A Succinct Analysis of Hypertension and its Management Strategies

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Received 01 June 2023, Accepted for publication 16 June 2023, Published 30 June 2023

ABSTRACT

Hypertension, which is generally known as high blood pressure, holds the utmost significance as a flexible risk factor for overall population worldwide. It is directly related with an increased risk of cardiac disorders. Unfortunately, under half of the sufferer of high BP don’t know about their condition, and the one who know, they are either untreated or not treated properly. However, successful management of this disease has the potential to crucially reduce the worldwide burden of disease and deaths due to hypertension. The cause of hypertension includes a typical reciprocity of natural and physiopathological factors that influence many structures, in addition to genetic predilection. When patients of hypertension are being evaluated with hypertension, this is important to conduct exact and standard BP measurements, assess their predicted risk other heart related problems, determine if there is any indication of organ damage, identify if there is another reason for hypertension, and consider the simultaneous existence of two diseases like cardiac and renal disease. Healthy life management plays a crucial part in lowering BP and inhibiting the occurrence of hypertension and its associated cardiovascular sequelae. These modifications encompass dietary adjustments, increased physical activity, weight management, and other healthy lifestyle choices. Drug therapy or medication is highly effectual in lowering blood pressure and hold back the adverse cardiovascular outcomes in a large no. of patients.

Keywords: Pathophysiological Factors, Genetics, Etiology, Antihypertensive Drugs, Therapy.

INTRODUCTION

Continual increased BP in the arteries is the indicator of arterial hypertension, or in simple words hypertension. The proportion of systolic BP to diastolic BP is the standard way to express blood pressure. A prevalent trend in patients with hypertension is the presence of a positive family history, indicating a genetic predisposition to the condition. Numerous studies estimate the heritability, which measures the influence of genetic factors on trait variation, to be between 35% and 50%. Notably, genome-wide association studies have made significant strides by identifying approximately 120 genetic regions linked to blood pressure regulation. Collectively, these regions account for 3.5% of the overall variability in blood pressure. These discoveries hold increasing significance as we strive to explore novel pathways and biomarkers that can fuel the development of more advanced rational and therapeutic approaches for hypertension. Particularly in the age of exactitude medicine, this ’omics‘-driven exploration opens doors to more tailored and effective treatment strategies.[1]

Numerous rare and monogenic forms of hypertension have been identified, highlighting specific genetic mutations responsible for their pathogenesis. Examples of such conditions include Liddle syndrome, glucocorticoid-remediable aldosteronism (an excessive state of mineralocorticoid production), and mutations in PDE3A, which affects the function of PDE. In
these cases, a one gene mutation can entirely account for the development of hypertension, pointing towards the most appropriate treatment approach. However, when hypertension occurs due to the result of another underlying disorder/disease like primary pheochromocytoma, aldosteronism, or kidney artery stenosis, is called as secondary hypertension. In these instances, the hypertension is a consequence of an underlying condition and necessitates tailored management strategies.\[^2\]

Hypertension stands as the most widespread modifiable jeopardize factor for a range of cardiovascular diseases, involving coronary artery disease, heart attack, stroke, congestive heart failure, arrhythmia as well as CKD and MCI. It is the solo and most significant disease which is the reason to all-cause death and disability globally. The relationship between high blood pressure (BP) and an elevated risk of CVD is increasing and ongoing, with the risk rise beginning with a reading as low as 115/75 mmHg, which is within the healthy range. Thus, addressing hypertension through effective prevention and treatment measures plays a pivotal role in reducing the burden of diseases and promoting longevity across global populations. When managing high BP, it is crucial to examine a person's predicted ASCVD risk in addition to their BP readings alone. This holistic approach recognizes that individuals with a high risk of CVD derive the greatest benefits from treatments that lower blood pressure. By integrating the assessment of ASCVD risk, healthcare professionals can better tailor treatment strategies to effectively mitigate the impact of hypertension and improve long-term outcomes.\[^3\]

This Primer’s aim is to give a diverse overview of primary hypertension, covering its epidemiology and pathophysiology. It will be divided into techniques for preventing the progression of blood pressure elevation, as well as its management approaches, which includes leading blood pressure targets, for reducing BP and inhibit CVD outcomes in person with prevailing hypertension. Furthermore, the Primer will examine the impact of antihypertensive treatments on normality and regularity of life. Lastly, it will address current knowledge gaps, anticipate future trends, and provide insights into the prospects of hypertension research and treatment in the coming decade. By exploring these topics, this Primer intends to offer valuable insights into the understanding and management of hypertension, thereby contributing to advancements in the field.\[^4\]

**EPIDEMIOLOGY**

In the societies before industrialization, blood pressure levels exhibited slight distributions, and the mean values remained relatively stable throughout different age groups, averaging around 115/75 mmHg. These values likely represent the standard/ideal blood pressure for humans during that time. However, in modern societies, systolic blood pressure levels gradually and consistently increase with increasing stages of life among both males and females. This widespread observation can be attributed to the fact that becoming older serves as a substitute for the probability and the prolongation of unveiling to various environmental factors that gradually elevate BP over time. Excess salt consumption, insufficient dietary potassium intake, increased body fat index and obesity, alcohol use, and physical inactivity are among these risk factors.\[^5-6\]

Additional variables, like genetical susceptibility or poor intra-uterine settings, such as prenatal hypertension, show tiny but observable relationships with adult increased blood pressure levels. It is important to note that even modest increases in the average BP within a population can result in significant rises in the absolute number of individuals with hypertension. This emphasizes the substantial impact that population-wide changes in BP can have on public health, underscoring the need for effective preventive measures and management strategies to address hypertension.\[^7\]
With the progression of economic development, a distinct shift can be observed in the distribution of hypertension. Initially, hypertension tends to impact individuals with higher socioeconomic status. However, as economic expansion accelerates, the frequency of instances of hypertension and its associated consequences rises among persons with lower social economic status. This tendency is visible not just inside individual countries, but also across borders.

Furthermore, it is noteworthy that the pace of change in hypertension prevalence has accelerated significantly during the period from 2000 to 2010 compared to previous epidemiological transitions. This rapid increase in hypertension prevalence suggests the emergence of new challenges and health implications associated with changing lifestyles, dietary habits, and environmental factors in contemporary societies.[8]

Understanding these socioeconomic patterns and the accelerated rise in hypertension prevalence is crucial for addressing health inequalities and designing effective techniques for inhibition, early detection, and control of hypertension. By targeting interventions that account for socioeconomic factors, policymakers and healthcare providers can work towards reducing the burden of hypertension and its impact on populations worldwide.[9]

DISEASE BURDEN

The global prevalence of non-optimal systolic blood pressure (BP) levels has reached a staggering figure, with approximately 3.5 billion adults having BP levels above the optimal range (>110-115 mmHg), and 874 million adults experiencing systolic BP levels equivalent to or more than 140 mmHg. This indicates that one in every four persons globally has hypertension.

Non-optimal blood pressure has a significant influence on population health. Between 1990 and 2015, the overall amount of years of good health of life lost due to high blood pressure grew by 43%. This rise is attributed to population growth, older age, and a 10% rise in age-standardized hypertension incidence.

Annually, hypertension leads to 9.4 million deaths and accounts for the losing of 212 million years of healthy life, which represents 8.5% of the entire worldwide. These figures highlight the urgent need to address hypertension as a significant public health concern worldwide.

Efforts aimed at prevention, early observation, and effective control of hypertension are important for decreasing the burden of disease and promoting healthier populations. By implementing comprehensive strategies, including lifestyle modifications and appropriate medical interventions, it is achievable to mitigate the impact of hypertension and make the global health outcomes better.[10-11]

CARDIOVASCULAR DISEASE RISK

Prospective research studies have consistently demonstrated a strong and consistent positive relationship between high BP and heart illnesses. The link between blood pressure and CVD remains true for systolic as well as diastolic albeit it seems to be slightly stronger for systolic blood pressure in adults.[12]

This association between BP and CVD is observed in both genders, across every age group throughout maturity and for various major incarnations of cardiovascular disease, including ischemic and hemorrhagic stroke, peripheral vascular disease, coronary heart disease, CHF, and end-stage kidney disease. Although the intensity of the correlations and the slopes of the graph changes, the relationship stays constant. Importantly, this association exists independently from various cardiovascular disease risk variables, and BP has been shown to represent a substantial integrant in all cardiovascular disease risk prediction models.[13]

Notably, individuals with hypertension or those receiving treatment with medicines to decrease the
BP at the age of thirty have approximately a 40% more at danger of encountering CVD event compared to their counterparts with lower BP levels, when age and sex are taken into account. Moreover, individuals with hypertension likely to have cardiac incidents roughly five years earlier than those with lower BP levels.

Managing hypertension effectively and maintaining optimal BP levels are essential for reducing the risk of CVD events. Early detection, lifestyle modifications, and appropriate medical interventions are key strategies in mitigating the effect of hypertension and delaying the onset of cardiac diseases. Independent of baseline values, a substantial increase in systolic blood pressure of 20 mmHg or diastolic BP of 10 mmHg is associated with a more than twofold rise in the risk of attack or fatality from ischemic heart disease in persons aged 40 to 69. Conversely, a reduction of 5 mmHg in systolic blood pressure can cause a 14% decrease in stroke mortality and a 9% decrease in cardiovascular disease (CVD) mortality. As individuals reach older age groups, particularly 80 years and above, the relative risk associated with BP changes becomes slightly lower. However, the absolute risk of adverse events becomes significantly higher compared to earlier stages of life.[14-15]

These findings highlight the importance of controlling and managing BP throughout the lifespan. Even modest reductions in systolic BP can have a major influence on stroke risk reduction and CVD mortality. The absolute risk of adverse events associated with BP differences increases substantially with age, emphasizing the critical need for effective BP management strategies, especially among older individuals.

PATHOPHYSIOLOGY OF HYPERTENSION

BP Regulation

Multiple characteristics within the cardiovascular system control blood pressure (BP), including the volume of blood, cardiovascular output, and the overall equilibrium of arterial tone, which is governed by intravascular volume and neurohumoral systems. Physiological BP control is a complicated interaction of many parts within the consolidated neurohumoral system. One important element involved in BP control is the renin-angiotensin-aldosterone system, which has an important part in balancing fluid balance & vascular tone. Additionally, the work of natriuretic peptides and the endothelium, which affects vasodilation and vascular function, is crucial in maintaining BP homeostasis. The sympathetic nervous system also has an important role in regulating blood pressure by controlling vascular tone and cardiac output. Finally, the immune system has been recognized as an additional player in BP regulation. Disruptions or malfunctions in these components can cause prolonged increase in mean blood pressure over time. These anomalies help to target organ damage, like left ventricular hypertrophy and CKD, along with an elevated risk of CVD consequences. Understanding the intricate mechanisms involved in BP regulation and the complex interactions between these systems is crucial in identifying potential targets for interventions aimed at preventing and treating hypertension. By addressing abnormalities in BP control and mitigating their impact on target organs and cardiovascular health, it is possible to decreased the risk of problems associated with high BP and improve patient outcomes. The pathophysiological mechanisms underlying hypertension (high blood pressure) are complex and involve both genetic and environmental factors. Multiple genes are implicated in primary hypertension, which happens to be the most prevalent kind, and certain allelic variations of these genes coincide with an increased chance of acquiring high BP, particularly in those with a positive family background.[16]

In addition to genetic predisposition, environmental factors also come up with the development of hypertension. High consumption of salt, poor sleep quality or insomnia, drinking
too much alcohol, and high severity of mental stress are all risk factors for hypertension. Aging is also a significant factor that increases the likelihood of developing hypertension. As individuals age, their arterial vasculature tends to become stiffer due to various factors, including gradual changes in vascular collagen and a rise in atherosclerosis. These age-related changes contribute to the initiation of hypertension. Immunological variables, particularly in the conditions of viral or rheumatological diseases like rheumatoid arthritis, can have a major influence on hypertension. These conditions can further complicate the pathophysiology of hypertension. The mosaic theory of hypertension recognizes the multifaceted nature of its pathophysiology, incorporating the interplay between genetic factors, environmental influences, aging-related changes in the vasculature, and potential immunological factors. Understanding these various mechanisms is important for generating beneficial strategies for prevention, diagnosis, and management of hypertension.\[17\]

**Sodium Homeostasis Regulation**

Sodium (Na+) is essential for blood volume regulation. When serum sodium concentrations are elevated, it encourages fluid retention, which raises blood volume and, consequently BP. When daily salt consumption increases in normotensive persons, compensatory hemodynamic modifications occur to keep blood pressure steady. These changes include decreased renal and peripheral vascular resistance as well as enhanced endothelial production of nitric oxide, a vasodilator. However, in individuals with endothelial dysfunction, which can be influenced by genetic or environmental factors, salt sensitivity may develop. Salt sensitivity is characterized by a significant increase in BP following a high sodium load. These individuals often have impaired bioavailability of nitric oxide and an overproduction of transforming growth factor β (TGF-β), which can lead to fibrosis and oxidative stress. Persistent high sodium intake can further exacerbate endothelial dysfunction, even in people who are initially salt-resistant. The impact of high sodium intake extends beyond endothelial dysfunction and affects the gut microbiota as well. It has been demonstrated that excessive salt consumption depletes beneficial microorganisms, such as Lactobacillus murinus, in the gut microbiota. This depletion can cause to hypertension and increased salt sensitivity. Additionally, high salt intake has been associated with the induction of T helper 17 (TH17) cells, which are involved in driving autoimmunity. Studies in mice have demonstrated that treatment with Lactobacillus murinus can prevent salt-induced exacerbation of salt-sensitive hypertension by modulating TH17 cells. Similarly, in a study involving homo sapiens, a moderate salt challenge resulted in reduced survival of good bacteria species in the gut, increased TH17 cell activity, and elevated BP. These findings suggest that the gut microbiota plays a role in salt sensitivity and the pathogenesis of hypertension. The interplay between sodium intake, endothelial dysfunction, and the gut microbiota highlights the complexity of the mechanisms involved in hypertension development and supports the importance of considering multiple factors in its management and prevention.\[18\]

**Renin-Angiotensin-Aldosterone System**

Angiotensin II is a hormone that plays a significant role in regulating blood pressure. It increases the activity of many transporters, including the sodium-hydrogen exchanger (NHE3), sodium-bicarbonate exchanger, and sodium-potassium ATPase, in the proximal tubule of the kidneys. It also induces the synthesis and release of aldosterone from the adrenal gland, which further promotes sodium reabsorption. Angiotensin II, on the other hand, is linked to endothelial dysfunction and has pro-fibrotic and pro-inflammatory properties. It can increase oxidative stress, leading to injury in the kidneys, heart, and blood vessels.
Through these mechanisms, angiotensin II contributes to target organ damage in hypertension.

Angiotensin-converting enzyme 2 (ACE2) has come to prominence as a key participant in the pathogenesis of hypertension, CVD, and renal illness. ACE2 metabolizes angiotensin II into angiotensin-(1–7), which has beneficial effects. Angiotensin-(1-7) stimulates vasodilation, diuresis, and natriuresis, as well as antiproliferative and antigrowth actions on the cells in the cardiovascular and renal systems. It additionally exerts cardiorenal protective effects via the Mas receptor, which involves signalling pathways such as MAPK, PI3K-AKT, NADPH oxidase, TGF-1, the EGF receptor, and NF-B activity.[19]

Aldosterone, another hormone involved in blood pressure regulation, plays an important role in hypertension. It binds to the mineralocorticoid receptor and induces non-genomic effects, meaning it does not directly modify gene expression. One of its effects is the activation of the epithelial sodium channel (ENaC) in the cortical collecting duct of the kidneys, leading to increased renal sodium reabsorption. Non-epithelial effects of aldosterone lead to endothelial dysfunction, vasoconstriction, and hypertension. These effects include increased oxidative stress, vascular smooth muscle cell proliferation, extracellular matrix deposition, fibrosis, and vascular remodelling. Overall, the complex interplay between angiotensin II, ACE2, aldosterone, and their effects on sodium reabsorption, endothelial function, and other physiological processes contribute to the development and progression of hypertension and its associated complications.[20]

Natriuretic Peptides

The hormones atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) have essential roles in salt sensitivity and hypertension. They contain natriuretic and vasodilator characteristics that aid in Na balance and BP regulation during salt loading. ANP and BNP are produced when the ventricles and atria of the heart are expanded owing to increasing blood flow. These hormones stimulate systemic vasodilation and fluid transfers via intravascular to the interstitial structure, resulting in reduced plasma volume and blood pressure. In conditions of volume expansion, natriuretic peptides enhance the rate of glomerular filtration by changing efferent arteriole tone, and they block renal sodium reabsorption by multiple mechanisms. Natriuretic peptides have direct effects on the kidneys by lowering the level of activity of Na+-K+-ATPase and the sodium-glucose co-transporter in the proximal tubule and blocking the epithelial sodium channel in the distal nephron. They indirectly block the releasing of renin and aldosterone, that regulate salt and fluid balance.

Deficiency of natriuretic peptides can contribute to hypertension. Cori-n, a serine protease predominantly expressed in the heart, is responsible for converting pro-ANP and pro-BNP into their active forms. Corin deficiency has been linked to volume overload, cardiac failure, and salt-sensitive hypertension. A lack of natriuretic peptides has also been related to insulin resistance and type 2 diabetes mellitus. Obesity is linked to a lack of natriuretic peptides, which might be related to increased expression of the natriuretic peptide scavenger receptor NPR-C in adipose tissue.

The metabolic syndrome, which includes high bp, high fasting glucose levels, abdominal obesity, high triglycerides, and microalbuminuria, has therapeutic promise for natriuretic peptides. The metabolic syndrome increases the chances of cardiovascular disease and diabetes mellitus. By targeting natriuretic peptide pathways, it may be possible to address multiple components of the metabolic syndrome and improve outcomes.[21-22]

The Endothelium

The endothelium, which lines the inner walls of blood arteries, regulates vascular tone and salt
sensitivity by producing numerous vasoactive chemicals. Nitric oxide (NO) is the most important vasodilator produced by endothelial cells and plays an important function in the control of blood pressure. Continuous release of NO in response to shear stress induced by blood flow leads to relaxation of vascular smooth muscles, resulting in vasodilation. In both animals and humans, disruption of NO synthesis, such as restricting endothelial NO synthase (eNOS), can result in higher blood pressure and the occurrence of hypertension. Several studies have found that hypertensive patients produce less NO than normotensive persons. Endothelial cells also release vasodilators such as prostacyclin, endothelial-derived hyperpolarizing aspects, and vasoconstrictors such as endothelin 1 (ET-1), angiotensin II, and various prostanoids. ET-1 is a powerful vasoconstrictor that stimulates receptors in vascular smooth muscles, whereas other vasodilators released by other cell types stimulate NO release from endothelial cells. Glucagon-like peptide-1 (GLP-1) is a gut hormone that regulates glucose and has vasodilating characteristics. The balance of these chemicals, comprising NO and ET-1, determine the endothelium’s overall influence on vascular tone.[23]

Endothelial dysfunction is important in the etiology of hypertension. Endothelium-dependent vasodilation is commonly compromised in the offspring of hypertensive parents, implying an inherited factor in the occurrence of endothelial dysfunction. Endothelial dysfunction in chronic hypertension is caused by both direct pressure-induced damage and a rise in oxidative stress. The production of reactive oxygen species is aided by systems of enzymes like NADPH oxidase, xanthine oxidase, and cyclooxygenase, along with the reduced activity of superoxide dismutase. Excess superoxide anions can bind to NO, lowering its bioavailability and causing the pro-inflammatory oxidant peroxynitrite to be produced. Reduced NO bioavailability is a key component in the connection between oxidative stress and endothelial dysfunction and hypertension. Individuals who are salt-sensitive may be more vulnerable to the hemodynamic stress generated by increased blood volume, resulting in excess production of transforming growth factor-beta (TGF-beta), oxidative stress, and a reduction in accessible NO. Angiotensin II, in conjunction with other variables like cyclic vascular stretch, endothelin-1, uric acid, systemic inflammation, norepinephrine, free fatty acids, and tobacco smoking, stimulates NADPH oxidase activity and contributes to the formation of oxidative stress in hypertension.

Sympathetic Nervous System

Baroreceptors are specialized mechanoreceptors located in various sites within the arterial tree, including the carotid sinus. They detect variations in blood pressure and send input to the brain, allowing sympathetic outflow to be regulated and blood pressure homeostasis to be maintained. When the artery walls, particularly those in the carotid sinus, stretch out as a result of high blood pressure, nerve bundles attached to baroreceptors send signals to the brain, resulting in a drop in the activity of sympathetic nerves and, as a result, a decrease in blood pressure. Individuals with hypertension frequently have more sympathetic nervous system (SNS) activity than individuals with normal blood pressure. SNS activity also tends to be higher in obese people, men vs women, younger people versus older people, and those with severe renal disease. Many hypertension patients have autonomic imbalance, which is characterized by increased sympathetic and reduced parasympathetic activity.[24]

SNS activation is important in the onset as well as maintenance of hypertension. In normotensive individuals with a family record of hypertension, studies in humans have revealed markers of sympathetic overactivity, like increased catecholamine spillover (the secretion of catecholamines out of sympathetic nerves into the bloodstream) and sural activity in the nerves.
analysed by microneurography. The degree of sympathetic activity evaluated by microneurography corresponds with the degree of severity of hypertension in hypertensive individuals. Plasma catecholamine levels and systemic catecholamine spillover investigations have shown that obese people, those with metabolic syndrome, and those with hypertension exacerbated by heart failure or renal illness had higher sympathetic activity. Various animal models have revealed the relevance of the sympathetic nerve system for the occurrence of hypertension. Obesity-related hypertension model have revealed that elevated renal activity of the sympathetic nerve and, as a result, increased renal sodium reabsorption are important variables in the maintenance of hypertension. Rats given phenylephrine (a sympathomimetic drug) suffered hypertension while the infusion in another animal study. After discontinuing phenylephrine, their blood pressure normalised on a low-salt diet, but when came across a high-salt diet, the animals turned hypertensive again. The severity of renal tubulo-interstitial fibrosis and a reduction in glomerular filtration rate were correlated with the degree of blood pressure elevated levels on the high-salt diet, implying that catecholamine-induced hypertension causes renal interstitial injury and a salt-sensitive phenotype which continues even after sympathetic overactivity is no longer present. Furthermore, increased sympathetic activity can cause alpha-1 adrenergic receptor-mediated endothelial dysfunction, vasoconstriction, vascular smooth muscle proliferation, and increased arterial stiffness, all of which contribute to hypertension development and maintenance. Finally, there is evidence that sympathetic overactivity improves salt sensitivity via decreasing activity of the WNK4 gene, which encodes a kinase that prevents the thiazide-sensitive sodium-chloride co-transporter, resulting in enhanced distal tubular sodium retention. These mechanisms underline the importance of overactivity of the sympathetic nervous system in the etiology of hypertension.[25]

The Immune System and Inflammation

Inflammation is a major factor in the emergence of hypertension and associated organ damage. It has been linked to increased vascular permeability and the production of powerful mediators such as reactive oxygen species, nitric oxide (NO), cytokines, and metalloproteinases. Cytokines contribute to the creation of neo-intima, which reduces the lumen diameter of resistance arteries and promotes vascular fibrosis, which raises cardiovascular resistance and stiffness. Cytokines can have an effect on renal tubular function by enhancing local angiotensinogen and angiotensin II production and encouraging salt and volume retention in high BP. Matrix metalloproteinases promote extracellular matrix disintegration, allowing immune cells to infiltrate and increasing apoptosis, collagen formation, and matrix deposition, eventually causing target organ damage.

While animal research provide convincing evidence of the link between the inflammation and hypertension, human data is scarce. Although associations have been discovered between hypertension and inflammatory indicators like C-reactive protein, TNF-alpha, and different interleukins, the connection has yet to be proven. A single nucleotide polymorphism (SNP rs3184504) in the SH2B adapter protein 3 has been linked to autoimmune and cardiovascular illnesses, including hypertension, according to genome-wide association studies (GWAS). Interestingly, drugs used for the treatment of inflammation, such as non-steroidal anti-inflammatory drugs (NSAIDs) and cyclosporine, have been found to raise blood pressure in hypertensive individuals, demonstrating the complexities of the correlation among inflammation and hypertension.[26]

In hypertension, immune responses that are both innate and adaptive contribute to the production of oxygen molecules that are reactive and
inflammatory alterations in the kidneys, blood vessels, and brain. Innate immunological actions, especially those mediated by macrophages, have been associated to angiotensin II, aldosterone, and NO antagonism-induced hypertension. Reducing the infiltration of macrophages in the kidney or the peri-adventitial area of the arteries has been proven to lower blood pressure and salt sensitivity. T cell-mediated adaptive immune responses have also been linked to the occurrence of hypertension and target organ damage. T cells express angiotensin II type 1 (AT1) receptors & are involved in the pathogenesis of angiotensin II-dependent hypertension. In animal models, depletion of mature lymphocytes is being shown to alleviate hypertension and renal damage caused by a high-salt diet. The development of hypertension is determined by the balance among pro-inflammatory T cell reaction and inflammatory suppression mediated by regulatory T cells. Several animal models have shown that adoptive transfer of regulatory T cells improves hypertension. Both pro-inflammatory and regulatory T cell abnormalities have been linked to hypertension-induced target damage to organs, since they control the processes of inflammation in the kidneys and vasculature that underpin hypertension-induced kidney disease.

**MANAGEMENT OF HYPERTENSION**

**Non-Pharmacological Management**

Modifications in lifestyle are strongly suggested for all individuals with hypertension as they can effectively lower blood pressure. The same interventions that are recommended for preventing hypertension are also beneficial for individuals with hypertension.

Reducing sodium intake is an important dietary approach for individuals with hypertension. Ideally, for people who are particularly susceptible to the impact of salt on blood pressure, sodium consumption should be no more than 2.3 grammes per day, or possibly less (1.5 grammes per day). A decrease of at least one gramme per day is beneficial and can reduce systolic BP by 2-4 mmHg; enhancing potassium intake to 3.5-5.0 grammes per day can have a comparable blood pressure-lowering impact. Because processed foods contain the bulk of dietary salt, population-wide guidelines to reduce salt intake are critical. It is crucial for the effectiveness of salt reduction program to enlist food producers and restaurants in gradually lowering salt added to their meals. Only a few countries have successfully reduced population salt intake so far.[27]

Moderate alcohol consumption is recommended, with a limit of up to 2 caliber drinks/day for males and up to 1 caliber drink/day for females. This can result in a 2-4 mmHg drop in blood pressure.

Regular little workout is beneficial for individuals with hypertension. Endurance training, such as aerobic activity, can reduce blood pressure more peoples with hypertension compared to those with standard blood pressure. Blood pressure is most effectively controlled by 40-60 minutes sessions completed at least 3 times per week. Isometric exercise (strength training) and dynamic resistance training also show blood pressure-lowering effects.

Weight loss is important for individuals with hypertension who are overweight or obese. Excess adiposity tends to raise blood pressure, and weight loss can result in reduction in both systolic and diastolic BP. Lifestyle therapies such as low-caloric diets and physical activity are advised, although the response to weight loss can vary between individuals.[28]

Overall, lifestyle modifications can play an important role in managing hypertension and decreasing blood pressure. It is important to note that these interventions may require long-term adherence to maintain their benefits, and individuals should consult with healthcare professionals for personalized guidance.

**Pharmacological Treatment (Antihypertensive Pharmacotherapy)**
Antihypertensive pharmacotherapy has undergone significant advancements over the years, with the formulation of various medication classes and wide-scale outcomes experiments demonstrating their advantages in reducing cardiovascular disease (CVD) morbidity and mortality. Today, clinicians have a large variety of antihypertensive medications from different drug categories and fixed-dose combinations to choose from.

The standard strategy to antihypertensive treatment is to begin with first-line medicines, either alone or in combination. In individuals with greater pretreatment blood pressure (BP), combination therapy may be preferable. The following are the first-line antihypertensive drug classes:

**ACE inhibitors:** These medications inhibit the angiotensin-converting enzyme, reducing the production of angiotensin II and promoting vasodilation. They are well-established first-line agents and have shown efficacy in wide-scale hypertension studies. ACE inhibitors are especially helpful in people with CHF and a low left ventricular ejection fraction, as well as diabetic nephropathy. They may, however, induce adverse effects such as decreased kidney activity, hyperkalemia (high blood potassium levels), coughing, and, less often, angioedema (swelling caused by fluid buildup).[29]

**Angiotensin II receptor blockers (ARBs):** These medications inhibit angiotensin II activity at its receptor sites, resulting in vasodilation. Like ACE inhibitors, ARBs have been extensively tested in large-scale trials and are considered first-line agents. They are well tolerated and reduce CVD risk in the same way as ACE inhibitors do. However, they may also induce hyperkalemia and deteriorating renal function, however coughing and angioedema are less probable.[30]

**Dihydropyridine calcium channel blockers (CCBs):** These drugs cause vasodilation by inhibiting calcium channels in vascular smooth muscle. They serve as efficient antihypertensive medicines that should be used in conjunction with another first-line medicines. Peripheral edema is a typical adverse reaction of dihydropyridine CCBs, especially in obese people. Non-dihydropyridine CCBs, such as verapamil, can also block cardiac calcium channels, lowering heart rate and contractility. Calcium channel blockers can also interact with other drugs due to their effects on drug metabolizing enzymes.

**Thiazide-type and thiazide-like diuretics:** These diuretics promote natriuresis (excretion of sodium) by inhibiting sodium and chloride co-transporters in renal tubules. Since the early trials establishing their advantages, they have been significant components of hypertension therapy. Thiazide-type diuretics, such as hydrochlorothiazide, and thiazide-like diuretics, like chlorthalidone and indapamide, are commonly used. These diuretics can impair glucose metabolism and raise the risk of developing type 2 diabetes. They can also cause electrolyte disruptions, such as hypokalemia (low blood potassium) and hyponatremia (low blood Na), which can have serious consequences. When thiazide diuretics are used with potassium supplementation or potassium-sparing medicines, the risk of hypokalemia is reduced.[31]

**Beta-blockers:** Beta-blockers reduce BP by decreasing cardiac output, heart rate, renin release, and the effects of the sympathetic nervous system. They are used in individuals who have heart failure and a low left ventricular ejection fraction or who have had a heart attack. Beta-blockers are also recommended as first-line antihypertensive medicines in several recommendations. However, they are generally considered menial to more first-line drugs in lowering CVD morbidity and mortality in the absence of these specific comorbidities.[31]

**New pharmacological agents:** The pharmaceutical industry has shown limited interest in recent years, new antihypertensive drugs have been developed. This is partly because many existing antihypertensive drugs have lost their patent
protection and are now available as inexpensive generics, reducing the financial incentives for developing new drugs in this class. Some of the currently approved drugs for other indications have shown potential in treating hypertension. For example, combined angiotensin II receptor & neprilysin inhibitors, originally approved for CHF, may also be beneficial in managing hypertension. Similarly, soluble guanylyl cyclase modifying medicines, which were originally intended to treat erectile dysfunction, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which are licenced for type 2 diabetes mellitus, have showed promise in decreasing blood pressure. There are also other pharmacological agents in various stages of preclinical or clinical development that could have implications for hypertension treatment. Newer mineralocorticoid receptor antagonists, aldosterone synthase inhibitors, angiotensin-converting enzyme 2 (ACE2)/angiotensin (1-7)/MAS receptor axis activators, and natriuretic peptide receptor agonists belong to them. Although they are being developed for indications other than hypertension, their mechanisms of action suggest they could be useful in treating high blood pressure. Furthermore, medicines with activities other than blood pressure lowering may be therapeutically helpful. Combining angiotensin II receptor blockage with neprilysin inhibition, for example, have been proven in improvement in insulin resistance in individuals which are obese and hypertensive, in addition to reduce the development of type 2 diabetes mellitus among patients with heart failure. It's important to note that while these newer pharmacological agents hold promise, further research and clinical trials are necessary to determine their effectiveness, safety, and optimal use.\

CONCLUSION

Hypertension, or high BP, is indeed acknowledged as the leading dangerous aspect for cardiovascular disease (CVD) worldwide. It is a major contributor to the development of conditions like heart failure, stroke, other heart diseases and kidney disease. Elevated blood pressure puts strain on the blood vessels, leading to damage and raising the possibility of atherosclerosis (artery hardening and constriction). This, as a result, can lead to complications such as heart attacks and strokes. Hypertension also contributes to the evolution and development of other cardiovascular conditions, comprises of heart failure & chronic kidney disorders. Managing and controlling hypertension through lifestyle modifications and appropriate pharmacotherapy is crucial in decreasing the risk of CVD and improving overall health outcomes. If it is still not controlled by these non-pharmacological methods then antihypertensive therapy is needed.

Conflicts of Interest: The authors declare no conflict of interest.

ACKNOWLEDGEMENT

The authors would like to thank Dr Vandana Arora Sethi and Lloyd Institute of management and Technology, Greater Noida for their assistance and for providing the necessary resources and data.

REFERENCES

identifies common and rare variants influencing blood pressure and overlapping with metabolic trait loci. Nat Genet [Internet]. 2016;48(10):1162–70. Available from: http://dx.doi.org/10.1038/ng.3660