Drug Mechanisms to Help in Managing Resistant Hypertension in Obesity

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Abstract Obesity is a major risk factor for the development of hypertension. Because the prevalence of obesity is increasing worldwide, the prevalence of obesity hypertension is also increasing. Importantly, hypertension in obesity is commonly complicated by dyslipidemia and type 2 diabetes mellitus and hence imposes a high cardiovascular disease risk. Furthermore, obesity is strongly associated with resistant hypertension. Activation of the sympathetic nervous system and the renin-angiotensin system, leading to renal sodium and water retention, links obesity with hypertension. There is also evidence for the release of factors by visceral adipose tissue promoting excessive aldosterone production, and a more central role of aldosterone in obesity hypertension is emerging. Randomized studies evaluating the effect of different classes of antihypertensive agents in obesity hypertension are scarce, short-lasting, and small. Considering the emerging role of aldosterone in the pathogenesis of obesity hypertension, mineralocorticoid receptor antagonism may play a more central role in the pharmacologic treatment of obesity hypertension in the near future.

Keywords Obesity · Hypertension · Aldosterone · Sympathetic nervous system · Renin-angiotensin system · Antihypertensive therapy · Mineralocorticoid receptor antagonism

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Introduction

Obesity, and especially central obesity, is one of the most common risk factors for the development of hypertension. Population studies indicate that two thirds of the prevalence of hypertension can be attributed to overweight or obesity [1]. In the National Health and Examination Survey (NHANES) III, the prevalence of hypertension according to body mass index (BMI) and adjusted for age was about 14% in participants with a BMI less than 25 kg/m^2 versus about 40% in participants with a BMI greater than 30 kg/m^2 [2]. Obesity hypertension is commonly accompanied by type 2 diabetes mellitus and dyslipidemia [3]. Furthermore, obesity hypertension is associated with increased risks for left ventricular hypertrophy, microalbuminuria, and renal hyperfiltration. Over time, the latter two factors predispose to impairment of renal function that may further aggravate hypertension [3].

Obesity is also the most important risk factor for the syndrome of obstructive sleep apnea (OSA); apart from obesity itself, OSA also can contribute to the development and maintenance of hypertension [4]. Finally, obesity and OSA are well-recognized patient characteristics that, along with older age, a higher baseline systolic blood pressure, and left ventricular hypertrophy, are associated with treatment-resistant hypertension [5, 6].

Obesity Hypertension: The Underlying Mechanism

Obesity hypertension is a complex condition and, as is true for hypertension in general, impaired pressure natriuresis is a key etiologic factor [7] (Fig. 1). The renal sodium retention in obesity hypertension occurs despite an increase in glomerular filtration rate, indicating increased renal

Fig. 1 Mechanisms linking obesity with hypertension
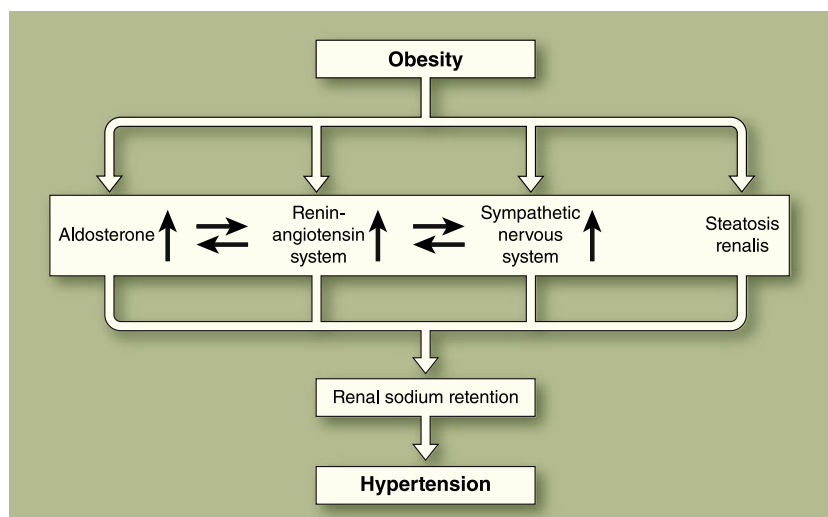
fractional tubular sodium reabsorption [8]. Driving forces for this sodium retention are an increase in renal sympathetic tone and activation of the renin-angiotensin system (RAS). Moreover, renal medullary compression by excessive adipose tissue, for which we propose the term *steatosis renalis* (analogous to steatosis hepatis), may also account for avid sodium retention [8]. Although renal plasma flow and glomerular filtration rate are increased in the initial phase of obesity hypertension to cope with the increased metabolic demands, glomerular injury contributing to the maintenance of hypertension is a feared complication in the long run [9].

Evidence that these mechanisms are involved in obesity hypertension comes mainly from experimental studies. Thus the development of obesity-induced hypertension in dogs exposed to a high-fat diet could be prevented by renal denervation and by agents that interfere with the renin-angiotensin system [10, 11]. Moreover, in a small clinical study, combined alpha-adrenergic and beta-adrenergic receptor blockade induced a greater reduction in blood pressure in obese than in lean hypertensive patients [12].

Obesity and Resistant Hypertension: The Emerging Role of Aldosterone

Resistant hypertension is defined as blood pressure that remains above the target value in spite of the concurrent use of three antihypertensive agents of different classes. Ideally, one of the three classes should be a diuretic and all agents should be prescribed at optimal doses [13]. The prevalence of resistant hypertension is unknown. In an analysis of NHANES III, only 53% of the population being treated for hypertension were controlled to a blood pressure less than 140/90 mm Hg [14]. Blood pressure remains uncontrolled

most often because of persistent elevation of systolic blood pressure. Patient characteristics associated with resistant hypertension are older age, obesity, the presence of left ventricular hypertrophy, and chronic kidney disease [5, 6, 15]. In a large cross-sectional study of 45,125 primary care patients, those with a BMI of 40 kg/m^2 or higher not only had a higher prevalence of hypertension, but also had a 5.3-fold higher probability of requiring four antihypertensive agents to achieve blood pressure control, compared with normal-weight patients, and they had a 3.2-fold probability of requiring three agents [16]. Studies performed in patients with resistant hypertension showed that the prevalence of primary aldosteronism (PA) is 17% to 22% [17, 18]. Patients with resistant hypertension without PA had higher plasma aldosterone levels and urinary aldosterone excretion rates and a larger intravascular volume than normotensive individuals [19]. The role of aldosterone in the metabolic syndrome has emerged more recently. In the Framingham offspring study, higher aldosterone levels were predictive for the development of the metabolic syndrome [20]. In blacks, plasma aldosterone, but not plasma renin activity, was higher in individuals with the metabolic syndrome than in those without, and a significant association between waist circumference and plasma aldosterone concentration could be established [21]. Moreover, weight reduction in obese individuals results in a decrease in plasma aldosterone concentration, providing further evidence for a stimulating effect of adipose tissue on adrenal aldosterone production [22, 23]. Although several mechanisms may underlie these higher aldosterone concentrations, one possibility is that it relates to the secretion of a mineralocorticoid-releasing factor by adipocytes [24, 25••]. This idea is of interest, given the concept of angiotensinogen release from adipose tissue and the documented synergistic action between aldosterone and angiotensin II [26–28].

The beneficial effect of low-dose spironolactone added to combinations of first-line antihypertensive agents in patients with resistant hypertension has been shown in several studies [29, 30•, 31–34]. As shown in Table 1, almost all patients included in these studies were overweight (BMI, 25–30 kg/m^2) or obese (BMI >30 kg/m^2). Based on the findings of these studies and the knowledge that plasma aldosterone is increased in obesity, aldosterone receptor antagonism seems a logical therapeutic option in obesity hypertension.

Randomized Trials with Antihypertensive Agents in Obesity Hypertension

Although obesity-associated hypertension is a highly prevalent condition, randomized studies evaluating the effect of specific classes of antihypertensive agents in this condition are scarce, small, and of short duration. Most of these studies investigated not only blood pressure reduction but also the occurrence of potential adverse metabolic effects. The Treatment in Obese Patients With Hypertension (TROPHY) trial is the first randomized, double-blind, placebo-controlled trial comparing the effects of the angiotensin-converting enzyme (ACE) inhibitor lisinopril (maximal dose, 40 mg once daily) with hydrochlorothiazide (HCT, maximal dose 50 mg once daily) in obesity hypertension [35]. In total, 232 patients (mean age, 52 years) with a mean BMI of 32 kg/m^2 were enrolled. Study medication was given for 12 weeks. At the end of the study, office and ambulatory blood pressures were reduced to a similar extent with both regimens, but the response rate was not higher than 40% in the lisinopril group and 33% in the HCT group, in accordance with the knowledge that a combination of different antihypertensive agents is almost always required for blood pressure control. Although neither treatment significantly affected serum insulin or lipid concentrations, glucose increased modestly with HCT compared

with lisinopril (difference, 0.5 mmol/L). On the basis of these findings, the authors concluded that a rational monotherapy approach for initial treatment of obese patients with hypertension may include an ACE inhibitor or a diuretic.

The CROSS study (Candesartan Role on Obesity and on Sympathetic System) was published in 2003 [36]. In this study, which enrolled 127 patients with an average BMI of 33 kg/m^2, the effect of candesartan (8–16 mg daily) was compared with HCT (25–50 mg daily) using a parallel-group, double-blind study design. Study medication was given for 12 weeks. Blood pressure reduction with both regimens was identical, with blood pressure normalization in about 80% of patients. Compared with HCT, candesartan was associated with improved insulin sensitivity and modestly lower muscle sympathetic nerve activity. (It should be remarked that these two measurements were performed in only a small fraction of the patients.)

In a third study the effects of valsartan, 160 mg daily, were compared with those of atenolol, 100 mg daily, in a double-blind, parallel-group study that included 132 patients with an average BMI of 33 kg/m^2 and a waist circumference of 110 cm [37]. Study medication was given for 12 weeks. If blood pressure was not normalized after 4 weeks monotherapy with valsartan or atenolol, HCT (12.5–25 mg daily) could be added. An interesting and unanticipated finding of this study was that the diastolic blood pressure reduction was greater with monotherapy atenolol than with valsartan. HCT was added to 49% of the patients allocated to atenolol, compared with 70% of the patients allocated to valsartan. At the end of the treatment period, blood pressure reduction with the two regimens was identical. No difference in serum lipids between the two regimens was observed, whereas in the atenolol group the homeostasis model assessment (HOMA) insulin index slightly worsened in insulin-sensitive patients but not in insulin-resistant patients. The authors concluded that beta-adrenoceptor blockers and angiotensin II type 1 (AT$_1$) receptor blockers, particularly in combination with low-dose

Table 1 Summary of studies evaluating the effect of add-on spironolactone treatment in uncontrolled or resistant hypertension

Study	Design	N	BW, kg	BMI, kg/m^2	Waist circumference, cm	Antihypertensives, n	Spironolactone dose, mg/day	BP reduction, mm Hg
Ouzan et al. [32]	Uncontrolled	25	NA	NA	NA	3.2	1 mg/kg	24/10
Saha et al. [33]	Placebo-controlled	23 (spironolactone)	NA	32.0	NA	2	25	5/2
		27 (placebo)	NA	35.7	NA	2	–	–
Sharabi et al. [34]	Uncontrolled	42	NA	30.6	NA	≥2	12.5–25	23.2/12.5
Lane et al. [31]	Uncontrolled	119	86.7	NA	NA	3.7	25–100	21.7/8.5
Chapman et al. [29]	Uncontrolled	1411		29.4	NA	≥3	25–50	21.9/9.5
de Souza et al. [30•]	Uncontrolled	175		30.2	100	≥3	25–100	14/7

BMI body mass index, *BW* body weight, *NA* not available

diuretics, effectively lower blood pressure in obese patients, but that AT_1-receptor blockers may be preferred because of the high diabetes risk in obesity.

In a more recent study, the direct renin inhibitor aliskiren has been compared with irbesartan and amlodipine in a placebo-controlled trial in obese hypertensive patients in whom blood pressure was still elevated after HCT monotherapy for 4 weeks [38]. A total of 489 patients with an average BMI of about 34 kg/m^2 were included. The mean reduction in blood pressure in the three active groups was identical. Rates of blood pressure control were 34% in the HCT group, 57% in the aliskiren/HCT group, 55% in the irbesartan/HCT group, and 45% in the amlodipine/HCT group. Adverse effects, mainly due to a higher incidence of peripheral edema, were highest in the amlodipine/HCT group.

Although these studies were not performed in patients with resistant hypertension, they all demonstrate that obesity hypertension responds to a variety of antihypertensive agents. As known from many studies in high-risk populations, the incidence of new-onset diabetes mellitus is increased with the use of beta-blockers and thiazide diuretics, compared with other antihypertensive agents [39]. Recently, it was shown that adverse metabolic effects, including new-onset diabetes, already occurred after short-term (9–18 weeks) exposure to atenolol, HCT, or their combination and that this effect was more common in patients with abdominal obesity [40]. Because the treatment of hypertension usually requires lifelong therapy and the likelihood of developing adverse metabolic effects increases with increasing exposure duration, not only the blood pressure lowering properties but also the anticipated adverse metabolic effects should be considered when these agents are prescribed.

Mineralocorticoid Receptor Antagonism in Obesity Hypertension

In our view, the accumulating evidence of the role of aldosterone excess in the pathogenesis of obesity hypertension and the knowledge that mineralocorticoid receptor blockers promote additional blood pressure reduction in patients with resistant or difficult-to-control hypertension provide a firm basis for a more liberal use of spironolactone (or its more selective counterpart, eplerenone) in obesity hypertension. In this regard it should be noted that, in the reported studies on the additional effect of spironolactone in uncontrolled or resistant hypertension, BMI was 30 kg/m^2 or higher in most of the populations studied (Table 1). Furthermore, a recent prospective study performed in patients with true resistant hypertension who had an average BMI of 30 kg/m^2 and waist circumference of 100 cm showed in a multivariate regression analysis that a higher waist circumference and an increased pulse wave

velocity were the two independent variables that predicted the systolic blood pressure response to spironolactone [30•].

Lifestyle Modification and Interaction with Antihypertensive Regimens

Without doubt, weight loss and reduction of dietary sodium intake, although not specifically evaluated in patients with resistant obesity hypertension, have a clear benefit in reducing blood pressure and often allow a reduction in the number of prescribed medications [41, 42••]. A meta-analysis of long-term weight loss studies indicates that a 10-kg weight loss is associated with a blood pressure reduction of 6.0 mm Hg systolic and 4.6 mm Hg diastolic [43]. Therefore, weight reduction and maintenance of weight loss are important steps in managing obesity hypertension. Unfortunately, nonpharmacologic approaches aimed at reducing body weight have limited sustainability in most patients, and adjuvant pharmacotherapy may be necessary for effective weight reduction and its maintenance [44].

The effectiveness of drug-based weight loss with sibutramine on the basis of different antihypertensive regimens was addressed in the Hypertension-Obesity-Sibutramine (HOS) study [45]. In this prospective, double-blind, placebo-controlled study, 171 patients receiving one of three antihypertensive combination therapies (felodipine plus ramipril, verapamil plus trandolapril, or metoprolol plus HCT) were assigned randomly to sibutramine (15 mg daily) or placebo for a period of 16 weeks. Compared with placebo, sibutramine resulted in a significantly greater decrease in body weight (5.7 vs 1.5 kg), BMI (2.0 vs 0.5 kg/m^2) and waist circumference (5.0 vs 0.8 cm). Remarkably, the sibutramine-induced weight loss, reduction in BMI, and reduction in waist circumference were significantly attenuated in the metoprolol plus HCT group compared with the other two groups. Despite the greater decrease in body weight, changes in office systolic and diastolic blood pressure did not differ between the sibutramine and placebo group. Ambulatory blood pressure recordings for 24 h revealed a small reduction in systolic blood pressure in both groups (0.3 mm Hg with sibutramine vs 0.9 mm Hg in the placebo group), but unfortunately an increase in diastolic blood pressure in the sibutramine group versus placebo (2.1 versus −0.3 mm Hg). The smaller decrease in body weight, BMI, and waist circumference with the use of sibutramine in the patients treated with metoprolol plus HCT was accompanied by less beneficial effects on glucose tolerance and hypertriglyceridemia. On the basis of these findings, the authors concluded that an antihypertensive combination therapy regimen that is based on ACE inhibitors and calcium channel blockers is more advantageous than a combination regimen based on diuretics and beta-blockers in supporting the weight-reduction

actions and concomitant metabolic changes induced by sibutramine in obese hypertensive subjects.

Conclusions

Obesity hypertension is a growing condition. In a proportion of patients with obesity hypertension, the response of blood pressure to combinations of antihypertensive agents is insufficient. For these patients, no specific recommendations or guidelines regarding additional treatment are available. In light of the emerging role of aldosterone in the pathogenesis of obesity hypertension and the findings of studies suggesting that adding a low dose of aldosterone can produce large blood pressure reductions in patients whose blood pressure is uncontrolled with conventional antihypertensive treatment, addition of a mineralocorticoid receptor antagonist as a fourth-line agent in resistant obesity hypertension is a logical choice. Conventional or nonvasodilating beta-blockers, although effective in reducing blood pressure in obesity hypertension, are not recommended as a first-line, second-line, or third-line agent because they reduce energy expenditure, lipolysis, and insulin sensitivity, and a negative interaction with sibutramine has been documented when they are combined with thiazide diuretics [45, 46]. The chance of developing diabetes mellitus is greater with thiazide diuretics than with agents that interfere with the RAS or with calcium channel blockers [47, 48]. This negative effect, among others, has been linked with the reduction in potassium and magnesium levels [49]. This effect may be less apparent when thiazide diuretics are combined with anti-RAS agents such as ACE inhibitors or AT_1-receptor blockers or with mineralocorticoid receptor antagonists.

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