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REVIEW

A critical review of the evidence supporting aldosterone in the etiology and its blockade in the treatment of obesity-associated hypertension

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Obesity is epidemic and is associated with increased blood pressure, which often manifests as treatment-resistant hypertension. Mineralocorticoids have been hypothesized to have a pathogenic role in human obesity-associated hypertension. In this review, we critically appraise the existing data regarding aldosterone in the pathophysiology and treatment of obesity-associated hypertension. We begin by reviewing the mechanisms by which obesity may increase mineralocorticoid activity. We then discuss human studies of plasma and urine aldosterone in obesity and with weight loss. From these studies, we conclude that aldosterone is often, but not always, mildly increased in obesity. Further study is needed to define circumstances in which aldosterone is increased in obesity. We discuss clinical studies in which measures of body size or weight were evaluated as potential predictors of response to mineralocorticoid receptor antagonists. In addition, we review three randomized, controlled clinical trials that exemplify a rigorous approach to determining the role of mineralocorticoid activity in a human disease. We propose that a similar clinical trial is warranted in order to definitively clarify the role of inappropriate mineralocorticoid activity in the etiology of human obesity-associated hypertension. Finally, we conclude that additional research is needed into the possible role of non-aldosterone mineralocorticoids in human obesity-associated hypertension.

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INTRODUCTION

Obesity is epidemic in many parts of the world. In 2009–2010, the age-adjusted prevalence of obesity in the United States was 35.5% among adult men and 35.8% among adult women.[1] In animal models[2] and humans,[3] obesity is associated with the development of hypertension. Data from the Framingham Study suggest that obesity is responsible for ~78% of hypertension in men and 64% of hypertension in women.[4] Moreover, in human clinical studies, weight loss lowers blood pressure (BP).[5] However, the mechanisms underlying human obesity-associated hypertension have not been completely elucidated. Thus, the optimal treatment for the often-resistant[6] hypertension caused by obesity is unknown. Among the leading hypotheses regarding the underlying mechanisms responsible for obesity-associated hypertension is the increased production of aldosterone and/or activation of the mineralocorticoid receptor by ligands other than aldosterone (that is, inappropriate mineralocorticoid hyperactivity). Increased mineralocorticoid activity in obesity-associated hypertension has been anticipated to have clinical implications,[6,7] but treatment of obesity-associated hypertension with mineralocorticoid antagonist therapy has not been tested in a clinical trial.

In this review, we briefly summarize the basic science data that suggest a role for increased mineralocorticoid activity in obesity. We then critically review the available human data bearing on increased aldosterone production as a mechanism of obesity-associated hypertension. Finally, we discuss three randomized controlled trials that provide a guide for studying an unanswered clinical question: 'Is mineralocorticoid receptor antagonist therapy more effective than other antihypertensive treatment in obesity-associated hypertension?'

MINERALOCORTICOID ACTIVITY IN OBESITY-ASSOCIATED HYPERTENSION

A recent review by Shibata and Itoh[8] provides details of the current theoretical framework surrounding mineralocorticoid activity in hypertension. We limit our review to mechanisms that would be expected to bear directly on obesity-associated hypertension. Based upon *in vitro* and animal models, several mechanisms have been proposed by which increased mineralocorticoid activity may contribute to human obesity-associated hypertension (Figure 1). Increased sympathetic nerve activity may drive the renin–angiotensin–aldosterone system in obesity. Adipocytes themselves may be responsible for the production of aldosterone in human obesity. Other ligands (potentially derived from adipocytes and/or indirectly increased by fat cells) may act as agonists of the mineralocorticoid receptor. Moreover, several studies have suggested that human adipocytes secrete factors that lead to the release of mineralocorticoids from the adrenal gland.

Increased sympathetic nerve activity in obesity

Muscle sympathetic nerve activity is increased in human visceral obesity.[9] Sympathetic nerve activity is thought to have a

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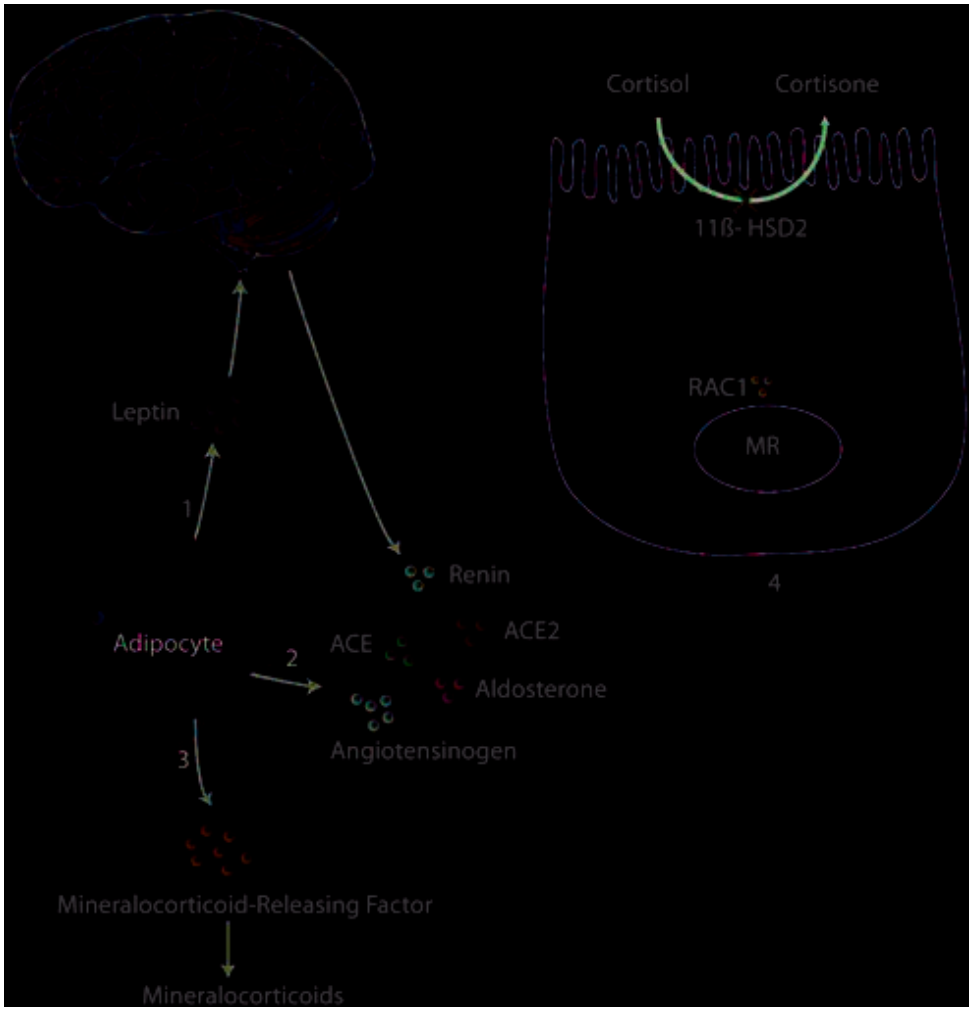

Figure 1. The figure illustrates various pathways hypothesized to link human obesity to hypertension. Factors such as leptin, free fatty acids and insulin, acting alone or together, increase central nervous system sympathetic nerve activity, which in turn increases renin secretion by beta-receptor activity in the juxtaglomerular apparatus (1). Visceral adipoctyes and/or peri-adventitial adipocytes directly release components of the renin–angiotensin–aldosterone system (2). One or more adipocyte-derived factors act on the adrenal glands to stimulate the release of mineralocorticoids (3). Molecules other than aldosterone, such as cortisol or RAC1, may activate the mineralocorticoid receptor in obese states. A decrease in 11-β hydroxysteroid dehydrogenase 2 activity or an overwhelming quantity of enzyme substrate may permit activation of the mineralocorticoid receptor by cortisol (4).

bidirectional relationship with the renin–angiotensin–aldosterone system. Sympathetic nerve activity stimulates renin release by the juxtaglomerular apparatus, and thereafter aldosterone may be increased by angiotensin II-mediated physiological pathways.

Intrinsic renin–angiotensin–aldosterone system in adipocytes

Subcutaneous, visceral and perivascular adipocytes have an intrinsic renin–angiotensin system. Angiotensinogen is expressed in periaortic adipose tissues in rats.[10] In mice with adipocyte-specific deficiency of angiotensinogen, plasma angiotensinogen and systolic BP are decreased.[11] In addition, adipocytes have been found to exhibit renin-like activity, converting angiotensinogen to angiotensin I.[12] Adipocytes express angiotensin-converting enzyme[13] and angiotensin-converting enzyme 2.[14] Moreover, human omental and subcutaneous adipose tissues express AT1 receptors,[15] and pre-adipocytes and adipocytes express AT2 receptors.[16,17] Renin receptors are expressed in visceral and subcutaneous human adipose tissue.[18] Human adipocytes also have been found to produce aldosterone.[19]

Activation of the mineralocorticoid receptor by molecules other than aldosterone

It is reasonable to speculate that there is clinically important activation of the mineralocorticoid receptor by mineralocorticoids other than aldosterone. Cortisol is found in much greater abundance in the circulation compared with aldosterone, and cortisol and aldosterone bind the mineralocorticoid receptor with equal affinity.[20] An enzyme expressed in epithelial tissues, 11-β hydroxysteroid dehydrogenase type 2 (11-β HSD2), converts cortisol to cortisone. Cortisone does not bind the mineralocorticoid receptor, and in this way specificity of binding is maintained by 11-β HSD2. Clinical conditions that decrease the expression or activity of 11-β HSD2 could result in activation of the mineralocorticoid receptor by cortisol. In conditions associated with very high levels of cortisol (e.g., Cushing syndrome and, more speculatively, severe obesity), the activity of this enzyme may be overwhelmed. Whether obesity decreases 11-β HSD2 activity is not well understood. Whether other mineralocorticoids, such as deoxycorticosterone, could be involved in obesity-associated hypertension is similarly poorly understood. Moreover, it has

been postulated that oxidative stress increases the sensitivity of the mineralocorticoid receptor through post-translational modification of the receptor.[8]

Alternatively, it is plausible the mineralocorticoid receptor is activated by molecules other than adrenal steroids in obesity-associated hypertension. Shibata *et al.*[21] demonstrated that RAC1, a small Rho family GTPase, activates mineralocorticoid receptor-dependent transcription in cell models and in a mouse model of Rho GDP-dissociation inhibitor-α deficiency. A RAC-specific small molecular inhibitor diminished the overactivation of the mineralocorticoid receptor in the mouse model. The same group demonstrated more recently that salt-loading Dahl salt-sensitive rats decreased aldosterone, but increased mineralocorticoid receptor activity. A RAC1 inhibitor diminished the effect of salt loading on BP and the kidney in this model of salt sensitivity.[22]

Adipocyte-derived mineralocorticoid-releasing factor

Isolated human adipocytes secrete a factor (or factors) capable of stimulating aldosterone release from cultured human adrenocortical cells.[23] This effect is not antagonized by the angiotensin type 1 receptor antagonist valsartan, and it is therefore not dependent upon adipose-derived angiotensin II. Complement-C1q TNF (tumor necrosis factor)-related protein 1 (CTRP1) increases aldosterone production in cultured human adrenal cortical cells, and serum CTRP1 expression was higher in a small number of hypertensive patients compared with healthy volunteers.[24] Whether a mineralocorticoid-releasing factor is involved in obesity-associated hypertension is unknown.

In summary, a variety of mechanisms that could lead to mineralocorticoid receptor activation in obesity have been demonstrated in cell and animal models. Rigorous *in vivo* human data to support specific mechanisms are unavailable, and the clinical importance of each of these mechanisms in human obesity-associated hypertension remains unknown.

PLASMA AND URINE ALDOSTERONE IN HUMAN OBESITY

As described above, there may be multiple pathways to the activation of the mineralocorticoid receptor, including some aldosterone-independent pathways. It would be very challenging to directly measure mineralocorticoid receptor activation in humans. However, a large body of literature describes aldosterone concentrations in human plasma and urine. A subset of these studies has measured aldosterone concentrations in obese patients.

In some contexts, plasma or urine aldosterone concentration has been found to be elevated in human obesity or has been found to decrease with weight loss. Studies reporting an association between various measures of obesity or adiposity and renin–angiotensin–aldosterone system activation are summarized in Table 1.

Although the studies summarized above and in Table 1, taken together, suggest an increased level of circulating aldosterone in obesity, the results from a recent study challenge this concept. In nearly 2000 members of the Framingham cohort across a wide range of body mass indices (BMIs), there was no significant association observed between measures of subcutaneous or visceral adiposity and plasma renin activity, plasma aldosterone concentration (PAC) or aldosterone-to-renin ratio (ARR). In a subset analysis of the 409 obese participants, there was no association between adiposity and plasma renin activity, PAC or ARR.[25] In other studies, the association was limited to a subset of obese patients. For example, Goodfriend[26] reported a strong association between obesity and PAC in women ($r = 0.66$, $P < 0.001$), but found no such association in men. In a different cohort, the same investigators found a correlation between these measures in men, as well.[27] Bentley-Lewis *et al.*[28] reported increased urine aldosterone in obese compared with lean subjects, but found no difference in basal PAC. Response to angiotensin II stimulation was stronger in obese subjects. Moreover, in a more recent study, only the most obese patients (BMI $> 35\,kg\,m^{-2}$) were found to have a higher PAC compared with non-obese patients.[29] It is plausible, then, that a nonlinear relationship between body weight and PAC has contributed to inconsistent findings in prior studies. For example, in the Framingham Cohort Study, the mean BMI was $26.6\,kg\,m^{-2}$, suggesting that the participants were too lean for the association to be detected.

Other limitations of the existing human studies of mineralocorticoid activity in obesity should be noted. It is reasonable to speculate that there is differential release of aldosterone by subtypes of adipocytes (that is, more release from visceral versus subcutaneous cells). More detailed metrics of fat distribution may permit superior estimates of the association between obesity and circulating aldosterone. Moreover, the validity of using urinary aldosterone as a surrogate for whole-body (or more importantly organ-specific) mineralocorticoid activity is not well established. It is plausible that patients with mineralocorticoid hyperactivity in specific organs (for example, heart or kidney) have normal plasma or urine aldosterone concentration. Imprecision of the assays for plasma and urine aldosterone also may limit the power to observe an association in smaller studies. In summary, the hypothesized dysregulation of aldosterone in human obesity appears to have some support from available studies; however, due to inconsistencies and limitations it remains a subject for further careful study. In particular, factors that modify the relationship between obesity and aldosterone production, and the possible nonlinearity of this relationship, as well as the impact of obesity subtypes (for example, fat distribution) merit additional investigation.

OBESITY AS A PREDICTOR OF RESPONSE TO MINERALOCORTICOID RECEPTOR ANTAGONISTS

Saha *et al.*[30] conducted a randomized, placebo-controlled, double-blind trial of amiloride, spironolactone, the combination, or placebo in 98 black hypertensive patients. The study participants had an elevated BP despite treatment that included a diuretic and a calcium channel blocker. Whereas both amiloride and spironolactone significantly reduced systolic BP, BMI did not predict response to treatment.

Chapman *et al.*[31] studied the addition of spironolactone, mostly as a fourth-line antihypertensive agent, in Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) participants. The study drugs to which participants were randomized in ASCOT did not include spironolactone. However, nonstudy drugs could be added by the investigators if the target BP ($< 140/90$ mm Hg or $< 130/80$ mm Hg in those with diabetes) could not be reached with the study drugs. The 1411 study participants in the retrospective analysis done by Chapman *et al.*[31] were a subset of participants treated with spironolactone (median dose 50 mg). The analysis included only those patients to whom spironolactone was prescribed for BP control and for whom BP data were available from before and during spironolactone treatment. Baseline weight and BMI did not predict response to spironolactone, nor did change in weight or BMI during the study.

Calhoun and White[32] conducted an open-label study of eplerenone (50–100 mg per day) in 52 resistant hypertension patients. Nine of these patients required reductions in their other antihypertensive drugs because of low clinic systolic BPs (< 110 mm Hg). BMI did not predict which patients would exhibit this robust response to eplerenone.

De Souza *et al.*[33] conducted an open-label study, in which the investigators added spironolactone to the regimen of 175 patients with resistant hypertension. BP was assessed by ambulatory BP monitoring before and during treatment with spironolactone.

Table 1. Evidence for and against mineralocorticoid dysregulation in human obesity

Study	Subject	BMI ($kg\,m^{-2}$)	Results
Cross-sectional studies			
Hiramatsu *et al.*[34]	961 Normotensive and hypertensive adults	Not provided	No difference in PAC, but decrease in PRA with increasing relative body weight
Andronico *et al.*[35]	39 Severely obese normotensives, 57 other hypertensives	Severely obese normotensives 47.8, hypertensives 28.0	PRA and PAC higher in severely obese normotensives compared with hypertensive subjects
Vasan *et al.*[36]	1688 Nonhypertensives, 58% female	28.1 Men, 26.2 women	BMI did not modify the effect of PAC on blood pressure (i.e., no statistical interaction between BMI and PAC)
Bochud *et al.*[37]	160 Men, 196 women	26.0 Without MS, 31.2 with MS	PAC increased with waist circumference (linear trend) only in men
Fallo *et al.*[38]	381 EH patients (also examined PA patients)	25.8 Without MS, 30.1 with MS	PAC not different in EH patients with and without MS
Bentley-Lewis *et al.*[28]	63 lean (BMI $<25\,kg\,m^{-2}$), 57 overweight (BMI $>25\,kg\,m^{-2}$), all normotensive	29.0 Obese, 22.9 lean	24-h urine aldosterone higher in obese versus lean subjects. Basal PAC, PRA, serum K+ not different in lean versus obese subjects. Higher angII-stimulated aldosterone release in obese subjects
Kidambi *et al.*[39]	215 Normotensive, 182 hypertensive blacks	Normotensive 27.8, hypertensive 29.6	After adjusting for age and gender, PAC correlated with waist circumference, BMI, and waist-to-height ratio
Mulè *et al.*[40]	249 Without MS, 201 with MS; all hypertensive	Without MS 26.4, with MS 30.9	Weak, highly statistically significant correlation between BMI ($r=0.17$)/waist circumference ($r=0.18$) and PAC in the overall population
Rossi *et al.*[41]	Overweight-obese HTN patients: PH 636 APA 37 IHA 58 394 lean hypertensive patients were also studied	27.4 For EH, 27.4 for APA, 26.9 for IHA	No correlation between PAC and BMI in lean HTN patients irrespective of etiology. No correlation between PAC and BMI in obese hypertensive patients with PA. $r=0.18$, $P<0.0001$ in overweight or obese hypertensive primary hypertension patients. No correlation between BMI and ARR
O'Seaghdha *et al.*[25]	992 Women, 897 men (Framingham cohort)	Mean BMI 26.6	No association between subcutaneous or visceral adiposity and PRA, PAC or ARR
Sarzani *et al.*[29]	295 Consecutive EH patients with uncontrolled BP	Men 30.9, women 32.6	No difference in PAC in non-obese versus class 1 obese patients. Higher mean PAC levels in class 2 and 3 obese patients compared with non-obese

Study	Subject	BMI ($kg\,m^{-2}$)	ΔBMI ($kg\,m^{-2}$)	ΔWeight (kg)	Intervention	Results
Weight loss intervention studies						
Tuck *et al.*[42]	25, All obese	Not provided	Not provided	−20.2 In both low-salt and high-salt groups	12 Weeks of 320 kcal per day diet	PRA and PAC declined with weight loss in high- and low-salt groups. Decrease in PRA, but not PAC correlated with weight loss
Rocchini *et al.*[43]	30 Non-obese, 10 obese adolescents	Not provided	Not provided	−2.5 (diet), −2 (diet + exer)	1500–1800 kcal diet ± exer for 20 weeks	PAC 17 versus 2 ng ml^{-1} in obese versus lean, decreased PAC with weight loss
Rocchini *et al.*[44]	60 Obese, 18 non-obese adolescents	Not provided	Not provided	Not provided in kg	20 Weeks of modified caloric exchange diet, details not provided. High-salt and low-salt diets studied	Higher PAC in obese versus lean adolescents, 'Significant' decrease in PAC, no decrease in PRA
Goodfriend *et al.*[26]	28 Premenopausal women, 27 men, all normotensive 17 women and 15 men, all obese, underwent weight loss	Lean women 22.9, obese women 33.5, Lean men 24.0, obese men 34.3	Not provided	12.2 for women, 14.5 for men	12 weeks of 800 kcal per day diet followed by 4 weeks of gradual increase to a maintenance diet	PAC higher in obese versus lean women, but not in obese versus lean men. $r=0.66$, $P<0.001$ for correlation between VAT and PAC in women. No correlation between PAC and any index of obesity in men. Obese men and women had higher PRA than lean and women. No correlation between PRA and PAC
Engeli *et al.*[45]	19 Obese women, 19 lean women for the observational portion; 17 women successfully lost >5% body weight during the weight loss intervention	Lean 23.5, obese 37.6	Not provided	Not provided	Intake reduced by 600 kcal per day combined with water gymnastics. Mean duration of intervention 13 weeks	Obese women had higher pAGT, renin (direct assay), PAC, and ACE and lower angiotensinogen expression in adipose tissue compared with lean women. PAC decreased with weight loss
Dall'Asta *et al.*[46]	Morbidly obese patients; 40 with HTN, 55 without	HTN: basal 44.7, normotensive: 44.0	HTN: −6.3, normotensive: −8.2	Not provided in kg	Before and 1 year after LAGB; a diet with increasing calories is described, but the timing is not discussed	BP, PRA and PAC decreased after weight loss

Abbreviations: ACE, angiotensin-converting enzyme; angII, angiotensin II; APA, aldosterone-producing adenoma; BMI, body mass index; BP, blood pressure; EH, essential hypertension; exer, exercise; F/E ratio, cortisol-to-cortisone ratio; HTN, hypertension; IHA, idiopathic hyperplasia of the adrenals; kcal, kilocalories; LAGB, laparoscopic-adjustable gastric banding; MS, metabolic syndrome; PA, primary aldosteronism; PAC, plasma aldosterone concentration; pAGT, plasma angiotensinogen; PRA, plasma renin activity; VAT, visceral adipose tissue

Twenty-four-hour systolic and diastolic BPs by ambulatory BP monitoring were 16 and 9 mm Hg lower, respectively, during spironolactone treatment. Waist circumference was marginally statistically significantly higher in those with a >10% systolic BP response compared with those who did not respond as robustly.

In summary, clinical studies have examined the relationship between body weight or size and responsiveness to mineralocorticoid receptor. These studies have differed in their design, including the metrics of body weight or size used, and the findings have not been identical. A randomized clinical trial mineralocorticoid receptor antagonists in obesity-associated hypertension is warranted.

ADDITIONAL CLINICAL PERSPECTIVES

An important clinical question is whether mineralocorticoid receptor antagonists have superior efficacy compared with other BP-lowering agents (in particular thiazide diuretics) in the treatment of obesity-associated hypertension. We are not aware of any clinical trial that has specifically been designed to address this question in obese humans. The findings from germane studies and retrospective analyses regarding the efficacy of mineralocorticoid blockade in human obesity are provided in Table 2. In addition, we discuss in the following section three relevant randomized clinical trials, although they did not specifically test this hypothesis.

The RENALDO trial was a randomized crossover trial, which compared spironolactone to bendroflumethiazide for BP-lowering efficacy. The investigators also evaluated whether the ARR predicts response to spironolactone. Of the 111 participants, 60 had a high ARR (ARR $>750\,\text{pmol l}^{-1}$ per $\text{ng ml}^{-1}\,\text{h}^{-1}$ and PAC $>250\,\text{pmol l}^{-1}$), and 51 had a low ARR ($<300\,\text{pmol l}^{-1}$ per $\text{ng ml}^{-1}\,\text{h}^{-1}$ and plasma renin activity $<10\,\text{ng ml}^{-1}\,\text{h}^{-1}$). At the doses used (50 mg spironolactone versus 2.5 mg bendroflumethiazide), spironolactone was more effective at reducing mean 24-h ambulatory systolic BP, irrespective of whether the ARR was high or low.

Results from the placebo-controlled, double-blind randomized crossover SALT trial provide some particularly germane information. Hood *et al.*[47] studied patients with normal potassium and an elevated ARR for their response to spironolactone versus bendroflumethiazide. Spironolactone 100 mg and bendroflumethiazide 5 mg caused similar reduction in systolic BP, and once again, 2.5 mg of bendroflumethiazide was less effective than 50 mg of spironolactone. The authors concluded that their findings argue against a large, undiagnosed group of primary aldosteronism among patients with low-renin hypertension. The investigators suggested that thiazide-like diuretics were just as effective (when dosed properly) as specific mineralocorticoid blockade, and thus low-renin hypertension states do not represent occult primary aldosteronism in the usual clinical scenario. However, since spironolactone was the more effective natriuretic drug (with greater increase in plasma urea, and greater reduction in plasma sodium and atrial natriuretic peptide), inappropriate aldosterone may still have an important role in low-renin hypertension.

In the double-blind, placebo-controlled multicenter ASPIRANT trial, Vaclavík *et al.*[48] studied 117 resistant hypertension patients who were randomly assigned to spironolactone or placebo as an add-on therapy. They found that the difference in mean fall of systolic BP on daytime ambulatory BP monitoring was significantly greater in the spironolactone-treated patients compared with placebo-treated patients. In contrast to the RENALDO trial findings, the baseline ARR predicted response to spironolactone. The study demonstrated the efficacy and safety of treating resistant hypertension patients with spironolactone as an add-on therapy. Although each of these studies represents a highly significant achievement toward understanding the role of mineralocorticoids in human hypertension, none addresses obesity-associated hypertension specifically.

CONCLUSIONS

Obesity is a well-known cause of human hypertension, and hypertension associated with obesity is often more resistant to treatment compared with lean essential hypertension. Our summary of the available studies suggests there is biologically plausible evidence to support increased mineralocorticoid activity as an etiologic factor in obesity-associated hypertension. However, obesity-associated hypertension (like other causes of high BP) likely has a degree of heterogeneity in its underlying

Table 2. Evidence bearing on the effectiveness of mineralocorticoid antagonism in human obesity-associated hypertension

Study	*Subject*	*Mineralocorticoid receptor antagonist*	*Findings*
RCTs			
Saha *et al.*[30]	98 Subjects with elevated BP during treatment with diuretic and CCB	Spironolactone (±amiloride) or placebo (double-blind)	BMI did not predict BP reduction in these patients (mean BMI $\sim 34\,\text{kg m}^{-2}$)
Non-randomized clinical trials			
Calhoun and White[32]	52 Men and women with uncontrolled resistant HTN	Eplerenone (50–100 mg per day)	BMI did not predict which patients' SBP would decrease below 110 mm Hg
de Souza *et al.*[33]	175 Patients with resistant HTN	Spironolactone (25–100 mg per day)	Higher waist circumference was associated with better response. PAC and ARR did not predict response
Retrospective/observational			
Nishizaka *et al.*[49]	76 Subjects, of which 34 had PA	Spironolactone (12.5–25 mg per day)	No correlation between degree of BP reduction and PAC, PRA, PAC-to-PRA ratio or UAldo
Chapman *et al.*[31]	1411 Subjects treated with spironolactone in ASCOT	Spironolactone	BMI and baseline weight did not predict decrease in SBP, nor did changes in weight or BMI during the study
Heshka *et al.*[50]	88 Patients with 'difficult-to-control' BP, with or without CKD	Spironolactone, 93% of patients started on 25 mg or less	Greater response in patients with higher starting BP and in patients with higher BMI (multivariable analysis)

Abbreviations: ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; CKD, chronic kidney disease; PAC, plasma aldosterone concentration; PRA, plasma renin activity; SBP, systolic blood pressure; RCTs, randomized clinical trials; UAldo, urinary aldosterone concentration.

pathobiology. It is therefore not surprising that not all studies are positive. It is likely that mineralocorticoids have a role in only certain clinical settings or in a subset of individuals with obesity-associated hypertension. More research is needed to clarify this issue.

Finally, our review suggests that it is reasonable to hypothesize that mineralocorticoid receptor antagonism is more effective than other antihypertensive drugs among obese hypertensive patients. However, the available studies do not provide conclusive evidence in this regard. A carefully conducted randomized, controlled study of mineralocorticoid receptor antagonism versus appropriate active therapy conducted specifically in obese hypertensive patients is warranted in order to reach definitive conclusions about the relative efficacy of mineralocorticoid receptor blockade in the management of obesity-associated hypertension.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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