Treatment of Arterial Hypertension in Obese Patients

Ulrich O. Wenzel, MD, Ralf Benndorf, MD,† and Sascha Lange, PhD**

Summary: Obesity is an increasingly observed pathologic entity in the industrialized world and causally linked to the development of hypertension. Consequently, not only the prevalence of obesity but also the prevalence of obesity hypertension is increasing worldwide. In the context of antihypertensive treatment, data from clinical trials indicate that all first-line antihypertensive drugs possess a similar efficacy in reducing systemic blood pressure and hypertension-related end-organ damage in obese hypertensive subjects. Nevertheless, some antihypertensive agents, such as β-blockers or thiazide diuretics, may have unwanted side effects on the metabolic and hemodynamic abnormalities that occur in both obesity and hypertension. However, current guidelines still do not include recommendations for state-of-the-art treatment of obese patients with hypertension. Hence, the aim of this article is to provide recommendations for the appropriate use of antihypertensive agents in obese patients mostly based on personal expertise and pathophysiologic assumptions. For instance, thiazide diuretics and β-blockers are reported to reduce insulin sensitivity and (at least transiently) increase triglyceride and low-density lipoprotein cholesterol levels, whereas calcium channel blockers are metabolically neutral and angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and renin inhibition may increase insulin sensitivity. The renin-angiotensin-aldosterone system in the adipose tissue has been implicated in the development of arterial hypertension and sodium retention plays a central role in the development of obesity-related hypertension. Therefore, treatment with a blocker of the renin-angiotensin-aldosterone-system and a thiazide diuretic should be considered as first-line antihypertensive drug therapy in obesity hypertension.
Semin Nephrol 33:66-74
Keywords: Arterial hypertension, obesity, antihypertensive treatment

According to the World Health Organization, "Obesity is one of the most important contributors to ill health." Worldwide, the prevalence of obesity in industrialized countries and in a substantial number of developing countries is increasing. Overweight or obesity occurs in approximately one third of Americans, with similar estimates for children and adolescents (32%), adult males (32%), and adult females (35%).[1] The progressive increase in the prevalence of obesity is accompanied by an increase in the prevalence of hypertension, and it is estimated that 60% to 70% of the risk of hypertension may be attributable to obesity.[1] Given the large increase in the number of obese individuals, the proportion of hypertensive patients with obesity is likely to increase sharply in the future.[2] Several studies have shown that weight gain increases, whereas weight loss reduces, systemic blood pressure. Blood pressure increases in a linear manner over the whole range of the body mass index or waist circumference. An increase in waist circumference of 4.5 cm for men and 2.5 cm for women or an increase in body mass index of 1.7 kg/m^2 for men and 1.25 kg/m^2 for woman corresponds to an increase in blood pressure of 1 mm Hg.[3] The prevalence of hypertension is higher in obese patients compared with normal weight patients and the rate of patients with adequate blood pressure control decreases with increasing obesity.[4] However, the response to antihypertensive drug treatment often is disappointing because obesity is associated with a need for multiple antihypertensive drugs and is one of the most important risk factors for treatment resistance.[5] To date, our fundamental and clinical knowledge of therapeutic particularities in the treatment of obesity hypertension is sparse and certainly inadequate,[6,7] which in turn may result in inadequate treatment of these patients. The increasing prevalence of hypertension in obese patients and the low control rates in overweight and obese patients reveal the challenge that blood pressure control in obese hypertensive patients imposes on the physician. This article is based on 2 recent articles by us[8,9] and additionally summarizes the key content of a comprehensive discussion regarding the differential use of first-line antihypertensive drugs in the pharmacologic management of obesity hypertension.[1,2,6-9]

GUIDELINES

Guidelines for the management of hypertension provide specific recommendations for a variety of special populations, including African or African American patients, patients with heart failure, pregnancy, coronary heart disease, diabetes mellitus, chronic kidney disease, or the elderly.[10] However, specific recommendations for anti-

**III Medizinische Klinik, Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany.*
†Institute of Anatomy and Cell Biology, University of Würzburg, Germany.
Financial support: none.
Conflict of interest statement: Ulrich Wenzel has received funding and speaker fees from Novartis.
Address reprint requests to Ulrich O. Wenzel, MD, III Medizinische Klinik, Universitätsklinikum Hamburg Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany. E-mail: wenzel@uke.de
0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2012.12.009

hypertensive therapy of obese hypertensive patients are not included in these guidelines. This is quite astonishing because most physicians treat more obese hypertensive patients than, for example, pregnant hypertensive patients. Most guidelines in general do not recognize obese patients as being "special" with regard to antihypertensive treatment and only recommend that these patients lose weight.[11,12] This indeed seems to be the most effective measure for the treatment of hypertension in obese patients, but, in practice, long-term outcome of weight management programs for obesity are generally poor and most obese patients need additional medical treatment for blood pressure control. It should be emphasized that if hypertensive obese patients reduce their weight they need significantly fewer antihypertensive agents than those with stable obesity. Therefore, weight loss not only lowers blood pressure but appears to be a useful tool in blood pressure management in patients who require medication to control their blood pressure.[13] Moreover, the World Health Organization technical report on prevention and management of the global epidemic of obesity does not contain any specific recommendations or guidelines for antihypertensive therapy in obesity hypertension.[12] This lack of specific recommendations may originate from the paucity of data from prospective intervention studies involving obese hypertensive patients. Large outcome studies investigating the management of hypertension in obese patients have not been performed to date. Moreover, obese patients frequently are excluded from large intervention trials and although obese patients may have been included in some of the large intervention trials, no subgroup analysis for these patients has been presented to date.[11,12] In conclusion, clinical trials urgently are needed to determine the most effective antihypertensive drugs for obese hypertensive patients.

Because of the lack of clinical data, recommendations or guidelines for antihypertensive treatment of obesity hypertension are based mostly on subjective expert opinion. In this review, we provide the reader with general recommendations that rely on widely accepted mechanistic or pathophysiologic assumptions in the field of hypertension and obesity. Each class of first-line antihypertensive drugs and potential advantages/disadvantages in the treatment of obese hypertensive subjects is discussed. The general principles of pharmacotherapy for obese patients are not different than those for nonobese patients.

RANDOMIZED TRIALS WITH ANTIHYPERTENSIVE AGENTS IN OBESITY HYPERTENSION

Usually, randomized studies evaluating the effect of specific classes of antihypertensive agents are small and of short duration.[14] The Treatment in Obese Patients with Hypertension trial was the first randomized trial comparing the effect of the ACE inhibitor lisinopril and the diuretic hydrochlorothiazide on systemic blood pressure control in obese hypertensive subjects. After 12 weeks of treatment, blood pressure was reduced to a similar extent with both regimens.[15] Also, in the Candesartan Role on Obesity and on Sympathetic System study, blood pressure reduction was very similar in patients treated with either hydrochlorothiazide (HCT) or candesartan. Nevertheless, insulin sensitivity was improved and sympathetic nerve activity was reduced in candesartan-treated patients.[16] Diastolic blood pressure reduction was slightly better in atenolol- than in valsartan-treated patients, but a similar reduction was achieved after additional treatment of the nonresponders in both groups with HCT. Insulin sensitivity was slightly better in valsartan- than in atenolol-treated patients.[17] Aliskiren and irbesartan combined with HCT achieved a higher responder rate (57% and 55%) than the combination of amlodipine with HCT (45%) in patients with obesity.[18]

OBESITY HYPERTENSION

Mechanisms of obesity-related hypertension include insulin resistance, sodium retention, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system (RAAS), and altered vascular function. There is extensive overlap among factors that induce these abnormalities, but growing evidence links abnormalities in the adipose tissue to blood pressure control. Dysfunctional adipose tissue in obesity is hypertrophied and characterized by increased macrophage infiltration and by marked changes in secretion of adipokines.[19] Three excellent recent review articles discuss this in detail.[1,20,21] Obesity-related hypertension is associated with renal sodium retention and impaired pressure natriuresis. The renal sodium retention in obesity occurs despite an increase in glomerular filtration rate, indicating increased renal fractional tubular sodium reabsorption. Driving forces for this sodium retention are an increase in renal sympathetic tone and activation of the renin-angiotensin-system (RAS). In the dog, renal denervation blunts sodium retention and attenuates the increase in blood pressure associated with dietary-induced obesity. It also has been suggested that increased intrarenal pressures caused by fat surrounding the kidneys and increased abdominal pressure associated with visceral obesity may impair natriuresis. Impaired pressure natriuresis also may be related to increased mineralocorticoid activity.[1]

Somewhat paradoxically, plasma aldosterone concentrations in obese patients are relatively high despite low renin activity in the plasma. The stimulus for increased aldosterone remains a matter of conjecture, however, recent reports have indicated that adipokines may stimulate aldosterone production directly.[22] Obesity hypertension is characterized hemodynamically by expanded intravascular volume associated with increased cardiopulmonary volume and cardiac output.[23] Because obese patients have sodium retention, even normal levels of renin activity must be considered as inappropriate.[24] Serum levels of almost all components of the RAS are increased in obesity and the adipose tissue is an impor-