OBESITY & HYPERTENSION – 'TWO PEAS IN A POD'

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ABSTRACT

There is a global epidemic of obesity and hypertension. These two relatively common disorders derive from a basic underlying pathophysiologic abnormality, like 'two peas in a pod' There is a consensus that obesity predicts the future development of hypertension and that the relationship between blood pressure and body weight is linear independent of gender, age, and socioeconomic status. This brief commentary outlines the pathogenetic mechanisms for the obesity-hypertension association. These mechanisms are likely complex, multifactorial, and polygenic with possible roots in early ontogeny. A unifying hypothesis should integrate food intake and excess (resulting in weight gain) with increased sympathetic nervous activity (resulting in increased blood pressure). The adipokine, leptin, appears well suited to fill that role - its hypothalamic signaling pathways and neurovascular outcomes are therefore explored in some detail. An understanding of these relationships from the perspectives of both epidemiology and pathophysiology is crucial to the management of both disorders – obesity with hypertension - and particularly more so in developing countries that lack the resources to deal with the looming epidemic of atherosclerotic cardiovascular disease,

Keywords: Obesity, Hypertension, Metabolic syndrome, Leptin, Sympathetic nervous system.

BACKGROUND

The prevalence of obesity has ballooned over the past several years, independent of gender, race, ethnicity, or socio-economic stratification. In global terms, the prevalence of obesity and associated cardiovascular disease (CVD) has increased to the extent that >1 billion people are overweight or obese with staggering economic costs. It is currently estimated that obesity accounts for 2–7% of total global healthcare costs.[1,2] In the US, about 68% of adults are either overweight or obese, and rates in children and adolescents are rising, now close to 33%. These observations are mirrored by reports from not only other developed countries of Europe and Australasia but also in developing countries.[1,2]

Concerning Africa, the World Health Organization (WHO; Africa Region) projected that 1 in 5 adults and one in 10 children and teenagers are likely to be obese by December 2023. The WHO further suggested that the prevalence of obesity among African adults and children/adolescents will range from 14 - 31% and 5 -17% respectively. In some support, a Lancet study from rural and urban Malawian subjects reported obesity rates of 9-44% in men and women, dependent on rural or urban domicile.[3] The problem of overweight children is particularly concerning – in 2019, the continent was home to 24% of the world's overweight children aged less than five years.

A systematic review and meta-analysis performed on a large number of subjects in Nigeria indicated that the respective prevalence rates of overweight and obesity were 26% and 15.0%, with an increasing trend, especially among urban dwellers.[4] A study conducted in the Enugu metropolis (South-Eastern region of Nigeria) reported that obesity increased the odds of hypertension by as much as 50%.[5]

It is well recognized that increased body mass is an important CVD risk factor contributing to the current epidemic of atherosclerotic cardiovascular disease (ASCVD) particularly with its association with metabolic syndrome, hypertension, diabetes, dyslipidemia, and insulin resistance.

In an almost parallel fashion to obesity prevalence, there is also recognition of an increasing global prevalence of hypertension. In 2010, 31% of the world's adults had hypertension with respective prevalence rates of 29% and 32% in high-income countries (HIC) and low to middle-income countries (LMIC).[2] This translates globally to about 1.4 billion people, distributed as 349 million in HIC and 1.04 billion in LMIC.[2]

Obesity & Hypertension

It has been estimated that 60%–70% of hypertension in adults is attributable to adiposity. This association between body weight and blood pressure (BP) increases over time with weight gain, even among lean individuals.

Reports from the US indicate that obese individuals have a 3.5-fold increased likelihood of having hypertension, and 60% of hypertensive adults are >20% overweight.[7] Indeed, in US adults and children, the increase in obesity rates was paralleled by the increased prevalence of hypertension from 25.0% to 28.7% over 10 years from 1991 to 2000. Lean subjects with hypertension are about 2–3 kg heavier than age- and sex-matched normotensive[7]. individuals.[6,7]

There is also evidence from a Chinese population study that increasing body mass is associated with the increasing prevalence of hypertension. Wang *et al.*[8] demonstrated that the prevalence of hypertension increased from 44% in those with BMI < 18.5 kg/m^2, to 55% (BMI 19-24 kg/m^2), 69% (BMI 24-28 kg/m^2), and 81% (with BMI >28 kg/m^2). These observations were independent of gender and reproduced with waist circumference (WC) as the index of body mass.[8]

Observations on African subjects are consonant with these reports. A study on about 30,000 adult Africans in 13 countries confirmed that hypertension was extremely common, with an overall prevalence of about 48%, and an age-adjusted prevalence of 33-34% in men and 44% in obese subjects. That study further indicated that obesity was independently associated with hypertension (odds ratio, OR, 2.5), with the odds of hypertension in obesity increasing with age from 2.0 in younger to 8.8 in older subjects. Obese and older Africans are more than twice as likely to be hypertensive.[9]

In addition, the sex-stratified proportions of hypertension were significantly higher among obese men than women (67-72% vs. 58-63%) while the adjusted odds ratio (aOR) of hypertension in the presence of obesity was consistently higher among women [2.1 - 14.1) than men [2.0 - 8.8], across all age categories. In both sexes, the aOR of hypertension in obesity was consistently higher in the older age groups. Overall, obese participants were twice as likely to be hypertensive (aOR, 2.4). This study concluded that hypertension and obesity are extremely common across multiple African countries, with the highest age-adjusted proportion in Western Africa and among men.[9]

Another systematic review of the determinants of systemic hypertension in older (age >50 years.) Africans resident in Ghana, Nigeria, CAR/Congo, South Africa, Uganda, Cameroon, and Tanzania. Kenya, Senegal, Burkina Faso, and Tunisia, reported that the key determinants of systemic hypertension in that age group were overweight/obesity, history of stroke, and female sex. There was a clear dose-response relationship between blood pressure and body mass - those with BMI >25 kg/m^2 were 1.2 - 2.0 times as likely as those with BMI <25 kg/m^2 to have hypertension. In Tunisia, for instance, hypertension prevalence was about 30% in normal-weight elderly subjects (BMI 18-25 kg/m^2), 49% among overweight non-obese (BMI 25-30kg/m^2), and 64% among overweight (BMI>30kg/m^2). Conversely, among South Africans, underweight (BMI < 18.5 kg/m^2) was associated with a lower prevalence of hypertension.[10]

Some reservations have however been expressed to the effect that the relationship between obesity and hypertension is perhaps not always straightforward.[1] Hypertension is not an invariable consequence of obesity, and there is some evidence that blood pressures are correlated with various measures of adiposity in normotensive but not in hypertensive individuals. While the prevalence of hypertension increased in all BMI strata, the upward shift of systolic blood pressures across the overall blood pressure distribution was observed only in BMI <25 kg/m^2 individuals.[1] The potential impact of adiposity on blood pressure is attenuated in obese, hypertensive individuals.[1] Also significant from the pathophysiologic perspective is that the distribution of body fat matters. Visceral fat is a more important determinant of BP elevation than peripheral body fat and is the major contributor to metabolic syndrome.[11]

Hypotheses

It is speculated that obesity-related hypertension is multifactorial and polygenic, and derived from mechanisms that likely involve genetic and epigenetic phenomena. While the morbid manifestations occur in adulthood, there are roots in early ontogeny. It is hypothesized that weight gain and blood pressure elevation are intermediate phenotypes of an underlying neuro-endocrine overactivity that needs to be further explored.[1,6,7,12] The pragmatic response is to attempt to establish a link between mechanisms that elevate blood pressure while at the same time stimulating food consumption and/or lowering energy expenditure.[12]

What is non-controversial however is that the association of obesity with hypertension significantly worsens cardiovascular disease risk. This is demonstrated in Figure 1, derived from the Chicago

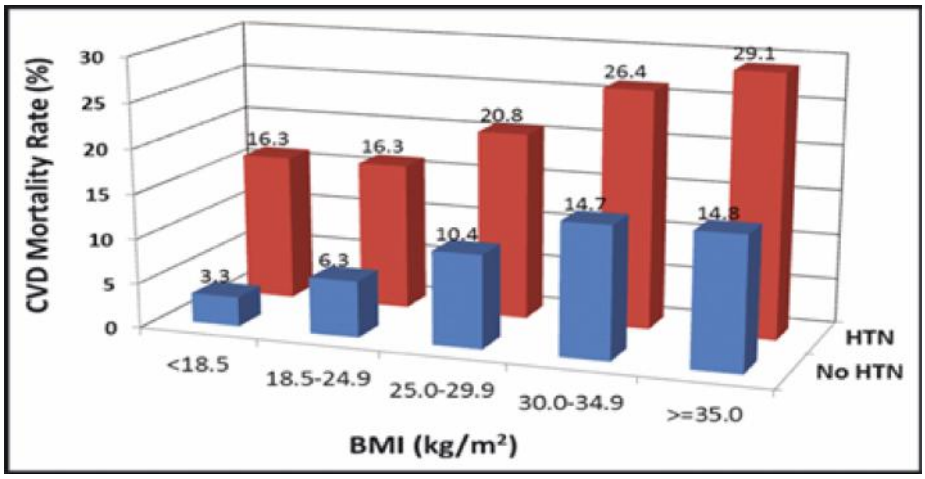

Figure 1: 32 yr. rates of death due to CVD in participants in the Chicago Heart Association Detection Project in Industry cohort, stratified by baseline BMI and HTN status.[13]

Heart Study, wherein for each incremental BMI category, the presence of hypertension increased cardiovascular disease mortality rates by about 13-15%.[13]

Pathogenetic Mechanisms

A. Molecular Genetics

Is obesity genetically determined? [6,12]. This is the subject of multiple research efforts. What is clear is that many of the described obesity-related genes are expressed in the brain and appear to modulate appetite, like the sites of action of leptin. Some adiposity-associated genes such as tumor necrosis factor-alpha (TNF-α), ß3-adrenergic receptor, and G-protein ß3 subunit [14,15] have been reported to contribute to the development of hypertension. Nevertheless, the specific genetic relationship between obesity and hypertension remains poorly understood. Undoubtedly environmental factors such as poor dietary choices, reduced physical activity, urbanization, stress, and other uncharacterized factors interact with genetics in the pathogenetic process.

B. Vascular, Metabolic and Neural Mechanisms

The mechanisms for the development of obesity-related hypertension are likely to be complex, interdependent, and possibly redundant. The suggestions include insulin resistance, sodium retention, impaired pressure natriuresis, increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system (RAAS), and endothelial dysfunction.[6,7,12] The primary mechanisms and possible underlying factors are outlined in Table 1 and will not be discussed in further detail in this perspective article.

Table 1: Vascular, metabolic and neural pathogenetic mechanisms of obesity-related hypertension[6,7,12]

Primary Mechanism	Possible Underlying Mechanisms
Sodium retention	Anti-natriuretic effect of insulin
	Increased renal SNS activity.
	Increased aldosterone
	Increased cortisol activity
Increased activity of the Sympathetic Nervous System (SNS)	Anatomic renal compression
	Insulin resistance
	Renin–angiotensin system
	Leptin/other adipokines
	Obstructive sleep apnea
	ß-Adrenergic receptor polymorphisms
	Psychological stress
Increased circulating and adipose tissue renin-angiotensin	Increased renal SNS activity
Impaired vascular endothelial function	Insulin resistance
Other vascular mechanisms	Insulin resistance
	Altered vascular ion transport

As Figure 2 indicates[7], however, the observed phenotype of obesity-associated hypertension likely results from interactions between multiple genes and the environment that have impacted pathophysiologic phenomena such as oxidative stress, endothelial dysfunction, renal damage, and activation of the renin-angiotensin system.[6,7,12] The effects on the vascular and circulatory systems influence the development of obesity and hypertension. Increased sympathetic nervous system activity is believed to be central to this process.[7]

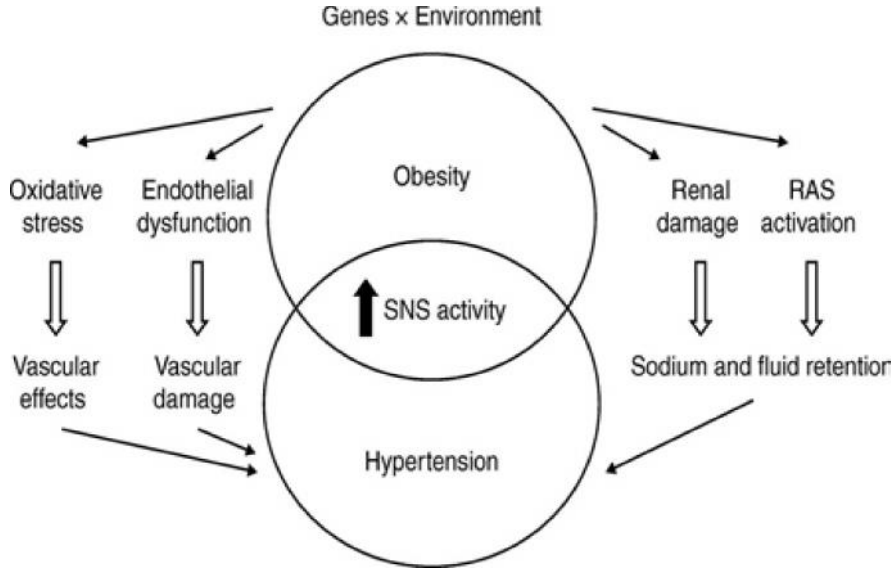

Figure 2: Relationship between obesity and hypertension and mechanisms by which obesity may cause Hypertension.[7]

A less understood but potentially therapeutically significant pathogenetic process is the obesity-related enhanced secretion and/or function of leptin and other adipokines.[12] The physiologic control of nutrient supply and availability (mediated by leptin) might, through central (hypothalamic) signal transduction pathways, result in activation of the sympathetic nervous system. The potential outcome is changes in both body mass (obesity) and vascular tone homeostasis (hypertension).

C. Leptin

Leptin is a 167 AA protein, a product of the *ob* gene, mostly produced by adipose tissue. Its physiologic effects are exerted at the median eminence of the hypothalamus after receptor binding in the arcuate nucleus, and subsequent downstream signaling is relayed to other interconnecting hypothalamic nuclei. Leptin is involved in regulating energy expenditure and appetite, immunomodulation, and reproductive function.[16]

Leptin levels are related to fat mass. Obesity is classically associated with hyperleptinemia and leptin resistance. Conversely, hypoleptinemia and/or leptin receptor dysfunction induce human and rodent hyperphagia and obesity. There is also some evidence that leptin may be important in the pathogenesis of hypertension. This is based on the following reports:[12,17,18,19]

- Leptin levels and blood pressure correlate modestly after adjustment for fat mass.
- Plasma leptin concentration can independently predict the onset of hypertension.

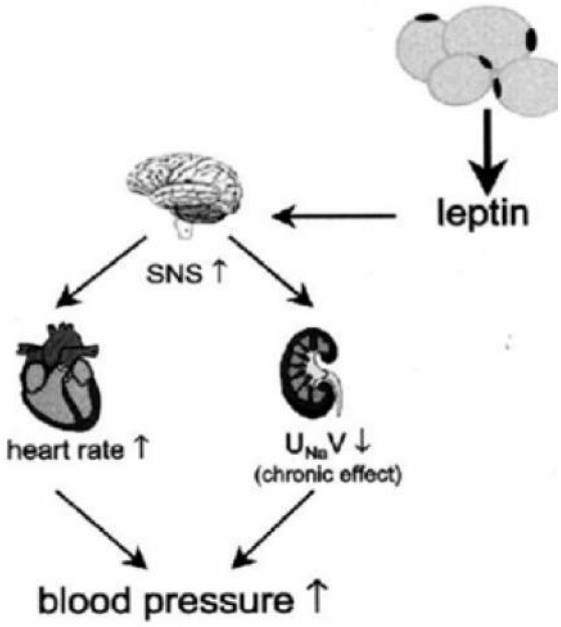

Figure 3: Consequence of sympathetic input to heart and kidney:[26]

- Increased cardiac output from increased heart rate and Na retention.
- circulatory volume expansion.
- elevated BP

- Chronic systemic and intra-cerebral administration of leptin increases blood pressure in rats.
- Overexpression of leptin is associated with hypertension despite weight loss.
- Blood pressure is not increased in obese, leptin-deficient *ob/ob* mice or obese, leptin-deficient humans.

The consensus is that obesity-associated leptin resistance is selective for anorexigenic effects and does not appear to influence leptin effects on natriuresis, the sympathetic nervous system (SNS), and the vasculature. It has indeed been suggested that increased sympathetic outflow by increased leptin may increase arterial pressure by both centrally mediated effects on the hypothalamus and peripherally.[17,18]

Some of these hypotheses have been supported by clinical studies in humans, a few of which are listed below:[19,20,21]

1. Obese and hypertensive individuals are hyperleptinemic and leptin activity-upregulating mutations can lead to hypertension with or without obesity.
2. Individuals with the rare congenital leptin deficiency, or loss-of-function leptin and leptin receptor (LR) mutations appear to be protected from the development of hypertension even in the face of obesity; patients present with postural hypotension from impaired SNS activity and/or reduced RAAS activation and chronic leptin treatment is beneficial in some of the patients.
3. Patients with essential hypertension tended to have higher baseline leptin levels, unchanged after 8 weeks of treatment - the baseline leptin level predicted the magnitude of post-treatment blood pressure reduction.
4. Genotypic differences in humans concerning leptin-induced susceptibility to obesity-associated hypertension:
    - The G2548A single nucleotide polymorphism (SNP) of the promoter region of the leptin gene influences leptin expression and has been associated with increased systolic blood pressure in pregnancy.
    - The Q223R and K109R SNPs located in the exons of genes for the LR, result in altered translated protein and are associated with lower blood pressure in middle-aged men.

The pathogenetic mechanisms downstream of leptin signaling in the hypothalamus have been described in a recent review article[12]. In brief, signal transduction pathways downstream to leptin binding to receptors in the arcuate nucleus result in increased production of pro-opiomelanocortin (POMC). Post-translational POMC processing produces melanocyte-stimulating hormone (MSH) that activates melanocortin receptors (MCR). The physiologic consequences of activation of MCR (and LR) include increased blood pressure and sympathetic activity in the kidneys and brown adipose tissue. Confirmation of the synergistic roles of the MCR and LR comes from observations that antagonizing MCR prevents some of leptin's effects.

Indeed, the peripheral autonomic nervous system responds to weight change by adjusting the body's energy expenditure. In nonobese humans, a weight loss of about 10% results in increased parasympathetic and decreased sympathetic activity, resulting in a reduction in mean arterial pressure (MAP); the opposite is seen with weight gain and associated increase in leptin levels. This observation reinforces the belief that leptin acts at least partly through the SNS and that the hyperleptinemia of obesity may explain some of the increase in sympathetic activity in that disorder. Further confirmatory evidence is derived from observations that leptin infusion did not increase MAP in obese mice after adrenergic blockade.[22,23,24,25]

Figure 3 graphically illustrates the cardiovascular and renal actions of leptin.[26] It increases SNS outflow by central hypothalamic mechanisms. The subsequently enhanced renal sympathetic activity decreases renal sodium excretion (UNaV) which together with increased heart rate will raise blood pressure in obese subjects.

CONCLUSION

Globally, prevalence rates of obesity and hypertension have increased, often together and in parallel, over the past several decades irrespective of gender, race, ethnicity, or socioeconomic groups. Increased body mass and blood pressure constitute important cardiovascular disease risk factors contributing significantly to morbidity and mortality from atherosclerotic cardiovascular disease. A significant proportion of hypertension in adults is attributable to adiposity and the association between body weight and blood pressure increases over time with weight gain, even among lean individuals. The increase in obesity rates occurs parallel to the increased prevalence of hypertension.

The pathogenesis of obesity-related hypertension is uncertain but may be related to a variety of factors including increased sympathetic activity, abnormalities of the renin-angiotensin system, sodium retention, and endothelial dysfunction, acting independently or in concert with increased circulating leptin.

This review has outlined the potential mechanisms through which changes in hypothalamic leptin signal transduction pathways mediate the pathogenetic relationships between obesity and hypertension. It is suggested that there is a nexus between leptin and blood pressure homeostasis, mediated primarily via the sympathetic nervous system. This hypothesis is worthy of further detailed investigation for a better understanding of the underlying physiologic principles and importantly, for potential pharmacologic manipulation of the pathways for prevention and treatment of obesity-associated hypertension and the complicating cardiovascular disease.

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