A Comprehensive Review on Obesity Induced Hypertension: Role of Sns, Raas and Physical Compression of Kidneys

Ramakrishna Shabaraya A\(^1\), Shreeraksha K\(^2\)

\(^{1}\)Department of Pharmacy Practice, Srinivas College of Pharmacy, Valachil, Mangalore
\(^{2}\)Department of Pharmacy Practice, Srinivas College of Pharmacy, Valachil, Mangalore

Submitted: 25-11-2023
Accepted: 05-12-2023

ABSTRACT

Obesity-induced hypertension refers to the condition where excess body weight, especially in the form of fat, contributes to the development of high blood pressure. This review aims to explore the major pathways leading to hypertension in obesity and their management. The major mechanisms behind this connection include overactivity of sympathetic nervous system, renin angiotensin aldosterone system and physical compression of kidneys. Sympathetic overactivation may be contributed by hyperleptinemia, hyperinsulinemia/insulin resistance, hyperadiponectinemia, baroreceptor dysfunction. Angiotensin II stimulates renal sodium retention and secretion of aldosterone, constricts efferent arterioles that leads to increased tubular sodium reabsorption. Physical compression of kidneys by visceral fat, perinephritic fat and renal sinuses fat increase BP in obese individuals. These factors collectively disrupt the body's natural blood pressure regulation, leading to elevated blood pressure levels in individuals who are overweight or obese. Managing weight through a healthy lifestyle, including proper diet and regular physical activity, can help mitigate the risk of obesity-induced hypertension. In conclusion, this review sheds light on the major mechanisms behind this connection, which is essential in managing the condition and to develop certain lifestyle changes that would prevent development of the same.

Keywords: Obesity; Hypertension; sympathetic nervous system; renin-angiotensin aldosterone system stimulation; physical compression of kidneys

I. INTRODUCTION:

Obesity is characterized by an excessive accumulation adiposity to the extent that impairs one’s health and is often defined using the body mass index (BMI). The WHO defines normal weight as BMI 18.5–24.9 kg/m\(^2\); overweight as BMI 25–29.9 kg/m\(^2\); and obesity as BMI ≥30 kg/m\(^2\). A BMI of 30 or higher is considered obese.\(^1\),\(^2\) The World Health Organization (WHO) has recognized them as major risk factors for various non-communicable diseases, such as cardiovascular disease, diabetes, and stroke. According to recent estimates from the World Health Organization (WHO), in 2016 over 1.9 billion adults were overweight and over 650 million of those persons were obese.\(^3\) It is predicted that if current trends continue, the prevalence of obesity would be higher than 21% in women and 18% in men worldwide by 2025.\(^4\) Obesity and hypertension are two interrelated health issues that have reached epidemic proportions worldwide. A number of metabolic and cardiovascular conditions are linked to obesity, including hypertension, which is the main factor mediating fat-induced cardiovascular illness.\(^5\) This comprehensive review aims to explore the complex relationship between obesity and hypertension, shedding light on the underlying mechanisms and management strategies.

RELATIONSHIP BETWEEN OBESITY AND HYPERTENSION:

Several studies have shown positive association between weight gain and increase in blood pressure.\(^6\),\(^7\)\(^8\) Research indicates that those who are obese have a 3.5-fold higher risk of developing hypertension, with an increase in adipose stores linked to 60% of cases of hypertension. According to NHANES data, the prevalence of hypertension is 42.5% in obese people with a BMI < 30 kg/m\(^2\), compared to 15.3% in lean people.\(^7\) Excessive visceral fat distribution is associated with numerous hormonal, inflammatory, and endothelial changes. All of these mechanisms, when triggered or activated, set off a series of events that lead to an increase in blood pressure and an increase in cardiovascular risk.
These events include the stimulation of the sympathetic nervous system and RAAS, the development of insulin resistance, impairment of baro- and chemoreflex cardiovascular control, endothelial dysfunction, and an increase in sodium retention. Visceral fat distribution in obese individuals is affected by genetic and environmental factors. Genetic factors include tumor necrosis factor-α, β3 adrenergic receptor, G-protein β3 subunit. Environmental factors include intake of alcohol, cigarette smoking, timing of onset of childhood obesity, alterations in daily-life habits, changes in lipid profile. The mechanisms underlying obesity-related hypertension are complex and include interactions between renal, metabolic, and neuroendocrine pathways. The important mechanisms include: over activation of sympathetic nervous system (SNS), renin-angiotensin aldosterone system (RAAS) stimulation, and physical compression of kidneys.

**BEHAVIOUR OF SNS IN OBESITY:**

Obesity, even in the absence of elevated blood pressure, exhibits adrenergic activation markers, such as elevated resting heart rate and plasma noradrenaline levels. Microneurographic studies have demonstrated that there is greater levels of sympathetic activation, and a direct relationship between sympathetic activity and waist-to-hip ratio or waist circumference in patients with visceral body fat distribution. Centrally located fat also plays a significant role in development of hypertension. Obese individuals have increased SNS activity which is assessed by plasma norepinephrine, urinary norepinephrine excretion, tissue norepinephrine spillover, or microneurography techniques. There exhibits a mild SNS activation in tissues such as kidneys and skeletal muscle. As compared to lean hypertensive subjects, pharmacologic antagonism of adrenergic receptor leads to greater reduction in blood pressure in obese individuals. Also, it is observed that in a high fat diet model of obesity in dogs, renal sympathetic denervation significantly reduces sodium and water retention and increase in arterial pressure. Thus, chronic sympathetic overactivity, which is characterized by elevated norepinephrine release and heightened SNS reactivity, is linked to obesity. SNS over activity manifests physiologically as increases in heart rate, cardiac output, and renal tubular sodium reabsorption. This elevated SNS activity in obese people is caused by a number of mechanisms, including: hyperleptinemia, activation of the central pro-opiomelanocortin/melanocortin-4 receptor (POMC/MC4R), hyperinsulinemia/insulin resistance, hypoadiponectinemia, increased angiotensin II levels, and baroreceptor dysfunction.

**Hyperleptinemia:**

Adipocytes release leptin in proportion to their fat mass, which acts on CNS, especially on the hypothalamus to regulate energy balance by reducing appetite and stimulating energy expenditure. Furthermore, leptin raises SNA to several tissues, including the kidneys and blood vessels, which are implicated in cardiovascular control. A study on rodents (lean animals) infused with leptin at a rate that raise the blood concentration to values that we would expect to see in severe obesity, has shown anorexic effect and tremendous weight loss in a short period of time, which was expected to lower blood pressure. But it lead to slow progressive increase in BP and heart rate, which was normalized by α and β adrenergic blockade, indicating it was due to sympathetic activation. Elevated serum leptin levels combined with selective leptin resistance have emerged as potential mechanisms driving sympathetic activation and hypertension in obesity. One of the main mechanisms for sympathetic overactivity is the action of leptin on hypothalamic pro-opiomelanocortin (POMC) neurons. Leptin activates melanocortin receptor 4 (MC4R) by stimulating its receptors in POMC neurons, which is mediated by α-MSH (α-melanocyte stimulating hormone) released from POMC neurons which regulates food intake, increased SNS activity and development of HTN. A study shows that when leptin receptors on POMC neurons are deleted, the blood pressure effect of leptin is completely abolished. Furthermore, pharmacologic blockade of CNS MC3R and MC4R completely abolished the hypertensive effect of leptin and acute effect of leptin on activation of renal SNS. According to a study in humans and rodents, a significant increase in BP was observed on chronic administration of MC4R agonist. Thus, in humans and rodents, activation of POMC-MC4R pathway leads to an increase in BP.

**Hyperinsulinemia/Insulin Resistance:**

Obesity and insulin resistance are frequently associated. Because insulin generally inhibits SNS function and decreased insulin
sensitivity throws this control off, insulin resistance can lead to an increase in SNS activity.\(^{32}\) Hyperinsulinemia can lead to hypertension through several mechanisms, that mainly includes increased reabsorption of sodium in the renal tubules that leads to extracellular fluid volume expansion-raising BP, vasoconstriction that raises peripheral vascular resistance, overactivity of SNS, inflammation and oxidative stress which damage walls of blood vessels and disrupt normal BP regulation.\(^{33}\)

**Hypoaldiponectinemia:**
Adiponectin, mainly synthesized in adipose tissue is a 244 amino acid protein of APM1 gene.\(^{34}\) Several clinical studies have shown a positive correlation between low serum adiponectin and hypertension.\(^{35,36}\) It exaggerates SNS activity through several ways including enhancing insulin resistance, increased inflammation, endothelial dysfunction (impaired vasodilation which is compensated by increasing SNS activity) and by negatively affecting baroreceptor sensitivity, leading to increased SNS activity.\(^{37}\)

**Baroreceptor dysfunction:**
Baroreceptors are specialized pressure sensors located in various blood vessels, especially in the carotid sinuses and the aortic arch. They play a crucial role in the regulation of blood pressure by monitoring changes in blood vessel stretch and relaying this information to the central nervous system to modulate the heart rate and vascular tone. Obesity is often associated with a decrease in baroreceptor sensitivity. Baroreceptors become less responsive to changes in blood pressure in obese individuals. This reduced sensitivity means that the baroreceptors may not effectively relay information to the central nervous system about changes in blood pressure, impairing the body's ability to regulate blood pressure appropriately. Furthermore, increased SNS activity, insulin resistance, inflammation and oxidative stress, hyperleptinemia impair the sensitivity and responsiveness of baroreceptor.\(^{38,39}\)

**ROLE OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM (RAAS):**
Studies in experimental animals and humans have proved activation of RAAS in obesity, which leads to elevated blood pressure.\(^{40,41}\) Experiments in obese dogs have shown that ACE (Angiotensin Converting Enzyme) Inhibitors and ARBs (Angiotensin Receptor Blockers) reduce sodium reabsorption, extracellular volume expansion and increased arterial pressure.\(^{40,41}\) Angiotensin II (ANG II) directly stimulates renal sodium retention and secretion of aldosterone.\(^{42}\) ANG II constricts efferent arterioles that leads to increased tubular sodium reabsorption by increasing peritubular capillary reabsorption and also increases glomerular hydrostatic pressure. Thus, RAAS activation in obesity may result in glomerular injury by aggravating increased glomerular pressure caused by increased arterial BP and vasodilation of afferent arterioles.\(^{42}\) According to a study in obese patients, plasma aldosterone levels are mildly elevated that acts on the kidneys to promote retention of sodium and excretion of potassium, resulting in an increase in sodium and water retention, leading to an expansion of blood volume, which increases blood pressure and hyperaldosteronism may lead to resistant hypertension is observed in obese individuals.\(^{43}\) In accordance with a study in obese dogs, mineralocorticoid receptor (MR) antagonism diminished retention of sodium, elevated BP and glomerular hyperfiltration. Combining MR antagonists with ACE inhibitors or ARBs may be particularly useful in preventing obesity induced sodium retention and hypertension.\(^{44}\)

**PHYSICAL COMPRESSION OF KIDNEYS:**
Physical compression of kidneys by visceral fat may raise blood pressure.\(^{45}\) As the kidneys are surrounded by a tight capsule, expansion of the extracellular matrix (ECM) in the kidney medullae could also contribute to renal compression and increased intrarenal tissue pressure. The kidneys of obese dogs and rabbits given a high-fat diet for several weeks showed nearly total encapsulation and fat penetration within the kidney sinuses. These modifications were associated with notable raises in the hydrostatic pressure of the renal interstitial space, which might exert compressive force on the Henle loop, decreasing the tubular flow rate and raising fractional sodium reabsorption.\(^{46,47}\) Renal compression may also be caused by high intra-abdominal pressure, which is a result of increased accumulation of visceral fat.\(^{48}\) Reduced sodium chloride transport to the macula densa due to high intrarenal pressures and a decreased flow rate into the loop of Henle would increase renin secretion and formation of ANG II and aldosterone, which would promote further sodium reabsorption. Aldosterone-independent mechanisms may also contribute to renal tubular mineralocorticoid receptor (MR) activation and increased sodium...
reabsorption. The increased renal sodium reabsorption leads to compensatory renal vasodilatation which, in combination with increased blood pressure, initially causes increased glomerular hydrostatic pressure and glomerular hyperfiltration, which may further exacerbate renal injury. Small elevations in renal interstitial hydrostatic pressure (3–4 mmHg) may prevent salt reabsorption in the renal tubules of obese dogs, however significant elevations of this kind (to approximately 19 mmHg) might boost the absorption of salt. Thus, one of the mechanisms that obesity leads to hypertension is through increase in intrarenal pressure caused by accumulation of fat within and around the kidneys. A study in elderly population has shown that in addition to renal compression due to visceral and perinephritic fat, accumulation of fat in renal sinuses may be related to stage II hypertension. Thus, physical compression of kidneys by visceral fat, perinephritic fat and renal sinuses fat collectively result in elevated BP in obese individuals.

MANAGEMENT STRATEGIES: 
Lifestyle modifications: 
Both obesity and hypertension are lifestyle related disorders; thus, lifestyle changes is the first recommended intervention. As per Dietary Approach to Stop Hypertension (DASH), diet rich in fruits, vegetables and low fat dairy products, which are rich in calcium, magnesium, potassium and dietary fibre, and less fatty acid and cholesterol has proved to reduce blood pressure among hypertensive patients. A meta-analysis of 25 RCTs has shown 4.4mmHg reduction in SBP and 3.57mmHg reduction in DBP with 5.5kg reduction of weight. Another meta-analysis has shown 4.5 and 3.2 mmHg reduction in SBP and DBP reactivity with 4kg reduction in body weight among hypertensive patients. The Trial of non-pharmacologic Interventions in the elderly (TONE) including 9745 individuals, aged 60–80 years, it was found that reduction of salt intake and bodyweight resulted in SBP/DBP decreases of 3.4/1.9 and 4.0/1.1 mmHg, respectively. The combination of both interventions resulted in an SBP/DBP decrease of 5.3/3.4mmHg. OSAS hypertensive patients with unhealthy lifestyle should consider modifying their lifestyle. Regular exercise and even a 10% reduction in body weight can improve abnormal breathing during sleep. Large BP-lowering effects can be achieved by combining caloric restriction and Continuous positive airway pressure (CPAP) in severe OSAS patients. The first line therapy recommended in obesity are calorie restriction and physical activity. In comparison, Targeted weight loss interventions in population subgroups found to be more effective than general-population approach for the prevention of hypertension.

Medications and multidisciplinary approach: 
Antihypertensive medications, including diuretic, ACE inhibitors and beta blockers, may be prescribed to control hypertension. In some cases, weight loss medications and bariatric surgery may also be considered. A collaborative care involving healthcare providers, nutritionists and mental health professionals may be considered.

II. CONCLUSION: 
Obesity and hypertension are intimately linked, forming a dangerous synergy that poses a substantial threat to public health. Understanding the mechanisms and epidemiology of this relationship is essential for effective prevention and management. The major mechanisms behind this connection include overactivity of sympathetic nervous system, renin angiotensin aldosterone system and physical compression of kidneys. By promoting lifestyle changes, early detection, and comprehensive care, it is possible to mitigate the impact of obesity-related hypertension, reducing the risk of cardiovascular complications and improving the overall health and well-being of individuals. Managing weight through a healthy lifestyle, including proper diet and regular physical activity, can help mitigate the risk of obesity-induced hypertension. Continued research and public awareness campaigns, policies promoting healthy lifestyles, improved nutrition and physical activity are vital in addressing this complex and pervasive issue.

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