free fatty acids, that once oxidized in the liver, serve as potent stimuli of aldosteronogenesis independent of angiotensin II.

Ehrhart-Bornstein et al. have also provided evidence of adipocyte secretory products that directly stimulate adrenocortical aldosterone secretion. In their studies, placing human adrenocortical cells into medium exposed to isolated adipocytes resulted in a 7-fold increase in aldosterone secretion (61). This stimulatory effect was not blocked by valsartan, an angiotensin receptor blocker, indicating an effect independent of angiotensin II. Subsequent studies by this same laboratory has demonstrated that human adipocytes induce an ERK1/2 MAP kinases-mediated upregulation of steroidogenic acute regulatory protein (StAR) and an associated angiotensin II sensitization of human adrenocortical cells (62).

In an experiment with obese, diabetic rats, Jeon et al. demonstrated that complement-C1q TNF-related protein 1 (CTRP1), a member of the CTRP superfamily, may also function as a potent aldosterone-stimulating factor (59). The investigators reported that CTRP1, which is expressed at high levels in adipose tissue and in the zona glomerulosa of the adrenal cortex, the site of aldosterone production, induces a dose-dependent increase in aldosterone production and that angiotensin II-induced aldosterone release is mediated by stimulation of CTRP1 secretion. These pathophysiologic studies linking visceral adiposity to aldosterone secretion provide mechanistic support for the hypothesis that obesity contributes directly to inappropriate release of aldosterone, resulting in a state of relative aldosterone excess.

Conclusion

Both obesity and aldosterone excess are common. Observational studies indicate that indices of adiposity such as BMI, waist circumference, and visceral tissue correlate with aldosterone

levels. *In vitro* studies suggest that adipocytes release factors that stimulate aldosterone secretion independent of renin-angiotensin II. Together, these studies support the concept that obesity contributes to hyperaldosteronism. Aldosterone excess has been shown to contribute importantly to both the development and progression of cardiovascular disease, particularly hypertension. Therefore, confirming that obesity contributes to the development of hyperaldosteronism would have several important clinical implications. Firstly, it would implicate aldosterone as an important mediator of cardiovascular risk in obese patients. Secondly, it would support preferential use of aldosterone antagonists to treat hypertension in obese patients, and more broadly, to minimize risk of cardiovascular complications. At present there is convincing data that inhibitors of the aldosterone receptor or the aldosterone-stimulated ENaC channel is associated with impressive reductions in sodium retention and blood pressure in patients with obesity and proteinuria. Furthermore, patients with CKD and obesity may also have preferential benefits from inhibitors of the aldosterone receptor to block ongoing renal fibrosis. However, the relative benefit of aldosterone and ENaC blockers vs. inhibitors of the renin-angiotensin system (RAS) are unclear. Given the large amount of data supporting the cardio- and reno-protective effects of the RAS inhibitors, it is likely prudent to use the RAS inhibitors as first line agents and consider aldosterone blockers as second or third line agents, depending on the parameters of proteinuria, electrolyte levels, sodium retention, and underlying cardiovascular status. Before such use can be routinely recommended, outcome studies testing these proposed benefits are needed.

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Figure 1.

Rates of blood pressure progression and incident hypertension among nonhypertensive participants. Age- and sex-adjusted incidence rates of blood pressure progression (A) and incident hypertension (B) at a mean of 3 years are shown across tertiles of aldosterone (A1 to 3=first to third tertiles) and renin (R1 to 3=first to third tertiles). Graded, continuous increases in the risk of blood pressure progression and incident hypertension are found across increasing aldosterone and decreasing renin tertiles. Shaded and black error bars represent lower and upper 95% confidence bounds. Reprinted with permission from Newton-Cheh C, Guo C-Y, Gona P, et al. Clinical and genetic correlates of aldosterone-to-renin ratio and relations to blood pressure in a community sample. *Hypertension* 2007;49:846-856.

Figure 2.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) values in resistant hypertensive subjects and control (top panel). There was a significant incremental increase in ANP and BNP values between controls, resistant hypertensive subjects with normal- and high-aldosterone status (bottom panel). Adapted with permission from Gaddam KK, Nishizaka MK, Pratt-Ubunama MN, et al. Characterization of resistant hypertension: association between resistant hypertension, aldosterone, and persistent intravascular volume expansion. *Arch Intern Med* 2008;168:1159-1164.