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HYPERTENSION IN OBESITY AND THE IMPACT OF WEIGHT LOSS

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Abstract

Purpose of Review—Several interrelated mechanisms play a role in the development of hypertension in obesity, often contributing to end organ damage including cardiovascular disease and chronic kidney disease.

Recent Findings—The treatment of hypertension in obesity is complicated by a high prevalence of resistant hypertension, as well as unpredictable hemodynamic effects of many medications. Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure. While lifestyle interventions can improve blood pressure, they fail to consistently yield sustained weight loss and have not demonstrated long-term benefits. Weight loss surgery provides more permanent weight reduction, corresponding with dramatic declines in blood pressure and attenuation of long-term cardiovascular risk.

Summary—Hypertension is closely linked to the prevalence, pathophysiology, and morbidity of obesity. There are multiple barriers to managing hypertension in obesity. Surgical weight loss offers the most promise in reducing blood pressure and decreasing end organ damage in this patient population.

Keywords

Obesity; morbid obesity; hypertension; metabolic syndrome; bariatric surgery; weight loss

INTRODUCTION

The obesity epidemic is a global crisis that is undeniably intensifying. In 2015, there were 603.7 million obese adults worldwide [1]. Over the past 25 years, the prevalence of obesity in both children and adults has doubled in 73 countries [1]. In the Unites States (US), based on the most recent data from the National Health and Nutrition Examination Survey

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

Jordana B. Cohen declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

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evaluating 2638 adult men and 2817 adult women between 2013 and 2014 [2], the age-adjusted prevalence of obesity was 37.7%, up from 22.9% ten to fifteen years prior [3]. While rates of obesity in US men are starting to plateau, there is a rising trend among women, with the greatest increase in rates of class 3 obesity (defined as a body mass index [BMI] ≥40 kg/m^2) [2]. Outside of the US, the prevalence of obesity continues to climb, particularly in developing countries [4].

A critical consequence of the increasing prevalence of obesity is the burden of illness associated with excess body weight. Excess body weight is associated with 7.1% of deaths from any cause and 4.9% of disability worldwide [1]. Elevated body mass index (BMI) is an independent risk factor for the development of type 2 diabetes mellitus, dyslipidemia, chronic kidney disease, ischemic heart disease, stroke, dementia, several malignancies, nonalcoholic fatty liver disease, and obstructive sleep apnea [5–12]. These myriad disease processes drive increased disability, morbidity, and mortality among the obese [1, 13–15], and promote poorer quality of life [16].

Many of the comorbidities associated with obesity are facilitated by or contribute to an extremely high prevalence of hypertension in the obese population [17–19]. About half of hypertensive patients in the US are obese [20]. Accordingly, over one-third of the US obese population has a diagnosis of hypertension, compared to less than one-fifth of normal-weight individuals [21]. The relationship between obesity and hypertension is multifaceted and closely intertwined with other comorbidities present in obesity. The diagnosis and monitoring of hypertension in obesity is often complicated by difficulties in accurately measuring blood pressure in these patients [22]. Furthermore, highly complex underlying pathophysiologic factors contribute to several challenges in treating hypertension in obesity [23], perpetuating the greater morbidity and mortality observed in this population.

PATHOPHYSIOLOGIC MECHANISMS OF HYPERTENSION IN OBESITY

Multiple pathophysiologic mechanisms play a role in the development of hypertension in obesity, which in turn propagate end organ damage including cardiovascular disease and chronic kidney disease (Figure 1). These highly interrelated mechanisms include insulin resistance, inflammation, oxidative stress, adipokines (such as adiponectin and leptin), the sympathetic nervous system, and the renin-angiotensin aldosterone system [24–28]. Many of these factors interact with one another in bidirectional pathways and are exacerbated by greater degrees of adiposity. Broadly, their activity can induce endothelial dysfunction and alter hemodynamics throughout the body, promoting the elevation in blood pressure commonly observed in obesity.

More specifically, increased adiposity is strongly correlated with endothelial dysfunction, attributed in part to amplified oxidative stress and reduced nitric oxide availability [26, 29]. Obesity is also linked to elevated circulating markers of inflammation including C-reactive protein, erythrocyte sedimentation rate, and plasminogen-activator inhibitor 1, as well as inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 [25]. In addition to oxidative stress, recent literature suggests that altered intestinal microbiota may be an important underlying mechanism in promoting inflammation in obesity by affecting

intestinal permeability [25, 30]. The heightened inflammatory activity observed in obesity often results in vascular dysfunction and development of hypertension in this patient population [31, 32].

Insulin resistance and oxidative stress observed in the setting of increased visceral adiposity contribute to heightened sympathetic nervous system activity [33]. Obstructive sleep apnea, which is extremely common in obesity, also causes sympathetic stimulation, further contributing to elevated blood pressure in this patient population [12, 34]. In addition to heightened sympathetic nervous system activity, excess adipose tissue is associated with increased angiotensin type 1 and 2 receptor expression as well as elevated circulating angiotensin II, angiotensin-converting enzyme, and aldosterone levels [28, 35, 36]. This elevated renin-angiotensin aldosterone system activity may in part be due to target organ effects of circulating adipokines [27]. As a result, this elevated renin-angiotensin aldosterone system activity is not systemically regulated, and alters the renal hemodynamics by causing afferent renal arteriolar dilation and efferent renal arteriolar vasoconstriction [36]. The combination of enhanced sympathetic nervous system activity and renin-angiotensin aldosterone system activity in obesity also cause impaired natiuresis, increased renal sodium reabsorption, and extracellular volume expansion, further propagating the development of hypertension in obesity [33, 36].

END ORGAN EFFECTS OF HYPERTENSION IN OBESITY

Much of the end organ damage associated with hypertension in obesity is related to the vascular impact of excess adipose tissue. Even after adjusting for traditional cardiovascular risk factors, obesity is strongly correlated with subclinical measures of atherosclerosis, including coronary artery calcification, increased internal and common carotid artery intimal medial thickness, and enlarged left ventricular mass [37]. Central adiposity is also independently associated with greater risk of arterial stiffness and microvascular disease [38–40], which are likely substantially mediated by the increased prevalence of hypertension in this patient population.

With regard to renal effects of hypertension in obesity, the upregulation of sympathetic nervous system and renin-angiotensin aldosterone system activity appreciated in obesity yields higher cardiac output and extravascular volume expansion [33, 36]. On the glomerular level, these altered hemodynamics expand renal plasma flow and increase glomerular pressure, often leading to glomerular hyperfiltration [33, 36]. These changes may ultimately result in glomerulomegaly, podocytopathy, focal glomerulosclerosis, and proteinuria [36, 41]. As such, obesity is associated with both the development of de novo renal disease as well as greater risk of progression of chronic kidney disease. In particular, class 3 obesity confers a 7-fold increased risk of the development of end stage renal disease compared to normal-weight individuals in the general population [7].

Hypertension in obesity is also highly associated with cardiac remodeling. The endothelial dysfunction caused by heightened sympathetic nervous system activity, renin-angiotensin aldosterone system activity, inflammatory cytokines, and oxidative stress in the setting of excess adipose tissue can contribute to left ventricular hypertrophy, ischemic heart disease,

cardiac fibrosis, and cerebrovascular disease [17, 27, 42]. These effects are amplified in severe obesity, with up to a 2-fold increased risk in ischemic heart disease and 6-fold increased risk of congestive heart failure reported in large-scale observational analyses among women with class 3 obesity compared to normal-weight women [43].

CHALLENGES IN THE PHARMACOLOGIC MANAGEMENT OF HYPERTENSION IN OBESITY

The physiologic complexity of hypertension in obesity engenders multiple challenges in its pharmacological management (Table 1), potentially contributing to the greater risk of target organ damage in this patient population. Obesity is strongly correlated with treatment resistant hypertension, often requiring the additive and synergistic effects of several antihypertensive medications to achieve adequate blood pressure control. The etiology of resistant hypertension in these patients is likely multifactorial, including dysfunctional neurohormonal pathways, particularly increased aldosterone secretion, as well as the systemic effects of adipokines such as leptin and adiponectin [27, 28]. Although obesity is not known to alter the oral absorption of medications, the pharmacokinetics and pharmacodynamics of many medications are also impacted by excess adiposity. These changes are mediated through a variety of pathophysiologic mechanisms, including abnormal drug handling, expanded volume of distribution, altered hepatic and renal clearance, and heightened neurohormonal activity [23, 44].

The volume of distribution of a medication describes the overall amount of the medication in a person’s body relative to the concentration of that medication in a particular body compartment, and provides an approximation of the extent to which a medication is delivered into soft tissue [23]. However, obese patients tend to have expanded plasma volume, which can alter the volume of distribution. This contributes to significant differences in plasma concentrations of some medications in obese patients compared to normal-weight patients, despite similar soft tissue concentrations [44]. In particular, the volume of distribution of lipophilic medications is affected by excess adiposity. Lipophilic medications tend to readily disperse into adipose tissue, making it difficult to achieve therapeutic plasma levels [45].

Nonalcoholic fatty liver disease plays in important role in dysfunctional drug clearance in obesity. Hepatic steatosis causes reduced hepatic microvascular blood flow, resulting in altered delivery of medications to the liver [46]. Additionally, nonalcoholic fatty liver disease contributes to abnormal hepatic enzyme function, leading to both increased and decreased rates of hepatic clearance of medications, depending on the enzyme involved in its metabolism [47, 48]. Altered renal clearance is also an important factor that complicates the predictability of medication clearance in obesity. Given that obesity is associated with amplified cardiac output and glomerular hyperfiltration [33, 36], obese patients can experience faster renal clearance of medications compared to normal-weight individuals. Conversely, obesity is also correlated with higher rates of chronic kidney disease, which can lead to reduced renal drug clearance. To further complicate the interpretation of renal drug clearance in obesity, creatinine-based equations for calculating renal clearance are often

highly biased in obesity due to inability to appropriately account for large body surface area, inaccuracies at higher levels of glomerular filtration, and difficulty estimating muscle mass (which generates creatinine) in these patients [49, 50].

Several studies have demonstrated differing responses to treatment with certain antihypertensive medications in obese compared to non-obese patients, highlighting that this patient population in susceptible to atypical responses to medications. Understanding that sympathetic nervous system activity and renin-angiotensin aldosterone system activity are upregulated in obesity, inhibition of these neurohormonal pathways has generated amplified hemodynamic responses in obese patients who do not have resistant hypertension. In an *in vivo* study directly measuring renal hemodynamics, obese patients had a greater renal vasodilatory response to short term angiotensin converting enzyme inhibition with captopril than normal-weight individuals [51]. Although there are no measurable changes in pharmacokinetic handling of beta blockers in obesity [52], another study demonstrated that obese patients had significantly greater blood pressure response compared to lean patients after treatment with combined alpha- and beta-adrenergic blockade [53]. We recently performed an observational study evaluating the renal effects of time-updated exposure to renin-angiotensin system blockade compared to any other antihypertensive therapy in over 200,000 obese, non-diabetic, hypertensive patients in the United Kingdom. The study demonstrated that incident renin-angiotensin system inhibition increased the risk of clinically significant, often-transient renal dysfunction in this patient population [54]. These findings may be due to exaggerated intrarenal hemodynamic effects of renin-angiotensin system inhibition, potentially as a result of the chronically heightened activity of this neurohormonal pathway in obese patients.

Several small studies have investigated the relative effects of different antihypertensive classes in obese patients, with mixed results. Combination angiotensin receptor blocker and thiazide therapy demonstrated a significantly greater decline in systolic blood pressure compared to combination calcium channel blocker and thiazide therapy (20.6 vs. 14.5 mmHg, p=0.011) in obese patients [55]. Obese patients also demonstrated a stronger reduction of systolic blood pressure when randomized to aliskiren monotherapy versus thiazide monotherapy (16.7 vs. 12.2 mmHg, $p < 0.001$) [56]. A *post hoc* analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial demonstrated higher frequency of blood pressure control in obese patients randomized to chlorthalidone compared to Lisinopril [57]. Collectively, these data suggest that renin-angiotensin system blockers seems to have a stronger effect on blood pressure control than calcium channel blockers in obese patients; the data are otherwise inconsistent or inconclusive. Additional studies are needed to elucidate optimal pharmacologic management of hypertension in this patient population.

Understanding the important role of aldosterone in driving sodium retention, endothelial dysfunction, cardiac fibrosis, and glomerulosclerosis in obesity [27, 28], mineralocorticoid receptor antagonists remain a promising option in the targeted treatment of hypertension in obese patients. Several studies have demonstrated renoprotective and cardioprotective effects of treatment with mineralocorticoid receptor antagonists in high-risk populations [58–61]. Data from a small, uncontrolled study suggest that mineralocorticoid receptor antagonists

may have a greater beneficial effect on endothelial function in patients with higher BMI and abdominal adiposity [62]; however, a small randomized controlled trial found no difference in endothelial function in obese patients treated with a short-term course of spironolactone vs. placebo [63]. Nonetheless, animal studies have demonstrated a reduction in the development of obesity-associated podocyte injury, systolic heart failure, and diastolic heart failure in rats treated with mineralocorticoid antagonists, independent of blood pressure lowering effects [64–66]. There have been no studies evaluating target organ effects of mineralocorticoid antagonists specifically in obese humans. Furthermore, the potential role of spironolactone as monotherapy in this patient population, rather than its usual role as adjunctive therapy, remains unclear.

EFFECTS OF LIFESTYLE INTERVENTIONS ON HYPERTENSION IN OBESITY

Several studies have demonstrated that weight loss corresponds to clinically significant declines in renin-angiotensin aldosterone system and sympathetic nervous system activity, which can have substantial effects on systemic blood pressure [67–70]. Observational evidence of non-surgical weight loss education demonstrates successful declines in body mass index, waist circumference, and blood pressure [71]. Non-surgical weight loss is also associated with improvement in renal function, both in conjunction with and independently of remission of hypertension [68, 72]. However, lifestyle interventions such as diet and exercise are limited in their magnitude of effect and sustainability. Although patients who undergo lifestyle interventions often see initial or modest improvements in blood pressure, behavioral counseling along with diet, exercise, or both does not result in persistent weight loss, and fails to attenuate long-term adverse cardiovascular outcomes resulting from obesity [73–75].

Many weight loss medications are effective in contributing to clinically significant weight reduction [76]; however, their influence on hypertension is mixed. In randomized controlled trials of hypertensive adults comparing weight loss medications to placebo, orlistat and phentermine/topiramate reduced blood pressure, while sibutramine increased blood pressure [77]. Many commercially available weight loss medications have not been studied in hypertensive populations, and data on their impact on long-term morbidity and mortality is greatly limited. Sibutramine has been removed from the market due to considerable risks of adverse outcomes, and phentermine/topiramate is not marketed in Europe due to similar concerns [77].

Given the close interplay between obstructive sleep apnea, obesity, and hypertension, there is a great deal of interest in understanding how management of obstructive sleep apnea can impact hypertension in obesity. A recent randomized controlled trial by Chirinos et al. evaluated the effects of weight loss, continuous positive airway pressure (CPAP) therapy, or both on markers of inflammation, insulin resistance, and intermediate measures of cardiovascular outcomes including blood pressure. Among patients who adhered to their assigned protocol, patients had a mean weight of 112–114 kg at the start of the study; patients in the weight loss intervention groups achieved 6.8–7 kg of weight reduction. The

combined intervention group achieved the greatest reduction in systolic blood pressure (14.1 mmHg), although all three intervention groups experienced clinically significant declines in blood pressure [78]. The combined intervention was also associated with greater reduction in insulin resistance and serum triglycerides compared to either intervention alone. Thus, combined CPAP therapy and non-surgical weight loss can have important effects on blood pressure and other cardiovascular risk factors in obese patients who have both hypertension and obstructive sleep apnea. No data exist regarding the effects of these interventions on long-term morbidity and mortality.

EFFECTS OF BARIATRIC SURGERY ON HYPERTENSION IN OBESITY

Surgical interventions have a more profound and lasting impact on weight loss and intermediate risk factors for cardiovascular disease than non-surgical interventions. Large magnitude weight loss following bariatric surgery is associated with high rates of hypertension remission. In a meta-analysis of randomized controlled trials, 50% of obese patients who underwent bariatric surgery had a diagnosis of hypertension prior to undergoing surgery; these patients experienced a 75% remission of hypertension [79]. These results were corroborated by more recent randomized controlled trials [80, 81]. A recent small prospective study demonstrated substantial, sustained declines in plasma leptin and muscle sympathetic nerve traffic following bariatric surgery, which likely facilitated the decline in blood pressure observed [82].

With regard to end organ effects of hypertension in obesity, echocardiography demonstrated regression of left ventricular hypertrophy and improvement in diastolic function following bariatric surgery [83]. The improvement in intermediate risk factors following surgical weight loss seems to be correlated to improved long-term renal and cardiovascular outcomes and mortality. Although there is no existing randomized controlled data, in observational studies, bariatric surgery is associated with a significant reduction in proteinuria [84], longitudinal renal function decline, and development of end stage renal disease [85]. Several observational studies have also demonstrated substantial reduction in long-term cardiovascular events and mortality in patients who underwent bariatric surgery compared to usual care [72, 86–88].

Surgical weight loss does confer perioperative risks due to the procedures themselves, including surgical complications, reoperation, acute kidney injury, and mortality [79, 89]. Nonetheless these risks have relatively low rates of occurrence [79], and seem to be outweighed by the improved morbidity and mortality observed following weight loss surgery.

CONCLUSION

Given the rising prevalence of obesity, it is critical to address modifiable risk factors to reduce the burden of illness in these patients. However, the closely overlapping and complex pathophysiology contributing to hypertension in obesity greatly complicates its management, further exacerbated by challenges in accurately measuring blood pressure in these patients. Moreover, obese patients have higher rates of resistant hypertension, altered

drug handling, and greater burden of comorbidities, engendering additional barriers to appropriate treatment. More investigations are needed to better understanding the optimal pharmacologic management of hypertension in this challenging patient population.

Weight loss can result in dramatic improvements in physiologic parameters contributing to hypertension. However, while excess food intake and inactivity are major contributors to the development of obesity, lifestyle interventions such as diet and exercise are often insufficient to generate clinically significant weight loss. Although associated with greater short-term risk, surgical interventions provide more sustained declines in body mass, with greater likelihood of reversal of hypertension. While data are limited regarding long-term outcomes, surgical weight loss seems to confer a significant renal, cardiovascular, and mortality benefit in obese patients.

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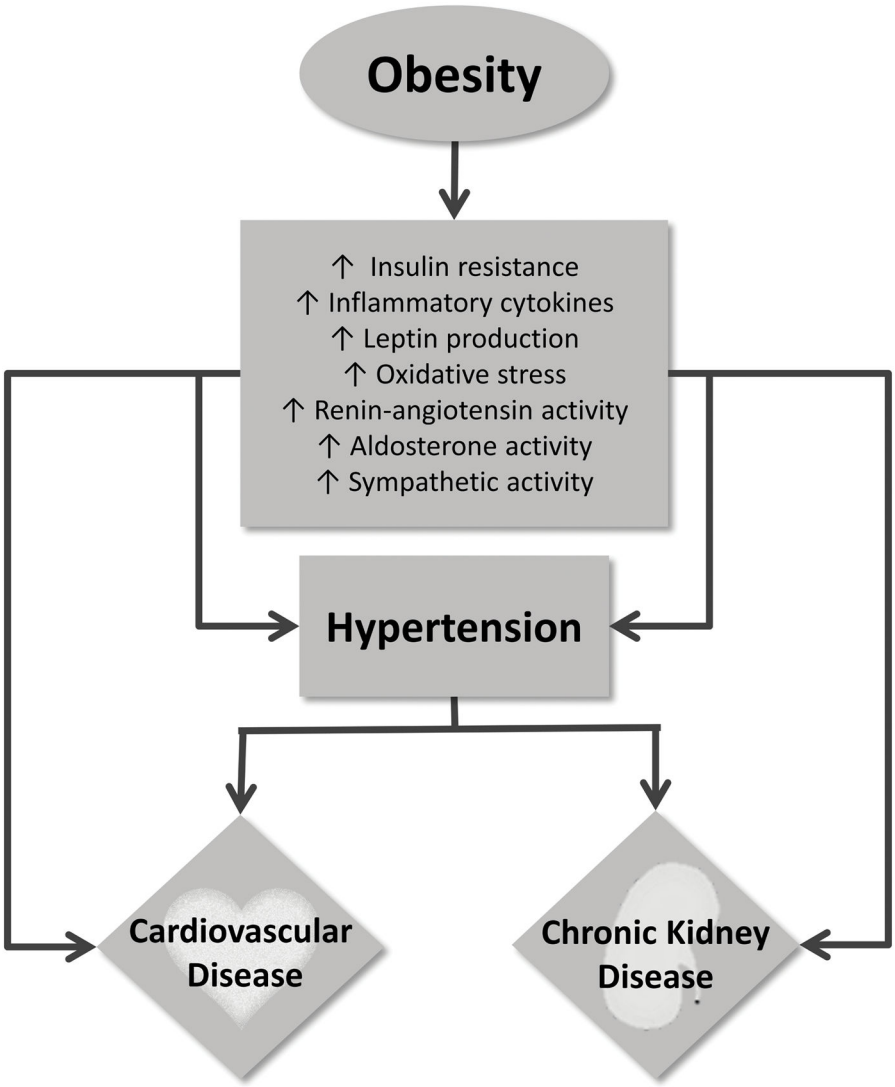

Figure 1.

Table 1

Potential Pharmacologic Challenges in Treating Hypertension in Obesity

Drug resistant hypertension
Altered neurohormonal pathways
Increased renal sodium reabsorption
Impaired natiuresis
Adipokines
Altered volume of distribution
Drug lipophilia
Expanded plasma volume
Altered clearance
Dysfunctional hepatic metabolism
Altered enzyme activity
High prevalence of nonalcoholic fatty liver disease
Increased cardiac output
Impaired estimation of renal clearance
Glomerular hyperfiltration
High prevalence of chronic kidney disease
Inaccuracies of creatinine clearance equations