International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

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, hypoadiponectinemia, 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 maechanisms of hypertension in obesity, knowledge of 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/m2, 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.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

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.[8] 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.[9] Environmental factors include intake of alcohol, cigarette smoking, timing of onset of childhood obesity, alterations in daily-life habits, changes in lipid profile.[10,11,12]

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.[8]

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.[13] 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.[14,15,16] Centrally located fat also plays a significant role in development of hypertension.[14,15,17] Obese individuals have increased SNS activity which is assessed by plasma norepinephrine, urinary norepinephrine excretion, tissue norepinephrine spillover, or microneurography techniques.[18,19] There exhibits a mild SNS activation in tissues such as kidneys and skeletal muscle.[20] As compared to lean hypertensive subjects, pharmacologic antagonism of adrenergic receptor leads to greater reduction in blood pressure in obese individuals.[21] 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 over activity, which is characterized by elevated norepinephrine release and heightened SNS reactivity, is linked to obesity.[5,22] 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.[23] 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.[24,25] Elevated serum leptin levels combined with selective leptin resistance have emerged as potential mechanisms driving sympathetic activation and hypertension in obesity.[26] One of the main mechanisms for sympathetic overactivity is the action of leptin on hypothalamic pro-opiomelnocortin (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.[27] A study shows that when leptin receptors on POMC neurons are deleted, the blood pressure effect of leptin is completely abolished.[28] 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.[29,30] According to a study in humans and rodents, a significant increase in BP was observed on chronic administration of MC4R agonist.[19,31] 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

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

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]

Hypoadiponectinemia:

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.[18] 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 amd aldosterone, which would promote further sodium reabsorption. Aldosterone-independent mechanisms may also contribute to renal tubular mineralocorticoid receptor (MR) activation and increased sodium

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

reabsorption. The increased renal sodium reabsorption leads to compensatory renal vasodilation 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.[49,50] 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.[51] 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 amd dietary fibre amd less fatty acid and cholesterol has proved to reduce blood pressure among hypertensive patients.[52, 53, 54] 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.[55] Another meta-analysis has shown 4.5 and 3.2 mmHg reduction in SBP and DBP reactively with 4kg reduction in body weight among hypertensive patients.[56] 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.[57, 58] Large BP-lowering effects can be achieved by combining caloric restriction and Continuous positive airway pressure(CPAP) in severe OSAS patients.[59] The first line therapy recommended in obesity are calorie restriction and physical activity.[60] In comparison, Targeted weight loss interventions in population subgroups found to be more effective than general-population approach for the prevention of hypertension [61]

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 imvolving healthcare providers, nutritionists and mental health professionals may be considered.[62]

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.

REFERENCES:

[1]. Shah NR, Braverman ER. Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. PloS one. 2012 Apr 2;7(4):e33308.

[2]. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res 1998;6 Suppl 2:51S-209S.

[3]. Obesity and overweight [Internet]. Who.int. [cited 2023 Sept 17]. Available from: https://www.who.int/news-

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

room/fact-sheets/detail/obesity-and-overweight

[4]. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet 2016;387:1377-96.

[5]. Davy KP, Orr JS. Sympathetic nervous system behavior in human obesity. Neuroscience & Biobehavioral Reviews. 2009 Feb;33(2):116–24.

[6]. Wang Y, Wang QJ. The prevalence of prehypertension and hypertension among US adults according to the new Joint National Committee guidelines. Arch Intern Med 2004;164:2126-34.

[7]. Landsberg L, Aronne LJ, Beilin LJ, Burke V, Igel LI, Lloyd-Jones D, Sowers J. Obesity-related hypertension: pathogenesis, cardiovascular risk, and treatment – A position paper of the Obesity Society and the American Society of Hypertension. Obesity 2013;21:8-24.

[8]. Seravalle G, Grassi G. Obesity and hypertension. Pharmacol Res. 2017;122:1–7.

[9]. Pausova Z, Jomphe M, Houde L, Vezina H, Orlov SN, Gossard F. Gaudet D, Tremblay J, Kotchen TA, Cowley AW, Bouchard G, Hamet P. A genealogical study of essential hypertension with and without obesity in French Canadians Obes Res. 2002;10:463-470.

[10]. Jensen MD. Role of body fat distribution and the metabolic complications of obesity. J Clin Endocrinol Metab. 2008;93:S57-S63.

[11]. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, Giannattasio C, Brunani A, Cavagnini F, Mancia G. Sympathetic activation in obese normotensive subjects. Hypertension 1995;25:560-563.

[12]. Seravalle G, Grassi G. Sympathetic nervous system, hypertension, obesity, and metabolic syndrome. High Blood Press Cardiovasc Prev. 2016;23:175-179.

[13]. Young JB, Macdonald IA. Sympathoadrenal activity in human obesity: heterogeneity of findings since 1980. Int J Obes Relat Meatb Disord. 1992:16:959-967.

[14]. Grassi G, Dell'Oro R, Facchini A, Quarti Trevano F, Bolla GB, Mancia G. Effects of central and peripheral body fat distribution on sympathetic and baroreflex function in obese normotensive. J Hypertens. 2004;22:2363-2369.

[15]. Alvarez GE, Ballard TP, Beske SD, Davy KP. Subcutaneous obesity is not associated with sympathetic neural activation. Am J Physiol. 2004;287:H414-18.

[16]. Canoy D, Luben R, Welch A, Bingham S, Wareham N, Day N, Knaw KT. Fat distribution, body mass index and blood pressure in 22090 men and women in the Norfolk cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Norfolk)study. J Hypertens. 2004;22:2067-2074.

[17]. Kanai H, Matsuzawa Y, Kotani K, Keno Y, Kobatake T, Nagai Y, Fujioka S, Tokunaga K, Tarui S. Close correlation of intra-abdominal fat accumulation to hypertension in obese women. Hypertension 1990;16:484-490.

[18]. Hall JE, Crook ED, Jones DW, Wofford MR, Dubbert PM. Mechanisms of obesity-associated cardiovascular and renal disease. Am J Med Sci. 2002;324(3):127–137.

[19]. Hall JE, da Silva AA, do Carmo JM, et al. Obesity-induced hypertension: role of sympathetic nervous system, leptin, and melanocortins. J Biol Chem. 2010;285(23):17271–17276.

[20]. Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. Circulation. 1997;96(10):3423–3429.

[21]. Wofford MR, Anderson DC, Brown CA, et al. Antihypertensive effect of alpha and beta adrenergic blockade in obese and lean hypertensive subjects. Am J Hypertens. 2001;14:694–698.

[22]. Kassab S, Kato T, Wilkins C, et al. Renal denervation attenuates the sodium retention and hypertension associated with obesity. Hypertension. 1995;25:893–897

[23]. Schwartz MW, Woods SC, Porte D, Jr., et al. Central nervous system control of food intake. Nature. 2000;404:661–671.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

[24]. Harris RBS. Leptin-induced increase in body fat content of rats. Am J Physiol Endocrinol Metab. 2013;304(3):E267–81.
[25]. Wofford MR, Anderson DC Jr, Brown CA, Jones DW, Miller ME, Hall JE. Antihypertensive effect of alpha- and beta-adrenergic blockade in obese and lean hypertensive subjects. Am J Hypertens 2001; 14:694–698
[26]. Simonds SE, et al. Leptin mediates the increase in blood pressure associated with obesity. Cell. 2014; 159(6):1404–16.
[27]. Vaneckova I, Maletinska L, Behuliak M, Nagelová V, Zicha J, Kunes J. Obesity-related hypertension: possible pathophysiological mechanisms. J endocrinol. 2014 Dec 1;223(3):R63-78.
[28]. do Carmo JM, da Silva AA, Cai Z, Lin S, Dubinion JH, Hall JE. Control of blood pressure, appetite, and glucose by leptin in mice lacking leptin receptors in proopiomelanocortin neurons. Hypertension. 2011;57(5):918–926.
[29]. Haynes WG, Morgan DA, Djalali A, Sivitz WI, Mark AL. Interactions between the melanocortin system and leptin in control of sympathetic nerve traffic. Hypertension. 1999;33(1 Pt 2):542–547.
[30]. da Silva AA, Kuo JJ, Hall JE. Role of hypothalamic melanocortin 3/4-receptors in mediating chronic cardiovascular, renal, and metabolic actions of leptin. Hypertension. 2004;43(6):1312–1317.
[31]. Greenfield JR, Miller JW, Keogh JM, et al. Modulation of blood pressure by central melanocortinergic pathways. N Engl J Med. 2009;360(1):44–52.
[32]. Kahn BB, Flier JS. Obesity and insulin resistance. The Journal of clinical investigation. 2000 Aug 15;106(4):473-81.
[33]. Bönner G. Hyperinsulinemia, insulin resistance, and hypertension. Journal of cardiovascular pharmacology. 1994 Jan 1;24:S39-49.
[34]. Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone adiponectin in human disease. European Journal of endocrinology. 2003 Mar;148(3):293-300.
[35]. Chen MC, Lee CJ, Yang CF, Chen YC, Wang JH, Hsu BG. Low serum adiponectin level is associated with metabolic syndrome and is an independent marker of peripheral arterial stiffness in hypertensive patients. Diabetology & Metabolic Syndrome. 2017 Dec;9:1-0.
[36]. Shankar A, Marshall S, Li J. The association between plasma adiponectin level and hypertension. Acta cardiologica. 2008 Apr 1;63(2):160-5.
[37]. Vlasova M, Purhonen AK, Jarvelin MR, Rodilla E, Pascual J, Herzig KH. Role of adipokines in obesity-associated hypertension. Acta Physiologica. 2010 Oct;200(2):107-27.
[38]. Lohmeier TE, Warren S, Cunningham JT. Sustained activation of the central baroreceptor pathway in obesity hypertension. Hypertension. 2003 Jul 1;42(1):96-102.
[39]. Skrapari I, Tentolouris N, Katsilambros N. Baroreflex function: determinants in healthy subjects and disturbances in diabetes, obesity and metabolic syndrome. Current diabetes reviews. 2006 Aug 1;2(3):329-38.
[40]. Hall JE, Henegar JR, Shek EW, Brands MW. Role of renin-angiotensin system in obesity hypertension. Circulation. 1997;96:1–33.
[41]. Robles RG, Villa E, Santirso R, et al. Effects of captopril on sympathetic activity, lipid and carbohydrate metabolism in a model of obesity-induced hypertension in dogs. Am J Hypertens. 1993;6(12): 1009–1015.
[42]. Hall JE, Brands MW, Henegar JR. Angiotensin II and long-term arterial pressure regulation: the overriding dominance of the kidney. Journal of the American Society of Nephrology. 1999 Apr;10(4 SUPPL.):S258-65.
[43]. Bomback AS, Muskala P, Bald E, Chwatko G, Nowicki M. Low-dose spironolactone, added to long-term ACE inhibitor therapy, reduces blood pressure and urinary albumin excretion in obese patients with hypertensive target organ damage. Clinical nephrology. 2009 Dec 1;72(6):449-56.
[44]. de Paula RB, da Silva AA, Hall JE. Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. Hypertension. 2004 Jan 1;43(1):41-7.
[45]. Hall JE, Brands MW, Henegar JR. Mechanisms of hypertension and kidney disease in obesity. Annals of the New

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 6 Nov-Dec 2023, pp: 1573-1579 www.ijprajournal.com ISSN: 2249-7781

York Academy of Sciences. 1999 Nov;892(1):91-107.
[46]. Hall JE. The kidney, hypertension, and obesity. Hypertension. 2003 Mar 1;41(3):625-33.
[47]. Hall JE, Jones DW, Kuo JJ, da Silva A, Tallam LS, Liu J. Impact of the obesity epidemic on hypertension and renal disease. Current hypertension reports. 2003 Oct;5(5):386-92.
[48]. Sugerman H, Windsor A, Bessos M, Wolfe L. Intra-abdominal pressure, sagittal abdominal diameter and obesity comorbidity. J Intern Med. 1997;241(1):71–79.
[49]. Alonso-Galicia M, Dwyer TM, Herrera GA, Hall JE. Increased hyaluronic acid in the inner renal medulla of obese dogs. Hypertension. 1995;25(4 Pt 2):888–892.
[50]. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001;12(6):1211–1217.
[51]. Chughtai HL, Morgan TM, Rocco M, et al. Renal sinus fat and poor blood pressure control in middle-aged and elderly individuals at risk for cardiovascular events. Hypertension. 2010;56(5):901–906.
[52]. Tanaka M. Improving obesity and blood pressure. Hypertens Res. 2020;43(2):79–89.
[53]. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med. 1997;336:1117–24.
[54]. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344:3–10.
[55]. Neter JE, Stam BE, Kok FJ, Grobbee DE, Geleijnse JM. Influence of weight reduction on blood pressure: a meta-analysis of randomized controlled trials. Hypertension. 2003;42:878–84.
[56]. Semlitsch T, Jeitler K, Berghold A, Horvath K, Posch N, Poggenburg S, et al. Long-term effects of weight-reducing diets in people with hypertension. Cochrane Database Syst Rev. 2016;3:CD008274.
[57]. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284:3015–21.
[58]. Sherrill DL, Kotchou K, Quan SF. Association of physical activity and human sleep disorders. Arch Intern Med. 1998;158:1894–8.
[59]. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med. 2014;370:2265–75.
[60]. Samadian F, Dalili N, Jamalian A. Lifestyle modifications to prevent and control hypertension. Iran J Kidney Dis. 2016;10(5):237–63.
[61]. Hall ME, do Carmo JM, da Silva AA, Juncos LA, Wang Z, Hall JE. Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis. 2014;7:75–88.
[62]. Henning RJ. Obesity and Obesity-Induced Inflammatory Disease Contribute to Atherosclerosis: A Review of the Pathophysiology and Treatment of Obesity. Am6 J Cardiovasc Dis. 2021; 11(4): 504–529.