The combination of obesity and hypertension: a highly unfavorable phenotype requiring attention

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Purpose of review
Body habitus is a key lifestyle characteristic whose current status and future projections are disconcerting. The percentage of the global population who are either overweight or obese has substantially increased, with no indication that any country has a solution to this issue. Hypertension is a key unfavorable health metric that, like obesity, has disastrous health implications if left uncontrolled. Poor lifestyle characteristics and health metrics often cluster together to create complex and difficult to treat phenotypes. Excess body mass is such an example, creating an obesity–hypertension phenotype, which is the focus of this review.

Recent findings
An increased risk for hypertension is clearly linked to obesity, indicating that the two conditions are intimately linked. The cascade of obesity-induced pathophysiologic adaptations creates a clear path to hypertension. Adopting a healthy lifestyle is a primary intervention for the prevention as well as treatment of the obesity–hypertension phenotype.

Summary
The obesity–hypertension phenotype is highly prevalent and has disastrous health implications. A primordial prevention strategy, focused on lifelong healthy lifestyle patterns, is the optimal approach for this condition. For those individuals already afflicted by the obesity–hypertension phenotype, interventions must aggressively focus on weight loss and blood pressure control.

Keywords
bariatric surgery, diet, exercise, healthy lifestyle, renal disease, weight loss

INTRODUCTION

The world is in the midst of a noncommunicable disease (NCD) crisis, which has been precipitated by unhealthy lifestyle characteristics (i.e., physical inactivity, smoking, poor diet, and excess body mass) and associated poor health metrics [hypertension (HTN), dyslipidemia, and hyperglycemia] [1,2,3▪,4]. The American Heart Association (AHA) has clustered these seven key health factors into a singular concept, life's simple 7, with each factor being designated into one of three categories—poor, intermediate, or ideal cardiovascular health [5]. We now recognize that improving life's simple 7 characteristics on a population level is the only way the NCD crisis can be resolved [6▪▪].

Body habitus is a key lifestyle characteristic whose current status and future projections are highly disconcerting [7,8,9▪]. Much of the world has evolved into a positive caloric balance culture, and excess body mass is the consequence. Globally, the percentage of the population, both children and adults, who are either overweight (i.e., BMI 25.0–29.9 kg/m^2) or obese (i.e., BMI $\geq$ 30 kg/m^2) has substantially increased over the last three decades; there is no indication any country has a solution to this issue [10]. In 2014, it was estimated that 1.3 billion adults around the world were overweight and 600 million were obese; the worldwide

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KEY POINTS

- Obesity and HTN are two of the most troublesome conditions from a population health perspective.
- Obesity-induced alterations in renal function, autonomic tone and key hormone levels lead to a substantially higher risk for HTN.
- The obesity–HTN phenotype is most effectively treated by primordial prevention; leading a healthy lifestyle is central to this goal.
- For those individuals who already manifest the obesity–HTN phenotype, interventions directed toward weight loss and blood pressure control are of paramount importance.

prevalence of obesity doubled from 1980 to 2014 [8]. In the United States, the percentage of individuals who are considered obese has, for the first time, surpassed the percentage of individuals classified as overweight [7]. It is estimated that obesity was the cause of 18.2% of the deaths between 1986 and 2006 in the United States [11]. Globally, it is estimated that 5% of the annual deaths are caused by obesity [12]. In 2010, excess body mass ranked sixth amongst 67 risk factors that accounted for global disease burden [13]. From a financial standpoint, it is estimated that the annual global economic impact of obesity is $2 trillion [12].

Like obesity, HTN is a key unfavorable health metric that has disastrous health implications if left uncontrolled [5,9▪]. In 2008, it was estimated that 40% of the global adult population (25 and older) had elevated blood pressure with approximately 1 billion cases of uncontrolled HTN, a 400 million individual increase from 1980 [14]. In the United States, 32.6% of adults have HTN, ≈80 million individuals [9▪]. Although 76.5% of these individuals in the United States with HTN are being treated for this health metric, only 54.1% are controlled effectively; 17.3% of US adults are not aware they have HTN [9▪]. In 2011, 65 123 deaths were attributable to HTN in the United States [9▪]; globally, HTN accounts for 9.4 million deaths annually [15]. Currently HTN is the leading contributor to global disease burden [13,16]. The direct and indirect cost of treating HTN in the United States in 2011 was $46.4 billion and is projected to increase to $274 billion by 2030 [9▪]. The costs of treating HTN on a global scale are exponentially higher [15].

Poor lifestyle characteristics and health metrics often cluster together to create complex and difficult to treat phenotypes. Excess body mass is such an example, facilitating a cascade of pathophysiologic sequelae that create an obesity–HTN phenotype, which increases cardiovascular risk [13,17,18]. The purpose of the current review is to describe the mechanism for obesity-induced HTN; describe the prevalence of the obesity–HTN phenotype; and discuss strategies to address the potential negative consequences of the obesity–HTN phenotype, from the perspective of both primordial prevention as well as treatment for those already impacted by this condition.

MECHANISMS FOR OBESITY-INDUCED HTN

There is a clearly established link between obesity and HTN [17–22]. The accumulation of excess adipose tissue initiates a cascade of events that give rise to an elevated blood pressure; obesity-induced HTN is a common pathway in both children and adults [18,22,23▪]. The pathophysiologic mechanisms linking obesity to HTN are described herein.

Increased sympathetic nervous system activity

There is an increase in sympathetic nervous system (SNS) activity in patients with obesity; evidence suggests that high caloric loads increase peripheral norepinephrine turnover, and high fat and carbohydrate diets stimulate α_1 and β-adrenergic peripheral receptors, which elevates SNS system activity [18,24▪]. Elevated free fatty acid levels, which are characteristic of the obesity–HTN phenotype, increase α-adrenergic vascular sensitivity and subsequently arterial tone. Distribution of body fat also plays a role in SNS variability, with central obesity being associated with greater SNS activation compared with subcutaneous obesity [25]. Lastly, baroreflex sensitivity, which when functioning normally has a sympathoinhibitory effect in elevated blood pressure conditions, is diminished in the obesity–HTN phenotype, further contributing to enhanced SNS activity [26].

Alterations in renal function

Obesity is associated with an increased risk for chronic kidney disease as well as end-stage renal disease [27]. Initially, blood pressure control through diuresis and natriuresis favors a shift toward HTN in obese individuals; this occurs prior to glomerular injury and loss of renal function [18,23▪,28]. During the initial onset of obesity, an increase in renal tubular reabsorption increases sodium retention. Renal vasodilation, which increases glomerular filtration and the filtered amount of both water and electrolytes, occurs in

an attempt to compensate for the increase in renal tubular reabsorption. This compensation is incomplete, however, and extracellular volume is expanded with an upward pressure recalibration of the pressure natriuresis. Thus, the impact of obesity on the renal system that favors HTN is consistent with a volume overload model. Obesity is associated with altered rennin–angiotensin–aldosterone-system (RAAS) function; plasma renin, angiotensinogen, angiotensin II, and aldosterone are all elevated with obesity. Increased levels of RAAS constituents favor vasoconstriction and volume expansion. Although obesity is associated with volume expansion, renin secretion by the kidney persists because of the effect of fat accumulation in and around the renal medulla. Adipose tissue itself is also a source of all components of the RAAS [18,29,30]; angiotensinogen produced by adipose cells is released into the circulatory system, increasing the amount available for conversion along the pressure elevating cascade, and RAAS receptors are well established in adipocytes [30]. This cascade of events results in elevated RAAS activity, which is no longer suppressed by the obesity-associated volume expansion. Excess visceral adipose tissue results in physical compression of the kidneys. Compression of the renal system impacts both the vascular and tubular systems that augment RAAS activation and sodium reabsorption [23▪]. The physical stresses that obesity places upon the kidneys initiate a deleterious progression from hyperfiltration to glomerulomegaly (i.e., enlargement of the glomeruli) to sclerosis of the glomeruli wall and nephron, ultimately leading to nephron loss, which negatively impacts pressure natriuresis [23▪]. These structural renal changes result in higher sodium retention and higher arterial pressure.

Hormonal function

Impaired glucose tolerance, increased insulin levels, and concomitant reductions in insulin sensitivity are commonplace in obese individuals; the clustering of these characteristics defines insulin resistance/metabolic syndrome [18,19,23▪,28]. Insulin increases sodium retention through a direct interaction with renal tubules. Thus, the obesity-induced hyperinsulinemia state contributes to elevated blood pressure through increased sodium retention and volume overload. Insulin also increases SNS activity through both hypoglycemia-induced mechanisms as well as a possible direct effect on the central nervous system. Chronic hyperinsulinemia is also linked to arterial dysfunction, favoring vasoconstriction. Leptin is secreted by adipose tissue, with a direct link between leptin secretion and fat mass [18,23▪]. Elevated circulatory leptin levels observed in obesity are also implicated in the increased risk of HTN. Leptin crosses the blood-brain barrier, interacting with the arcuate nucleus, initiating an appetite suppression and increased energy expenditure signal that is mediated through increased SNS activity. Leptin also has been linked to endothelial dysfunction by negatively impacting nitric oxide synthase expression and augmenting SNS activity [18,26]. Adiponectin is secreted by adipose tissue, plays a role in regulating energy balance and promotes insulin sensitivity. Increased adipose mass is associated with decreased adiponectin levels and thus contributes to insulin resistance. Glucocorticoids, acting within adipose tissue, appear to promote HTN through increased RAAS activity [18,23▪].

Endothelial function and structure

Obesity creates a state of insulin resistance and systemic inflammation that promotes endothelial dysfunction and HTN [18,23▪]. Insulin resistance decreases nitric oxide synthesis and hyperinsulinemia promotes vasoconstriction through increased endothelin-1 levels. A host of proinflammatory and inflammatory compounds secreted by adipose tissue, including interleukin-1β, interleukin-6, tumor necrosis factor, and C-reactive protein, also promote endothelial dysfunction and thus HTN [18]. Obesity is also associated with increased carotid artery thickness, intima media thickness, and arterial remodeling and stiffening [31]. Chronic hyperglycemia, as well as increased RAAS activation and SNS activity, contributes to changes in vascular structure that favor increased pressure and HTN.

Individual obesity to hypertension tsunami

The rising incidence and prevalence of obesity have been referred to as a tsunami from a population perspective [32]. The mechanism for obesity-induced HTN described in this section creates a tsunami scenario on an individual level, which is depicted in Fig. 1. Excess adipose tissue (wave 1) alters the function of several key systems (wave 2), which in turn alters endothelial structure and function (wave 3). The end result of this individual tsunami is HTN and its deleterious consequences.

PREVALENCE OF THE OBESITY–HYPERTENSION PHENOTYPE

The preceding section highlighted a multifactorial and complex cascade of pathophysiologic mechanisms that link obesity to a substantially increased

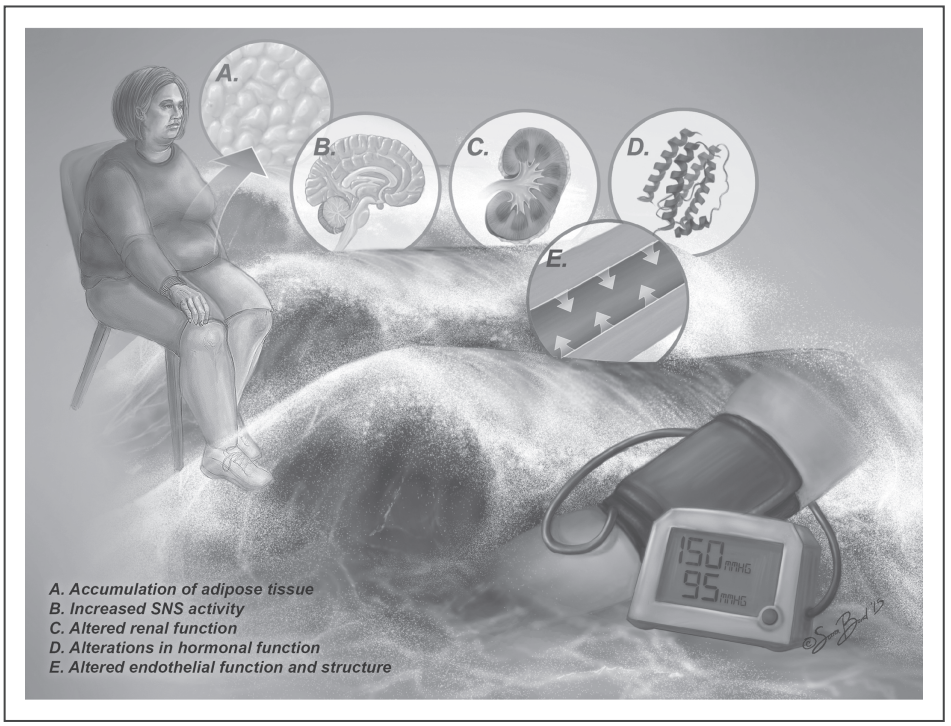

FIGURE 1. Individual obesity to hypertension tsunami.

risk for HTN. The extremely high prevalence of the obesity–HTN phenotype should, therefore, be no surprise. In the United States, more than 40 and 25% of the obese and overweight population, respectively, also have HTN. This is compared with a HTN prevalence of approximately 15% in normal weight individuals [21]. This clearly demonstrates a stepwise increase in HTN risk with increasing body mass. It is estimated that 78% of the risk for developing essential HTN in men and 65% of the risk for developing essential HTN in women is attributed to excess body mass [23▪]. Evaluating the relationship from the reverse perspective (i.e., the HTN population exclusively), more than 70% of individuals with HTN are overweight or obese [33]. In those with type II diabetes mellitus, the prevalence of the obesity–HTN phenotype is variable by country and defining blood pressure threshold, ranging from 33 to 93% [34]. Collectively, these data indicate a high prevalence for the obesity–HTN phenotype, warranting a focus on prevention and treatment.

PREVENTION AND TREATMENT OPTIONS FOR THE OBESITY–HYPERTENSION PHENOTYPE

The obesity–HTN phenotype works synergistically to exponentially increase cardiovascular disease risk, chronic renal disease, and associated adverse events [9▪,21,28,35,36]. Given the incidence and prevalence, poor clinical outcome, and quality of life as well as negative financial implications of the obesity–HTN phenotype, aggressive prevention and treatment strategies are imperative.

Primordial prevention of obesity through adoption of a healthy lifestyle

Promoting the maintenance of a life-long normal body weight is the optimal approach to preventing the deleterious consequences of the obesity–HTN phenotype. If obesity were removed from the equation, the risk of developing HTN would be minimized for a significant proportion of the population. The prevention of obesity from occurring requires a multipronged approach by numerous stakeholders working together toward a common goal. The focus is to encourage adoption of a healthy lifestyle, from the individual to population level across the lifespan. The core tenets of a healthy lifestyle as it relates to maintenance of a normal body weight include sufficient levels of physical activity and consuming a nutritious, calorically balanced, diet. The AHA has defined ideal physical activity and dietary characteristics that all individuals should strive toward [5]. Recently, the AHA, European Society of Cardiology, European Association for Cardiovascular Prevention and Rehabilitation, and American College of Preventive Medicine published a policy statement that proposed a nonhierarchical connectivity model for key stakeholders who must collaboratively work together to

address the NCD crisis through healthy lifestyle interventions [6▪▪,37▪]. Primordial prevention strategies were a significant focus in this document. Professional organizations, educational systems, government on all levels, healthcare organizations, the insurance industry, nonprofit and community organizations, media outlets, and mobile health and technology companies and employers were all identified as healthy lifestyle stakeholders in this policy statement. With respect to promoting maintenance of a healthy body weight across the lifespan, numerous collaborative strategies can be implemented. Examples include: creation of walker-/biker-friendly public spaces; robust K-12 physical and health education programs as well as healthy food choices in schools; well-designed worksite health and wellness programming; health insurance incentives for maintenance of a healthy lifestyle; and broad adoption of healthy lifestyle assessments and interventions in healthcare systems. The aforementioned policy statement encourages creativity in developing healthy lifestyle initiatives, allowing stakeholders to capitalize on resources and infrastructure at the local level. Moving forward, prevention of unhealthy lifestyle characteristics, including obesity, from ever developing must become a primary focus.

Weight loss strategies for individuals with excess body mass

Although we must plan for the future and initiate primordial prevention strategies for lifelong maintenance of a normal body weight, the obesity crisis that currently is upon us must also be addressed [38,39]. Weight loss is a key goal for treating patients presenting with the obesity–HTN phenotype. Additionally, increasing levels of cardiorespiratory fitness has major implications not only for the prevention of HTN, but also for improving overall prognosis in most groups with cardiovascular diseases [40,41].

Structured exercise, nutritional, and physical activity interventions

The literature convincingly demonstrates that individuals with an excess body mass experience significant weight loss through participation in healthy lifestyle interventions that ideally includes a structured exercise program, nutritional counseling, and promotion of increased physical activity throughout the day [42,43,44▪,45–48]. Ensuring these programs are prescribed in a way that creates an appropriate, daily, negative caloric balance (i.e., 500–1000 kcal deficit per day) is essential for weight loss and its maintenance [48,49▪]. With respect to the structured exercise program, combing aerobic and resistance training is considered advantageous with respect to facilitating weight loss while preserving lean mass [45,48]. Behavioral counseling is also considered an important component of healthy lifestyle interventions directed toward promoting weight loss [50–52], ensuring individuals are properly motivated to lose weight and maintain improvements in body habitus over the long term. Research has shown that individuals who lose weight through exercise and nutritional interventions demonstrate significant reductions in blood pressure, as well as improvements in the pathophysiologic cascade associated with the obesity–HTN phenotype, including improved arterial structure and function [19,24▪,53–56]. In individuals in the early stages of HTN, exercise training in and of itself, after controlling for baseline body weight and weight loss following an intervention, reduced the risk of developing left ventricular hypertrophy [55]. Exercise training also significantly reduces left ventricular mass in those with HTN where cardiac structural abnormalities have already developed [55]. Also, increased physical activity and exercise is particularly important for long-term weight maintenance [57].

Bariatric surgery

Significant weight loss is achieved in individuals who undergo bariatric surgery, and it should therefore be considered in those who are eligible [58,59]. Bariatric surgery is also associated with a significant reduction in blood pressure and improvements in the pathophysiologic alterations (e.g., SNS, renal system, and systemic inflammation) precipitated by obesity [19,58,60,61]. In patients undergoing bariatric surgery, healthy lifestyle interventions (i.e., exercise training and nutritional counseling) are vital components of the overall care plan to further promote weight loss and maintain a healthier body weight; improve functional capacity and quality of life; and further improve abnormalities in the SNS, renal, hemodynamic, vascular, and systemic inflammatory profile associated with the obesity–HTN phenotype [19,24▪,53,54,60,62–64]. Behavioral counseling should also be integrated into the healthy lifestyle intervention plan for patients undergoing bariatric surgery. Arena and Lavie [65] recently proposed broadly embedding healthy lifestyle teams (e.g., exercise scientist, registered dietician, behavioral counselor, etc.) into the clinical setting to deliver individually tailored healthy lifestyle medicine (HLM) to those requiring these services. Integrating a healthy lifestyle team into clinical practices caring for patients undergoing

bariatric surgery, both pre- and postoperatively, is certainly warranted given the importance of HLM for this population.

Other treatment considerations

Pharmacologic interventions

Healthy lifestyle interventions and bariatric surgery both can result in a significant reduction in blood pressure in patients with the obesity–HTN phenotype; significant weight loss is central to achieving blood pressure reductions. Where healthy lifestyle interventions are unsuccessful in producing weight loss and an individual is not a candidate for bariatric surgery, pharmacologic options are available. There are currently six antiobesity drugs approved by the Food and Drug Administration; other pharmacologic options are under development [66▪]. Moreover, for those individuals in whom HTN persists following front-line weight loss interventions, pharmacologic blood pressure control options should be considered; there are a host of options available [19]. As obese individuals generally have a relative volume overload state and often have low plasma renin HTN [40,41,67], they typically respond particularly well to diuretics and calcium entry blocking agents. However, considering the adverse renal effects in the obesity–HTN phenotype, angiotensin converting enzyme inhibitors and angiotensin receptor blockers may provide renal protection in addition to lowering blood pressure; these agents also produce a 25–30% reduction in the development of type 2 diabetes mellitus and are the best agents to reduce left ventricular hypertrophy, which is highly prevalent in the obesity–HTN phenotype [68–70]. Although β-adrenergic blockers are not currently considered a first-line treatment for HTN (except in those with coronary heart disease, heart failure, atrial fibrillation, or other conditions helped by beta blocking agents), these agents, especially the vasodilating beta blockers [71], may also be useful in the obesity–HTN phenotype, particularly given their heightened SNS responses. In summary, managing blood pressure is a key goal and should be achieved through all clinically available means possible.

Treatment of obstructive sleep apnea

Individuals presenting with obesity are at higher risk for obstructive sleep apnea (OSA), a condition that elevates blood pressure and increases cardiovascular risk [19,72]. As such, individuals who are obese should be screened for OSA and receive appropriate treatment (i.e., continuous positive airway pressure) when identified [72].

CONCLUSION

Obesity and HTN are two of the most significant health burdens in the world today, resulting in increased risk for NCDs and associated adverse cardiovascular events, as well as resulting in trillions of dollars in direct and indirect costs annually. The obesity–HTN phenotype is common and is associated with a complex cascade of pathophysiologic adaptations to multiple systems. When these conditions are combined, there is an increased risk for adverse events and poor outcome; unfortunately, the prevalence of the obesity–HTN phenotype is high. As such, aggressive treatment of this condition is imperative. Primordial prevention of obesity must become an integral component moving forward and requires a collaborative approach by key stakeholders across multiple sectors; promoting healthy lifestyle behaviors across the lifespan is a key component of primordial prevention and HLM; these healthy lifestyle interventions are also a primary intervention in all individuals presenting with the obesity–HTN phenotype. Surgical and pharmacologic options should also be considered in eligible patients. The overarching goals are long-term maintenance of weight loss, blood pressure control, and reversal of the pathophysiologic cascade associated with this condition.

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Conflicts of interest

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