Reviving the use of aldosterone inhibitors in treating hypertension in obesity

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Abstract

Obesity is a multifactorial disease associated with hypertension. In the obese population, the incidence of hypertension is high and resistant hypertension is commonly observed. Mechanisms to explain the resistance to current anti-hypertensive treatments are still poorly understood. Emerging knowledge of the role of aldosterone in controlling blood pressure in obesity may have therapeutic benefit. Mineralocorticoid receptor (MR) inhibitors are currently used as the fourth line of treatment. Clinical studies summarized in this short review suggest that MR antagonists have a strong efficacy in decreasing blood pressure in the hypertensive obese population and could be used as a primary anti-hypertensive in obesity.

Keywords: Hypertension, Obesity, Aldosterone
Introduction

Obesity affects 1/3 of the adult US population and is commonly associated with hypertension, a need for a higher number of antihypertensive medications, and an increased likelihood of never achieving blood pressure control (1, 3). The Framingham study showed that excess weight accounts for up to 75% of the risk for hypertension (78% for men, 64% for women)(13) and that losing weight is effective to reduce blood pressure (18). However, lifestyle modifications are poorly followed and medications are generally required to reduce blood pressure. The current guidelines from the American Heart Association recommend the use of ACEi/ARBs/diuretics as a primary line of treatment for hypertension in both lean and obese populations. Epidemiologic studies have shown that this course of action is not effective for obese patients (19). Recent studies have reported the presence of increased levels of aldosterone in the obese population, independently of the renin-angiotensin system (24). Additionally, basic and clinical observations report the efficacy of aldosterone inhibition on blood pressure control in obese patients (6). Despite these observations, aldosterone inhibitors are rarely utilized in the control of hypertension. This review will summarize clinical studies reporting the superior efficacy of MR (mineralocorticoid receptor) blockers in the treatment of hypertension and resistant hypertension in the obese population. Concurrently, we will show that obesity is strongly associated with increased aldosterone.

Hypertension in obesity

The mechanisms linking obesity and increased blood pressure are not well elucidated and numerous hypotheses have been reported. Obesity drives sympathetic nervous system hyperactivity, impaired renal function, increased levels of aldosterone and angiotensin II, insulin metabolism, and induced sodium retention, all potentially leading to hypertension (14, 16). Due to the absence of clear physiologic links between obesity and blood pressure, the American Heart Association recommends same therapeutic approaches for the treatment of lean and obese hypertensive patients (additionally to lifestyle changes). Data from the Hypertension and Diabetes Risk Screening and Awareness (HYDRA) study, a cross-sectional study of 45,125 primary care patients, reported that patients with a body mass index >40 kg/m2 had a higher prevalence of hypertension, as well as higher probability of requiring 4 (5.3 fold increase) or 3 (3.2 fold) antihypertensive drugs, to achieve blood pressure control compared with patients with normal weight (BMI ≤25 kg/m2)(19). In the recent Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, only 30% of patients had their blood pressure controlled at year 5 (1, 10). Resistant hypertension, defined by a blood pressure level that remains above goal in spite of the use of 3 optimally dosed antihypertensive medications of different classes, has a higher prevalence in the obese population (3, 19). Despite these reports, there are few studies looking at the appropriateness of current guidelines for hypertension treatment in the obese population.

High levels of aldosterone in overweight/obese patients

Aldosterone is a hormone synthesized in the zona glomerulosa of the adrenal glands in response to angiotensin II and increases in plasma potassium, principally, and to a lower extent to the adrenocorticotropic hormone. Recent works highlighted the importance of the adipose tissue as new
The source of aldosterone (4) as well as a producer of yet unidentified factor(s) (7, 23) promoting aldosterone release. It is generally accepted that obesity is associated with inappropriately high aldosterone levels. As early as 1981, a study showed that weight loss in an obese population was associated with decrease aldosterone (24). Numerous studies followed looking at plasma and urine aldosterone levels, in the overweight and obese populations (5). These studies revealed a relationship between BMI and plasma aldosterone concentration, apparently influenced by factors such as fat distribution, lipidemia, insulin resistance and kidney disease. Human studies looking at sub-types of obese populations are especially likely to find a relationship between BMI and aldosterone levels; a clear link has been demonstrated in obese women (15), in a population from African descent (2) and in class 2 and 3 obese patients (21). This relationship is non-existent in lean population (BMI <26.6 kg.m⁻²) (25).

### Effectiveness of aldosterone inhibition in obesity

The guidelines from the American Heart Association on the treatment of hypertension recommend using mineralocorticoid receptor (MR) inhibitors as a fourth line of medication. One of the reasons cited for delayed initiation of MR therapy was the concern that a potential increase in plasma potassium (K⁺) associated with the treatment could lead to fatal arrhythmia (22). A recent study on the use of MR inhibitors showed that only few patients have increased K⁺ and that plasma K⁺ can be easily controlled by regular blood samples, dose adjustment in the first few weeks of treatment (17), or addition of a diuretic (12). Several studies have looked at the effect of adding spironolactone or epleronone to classic treatment (ACEi/ARBs/diuretics) to treat hypertension and resistant hypertension in obese population(6, 8, 11, 20). No increase in mortality due to K⁺-arrythmias was observed in the groups receiving aldosterone inhibitors. Results showed a significant decrease in blood pressure, but specific studies must be conducted to determine the efficacy of aldosterone inhibition and the potential benefit of using it as the first line of treatment. A pilot study conducted by Costa et al. (9) on 11 obese hypertensive subjects showed the efficacy of spironolactone in controlling blood pressure but the small sample size is a limitation. We discussed above that plasma aldosterone concentration varies within the obese population; this could be a limit to the efficacy of MR blockade. Together these data highlight the limits of the extrapolation of the results gathered in the lean population, in term of drug efficacy and stress the need for more basic and clinical studies testing the efficacy of therapies in the obese population, specifically. In addition, further studies are also required to determine the source of the inappropriately high plasma aldosterone exhibited by obese patients. Confirmation of contribution of aldosterone to obesity-associated hypertension should likely lead to a change in the guidelines on the treatment of hypertension and to the use of MR blockers as a first line of treatment in patients with inappropriately high aldosterone levels (Fig. 1).
Perspectives and significance

Prevalence of obesity is predicted to grow across the globe in the next few decades. Treatments for hypertension, one of the most common side effects of obesity, represent a cost of billions of dollars. Current treatments were developed in the lean population and the efficacy was not studied in the subset of overweight/obese population. Resistant hypertension has a high prevalence in the obese population and to date there remains a lack of complete understanding of the mechanisms involved in the regulation of the blood pressure in obesity. Our review showed the basic and clinical evidences for using aldosterone inhibitors as a first-line option for controlling blood pressure in the obese population. Additionally to control more efficiently hypertension, reducing the number of drugs needed to achieve blood pressure control (Fig.1) will reduce the health care burden and increase the compliance and quality of life of the obese population.


Figure 1: Proposed scheme to decide treatment in the hypertensive obese population. HTN=hypertension; PAC=Plasma aldosterone concentration; ACEi=angiotensin converting enzyme inhibitors; ARBs=angiotensin receptor blockers; BP=Blood Pressure; MR inhibitors: mineralocorticoid inhibitors.
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