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Hypertension: Is there always a cause?

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Abstract:

Elevated blood pressure and consequently systemic hypertension (HTN) are common. HTN was divided into either essential, which counts for more than 90% of cases (where the patient needs a medication for life), and secondary (less than 10% of cases). In clinical practice, when we Look at blood pressure as a vital sign, the elevation of blood pressure is always secondary, where there is always a cause behind its elevation. During our clinical practice and observation, this complex vital sign should be approached in a totally different manner, where solving the cause or at least targeting it, can achieve early diagnosis, better survival and reduction in the number of anti-hypertensive medication if not stopping all of them. In this article we proposed a new classification and approach for hypertensive patients and reviewed the different etiologies behind the elevation in blood pressure.

PCI (Primary Coronary Intervention). CABG (Coronary Artery Bypass Grafting).

Keywords： Hypertension. causes of hypertension. secondary hypertension. resistant hypertension.

Introduction:

Elevated Blood Pressure (BP) and consequently HTN are common, with a prevalence ranging between 18% and 52% and a mean of 44% in adult population (1). Global age-standardized prevalence of raised blood pressure was 24·1% (21·4-27·1) in men and 20·1% (17·8-22·5) in women in 2015; The number of adults with raised blood pressure increased from 594 million in 1975 to 1·13 billion in 2015, with the increase largely in low-income and middle-income countries. The global increase in the number of adults with raised blood pressure is a net effect of increase due to population growth and aging and decrease due to declining age-specific prevalence (2). Elevated BP is increasing strikingly among all aged groups in the adult population with the most percentage in the aging population. Furthermore, this elevation affects all socioeconomic levels. It is estimated the number of people with hypertension will increase by 15–20% by 2025, reaching close to 1.5 billion (3). Over half of all adults with hypertension (54.2%) do not achieve target levels of systolic blood pressure ≤ 130 mmHg and diastolic blood pressure ≤ 80 mmHg (4). A total of 40 to 50% of patients with hypertension remain inadequately treated (5, 6). Resistant hypertension is common among adults with hypertension affecting up to 30% of patients (7).

Blood pressure values are subjected to complex interacting mechanisms including arterial stiffness and resistance, atherosclerosis, inflammatory process and mediators, nervous and autonomic functions, and the endothelial system, oxygen delivery, and renal system at the micro and macro levels. The crucial step is the translation of these etiologies at the clinical level.

Causes of Elevated blood pressure (HTN):

1-Vascular / Atherosclerotic HTN:

By Far the association between atherosclerosis and elevated blood pressure is common. The evidence of atherosclerosis as a consequence of HTN has been yielded extensively in many articles, while the evidence of the vice versa relationship was not pointed out thoroughly. Bidirectional interaction between hypertension and atherosclerosis appears to be the most likely explanation (8). For example, 85% of patients with Diabetes Mellitus II, which is one of the major risk factors of atherosclerosis, have elevated blood pressure (9). Diabetes is associated with both macrovascular (involving large arteries such as conduit vessels) and

microvascular (involving small arteries and capillaries) disease (10). Endothelial cells produce and release a variety of bioactive substances to control and maintain the function and structure of intact vessels through balancing between oxidation and anti-oxidation, and inflammation and anti-inflammation in the vascular wall; proliferation and anti-proliferation of vascular smooth muscle cells; dilation and contraction of vessels; and coagulation and fibrinolysis of blood. Accordingly, increased low-density lipoprotein (LDL) cholesterol levels, hyperglycemia, oxidative stress, and smoking may cause vascular endothelial dysfunction that may result in atherosclerosis (11, 12), which in turn causes the elevation of the blood pressure as more extensive the atherosclerotic lesion as it becomes. It has been observed that many patients with obstructive coronary artery disease showed improvement in blood pressure measurements after revascularization (PCI or CABG). Patients with extensive atherosclerotic disease (that may involve multi-organs – including the Cerebrovasculature, the coronary circulation, the intestinal vasculature, the renal vasculature or peripheral arteries) showed resistance to anti-hypertensive medication, while sometimes strict blood pressure control may decrease the target perfusion in the diseased vessel and may exacerbate deterioration in the function of the involved organ. The peri-vascular adipose tissue (PVAT) plays an important role in the pathogenesis of HTN and atherosclerosis beyond simple vascular narrowing through its inflammatory role (secretion of proinflammatory adipokins and enhancement of insulin resistance) and endothelial dysfunction (13). Both coronary microvascular spasm and/or a reduced microvascular vasodilator capacity have been demonstrated to cause myocardial ischemia and anginal symptoms in patients with hypertension and microvascular angina (14,15).

Hypertension is often associated with vascular remodeling and rearrangement of various components of the vascular wall including ECM (extracellular matrix). Several MMPs (Matrix Metalloproteinases) and TIMPs (Tissue Inhibitors of Matrix Metalloproteinases) may be involved in the vascular remodeling associated with hypertension. Elevated plasma levels of some MMPs in hypertension may cause excessive elastolysis or accumulation of collagen degradation products in the vascular wall (16). VSMC (Vascular Smooth Muscle Cell) proliferation at sites of endothelial cell injury and subsequent lipid deposition play a role in atheroma formation, and MMPs appear to be involved in these processes (16). MMP expression is increased in the atherosclerotic plaque, and activation of MMPs appears to facilitate atherogenesis, platelet aggregation and plaque destabilization (16, 17, 18). Consequently, the effect of MMPs disequilibrium is linked to atherosclerosis and vascular

inflammation, which may explain the elevation in blood pressure. The same mechanism may also explain a part of the elevated blood pressure and pre-eclampsia in pregnant with elevated blood pressure, where higher plasma levels of MMPs such as MMP-2 and lower levels of TIMPs have been observed in women with preeclampsia or who subsequently develop preeclampsia, and consequently decrease uteroplacental vascularization and spiral arteries remodeling (19).

Microvascular rarefaction, perivascular fibrosis, and medial thickening of arterioles with reduced luminal areas have been observed in patients with hypertension without obstructive CAD (20,21,22). These changes increase microvascular resistance, reducing blood flow. Furthermore, endothelial dysfunction impairs flow-mediated vasodilation of arterioles, leading to chronic subendocardial ischemia and impaired myocardial mechanical function (20, 23, 24). Hypertension occurs in 80% of diabetic patients where there is an equivalent correlation between insulin resistance and elevated blood sugar in a side and activation of RAAS (Renin Angiotensin Aldosterone System) and SNS (Sympathetic Nervous System), vascular inflammation, reduction of NO (Nitrous Oxide) bioavailability, oxidative stress, and endothelial stiffness in another side (25). In clinical practice, strategies for the treatment of atherosclerosis focus on the reduction of the risk factors of this pathological condition and on interventional or surgical revascularization. However, atherosclerosis is generally seen as a predominant problem of macrocirculation with a focus on the formation of atherosclerotic plaques, rather than a disease affecting the whole circulatory system (8). In conclusion, atherosclerosis and consequently significant hypoperfusion is a major cause of elevated blood pressure and should be managed rather than controlling blood pressure values alone.

2- Obesity-induced HTN:

Over time, several hypotheses have been advanced for explaining the occurrence of a high blood pressure state in the obese population, from the hemodynamic changes with the hypervolemic effects, and other pathophysiological features that have been identified as the “driving forces” of the disease which include renin-angiotensin activation, stimulation of the sympathetic nervous system and early occurrence of a renal dysfunction leading to glomerular hypofiltration, sodium retention as well as to microalbuminuria (26). Obesity causes chronic inflammation that contributes to atherosclerosis (27). The pathophysiologic mechanisms in obesity that contribute to inflammation and atherosclerosis include activation of

adipokines/cytokines and increases in aldosterone in the circulation (27). Although the Body Mass Index (BMI) is used usually to determine obesity, it is not the only determinant (28) since the distribution of fat between subcutaneous fat and visceral fat plays an important role in atherosclerosis (29). IL-6 (Interleukin-6), an inflammatory marker that is correlated to endothelial dysfunction and increased risk of coronary artery disease, is also positively correlated with BMI (metabolic disease) and MAP (Mean Arterial Pressure) in hypertensive subjects (30). In addition, some individuals who have a normal weight or who are overweight are at high risk for atherosclerosis if they have an excess of visceral adipose tissue with ectopic fat deposition in the heart, liver, and skeletal muscle (27). The adipose tissue with the PVAT increases the activity of RAAS. Angiotensinogen is found in adipose tissue; activation of Angiotensinogen receptors promotes vascular inflammation, endothelial dysfunction and consequently elevated blood pressure (13.31.32). Furthermore, aldosterone acts on PVAT and promotes vascular inflammation (13). Furthermore, when weight reduction surgery was done, there were higher rates of recovery from diabetes, hypertriglyceridemia, low levels of high-density lipoprotein cholesterol, hypertension, and hyperuricemia (33). Gut microbiota regulates BP by secreting vasoactive hormones and short-chain fatty acids. BP-lowering effects of probiotics and antibiotics have been reported. Bariatric surgery improves metabolic disorders and hypertension due to increasing GLP-1 secretion, decreasing leptin secretion and SNS activity, and changing gut microbiome composition (34).

3- Pulmonary and Sleep disorders-induced HTN:

Oxygen delivery plays an important role in controlling blood pressure values. Hypoxia and decrease oxygen delivery to tissues is an important cause of elevated blood pressure. Optimization of treatment of hypoxic status plays an important role in controlling blood pressure. Patients with asthma are more likely to have hypertension than those who do not, independent of traditional risk factors (35,36). Asthmatic subjects with comorbid hypertension display evidence of enhanced asthma morbidity (37). Hypertension is the most common concurrent disorder among patients with COPD, where the activated inflammatory cascade, endothelial dysfunction, increased vascular stiffness and hypoxia are predominant (38). Exposure to chronic intermittent hypoxia (CIH) increased mean arterial pressure (MAP) which persisted beyond the period of exposure to CIH (39). Hypoxia and Hypoxia induced mediators, some of which control the production of Nitrous Oxide (NO), play a role in the elevation of Blood pressure, in addition to the enhancement of inflammatory process and

vascular stiffness (40). In addition, when studied in OSA, chronic intermittent hypoxia led to elevated nocturnal mean arterial pressure (MAP) as a response to hypoxemia, as well as inappropriately elevated diurnal MAP in response to maladaptation (41)

In physiological conditions, our blood pressure follows a diurnal pattern with a fall at night whilst we rest and sleep (referred to 'nocturnal dip'). This fall is due to a variety of mechanisms, including supine position, muscle relaxation and reduced sympathetic tone. However, in recent years, it has become apparent that many individuals may not present the expected nocturnal dip in blood pressure ('non-dippers'). Early findings from British and American studies suggest associations between sleep duration and hypertension risk. The effect is detectable early in childhood and adolescence affecting both day-time and night-time blood pressure [31], suggesting that sleep disturbances not only raise night blood pressure by disrupting sleep but exert prolonged carryover effects on day-time blood pressure leading to hypertension (42).

OSA is related to an increased risk of resistant hypertension. Mild, moderate and severe OSA are associated with essential hypertension, as well a dose-response manner relationship is manifested (43). Increased BP in people with OSA is hypothesized to occur primarily due to sympathetic nervous system overactivity. Obstructive sleep apnea is common disorder affecting approximately one quarter of the common population. Studies conducted in Asia and Europe have suggested that poor subjective sleep quality is associated with significantly higher odds ratios (ORs) of hypertension. Poor sleep has also been associated with significantly higher levels of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) in Asian, and European studies (44). Prevalence is even higher in a population with increased vascular risk. Li et Chang analyzed 12,166 adults aged 30-79 years who participated in the 2007-2014 National Health and Nutrition Examination Survey. Sleep duration, self-reported trouble sleeping and sleep disorders were collected using a standardized questionnaire. The overall prevalence of hypertension was 37.8%. A short sleep duration (OR = 1.20, 95% CI: 1.08 to 1.33, $p = 0.001$), self-reported trouble sleeping (OR = 1.45, 95% CI: 1.28 to 1.65, $p < 0.001$) and sleep disorder (OR = 1.33, 95% CI: 1.07 to 1.66, $p = 0.012$) were related to the risk of hypertension. Poor sleep patterns were closely correlated with the risk of hypertension (OR = 1.90, 95% CI: 1.62 to 2.24) (45). Obstructive sleep apnea is a significant risk factor for hypertension, with approximately 50% of obstructive sleep apnea patients suffering hypertension (46). Overnight intermittent hypoxia and negative intrathoracic pressure lead to chemoreceptor activation and increased sympathetic outflow that persists

during wakefulness. In people with OSA, changes occur in regions of the brainstem known to be responsible for setting resting sympathetic activity; The pathophysiology of sleep apnea–associated hypertension is characterized by sustained adrenergic activation and volume retention often posing treatment challenges in patients with resistant hypertension (7), changes that are reversible with CPAP therapy. Intermittent hypoxia in OSA also results in increased oxidative stress, metabolic dysregulation, and systemic inflammation, contributing to vascular remodeling, endothelial dysfunction, and atherosclerosis. OSA causes hyperaldosteronism by stimulation of the renin–angiotensin system as evidenced by reduced plasma renin and angiotensin II levels following CPAP treatment. Hyperaldosteronism can lead to hypertension through several mechanisms including (i) a higher incidence of metabolic syndrome through altered carbohydrate metabolism, (ii) vascular remodeling *via* pathological collagen synthesis, and (iii) electrolyte imbalances leading to abnormal fluid retention. Of particular interest is that hyperaldosteronism might also act to increase the severity of OSA. Given evidence for at least 1 bidirectional pathway linking OSA and hypertension, it is interesting to note that a 2016 systematic review (11 studies) assessing the effects of antihypertensive medications on the severity of OSA found that treatment with antihypertensive agents results in a small but statistically significant reduction in the severity of OSA (47). In updated meta-analyses in 2016 and 2017, OSA treatment was effective for blood pressure lowering across the BP ranges of hypertension (4). Prior reports describe an association of other sleep disturbances including sleep restriction, insomnia, and non-restorative (poor quality) sleep, with the prevalence and incidence of hypertension (4,48,49). Two pathophysiologic processes highlighted in the prior review as linking OSA with resistant hypertension are endothelial dysfunction and sympathetic nervous system stimulation [4, 50]. These pathophysiologic processes, in addition to inflammation, are observed in the presence of other sleep disturbances including short (< 6 h/night) or long sleep (> 9 h/night), circadian rhythm disorders, and insomnia [4,51,52]. In turn, these pathophysiologic processes are associated with hypertension prevalence (4, 53). The MORGEN study, a population-based cohort study that followed 20 432 men and women aged 20–65 years over a period of 10 – 15 years, with no history of cardiovascular disease in the Netherlands showed that poor sleep quality even more than quantity, increased the risk of cardiovascular disease and coronary heart disease (54). Fung *et al*. studied 782 elderly men over a 3.4-year follow-up interval, 243 men developed incident HTN. Those with incident HTN had poorer sleep architecture as evidenced by significantly less SWS (mean 9.8% versus 11.2%, P=0.002). After adjusting for age and BMI, those with decreased SWS (slow wave sleep) experienced an approximate 80%

increase in risk of incident HTN as compared to those in Q4 (OR 1.81 with 95% confidence interval 1.18-2.80) (55). Metanalysis of a total of 54 studies (involving 1,074,207 subjects) showed that raised blood pressure was associated with obstructive sleep apnea (OSA), oxygen desaturation index (ODI), short sleep duration, and long sleep duration. The differences in ≤ 5 h, 6 h, ≥ 9 h, and 10 h groups had statistical significances, while there was no significant difference in ≥ 8 h group. Snoring is a risk factor of hypertension (OR = 1.94, 95%CI 1.41–2.67) (56)

Even in pediatric population, a positive association was observed between reduced sleep hours and HTN. This is consistent with a recent meta-analysis,34 and highlights the duration of sleep as a factor capable of regulating cardiovascular risk in children and adolescents (57). This study estimated that the prevalence of SDB and snoring in a population of adolescents (mean age: 13 years) was 7.0 % and 9.7 %, respectively. SDB and snoring were more prevalent among adolescents with obesity. A reduction in sleep hours and the presence of obesity were significantly associated with higher BP recordings (58)

4- Renal Hypertension:

Renal and urologic evaluation, functional and anatomic, is essential in the evaluation of patients with elevated blood pressure. The kidneys, which have a high specific metabolic rate, play an essential role in the long-term regulation of arterial blood pressure (59). Numerous epidemiological studies have reported systemic hypertension (HTN) to be associated with renal dysfunction (Horowitz, Miskulin, & Zager, 2015) and low nephron number would lead to hyperfiltration of remaining glomeruli, followed by glomerular hypertrophy and intraglomerular HTN, resulting in further nephron loss and reduced-sodium excretory capacity, thereby leading to HTN and CKD (60). Shifts in transporter location and function can be mediated by angiotensin II, inflammatory cytokines, loss of nitric oxide and adrenergic stimulation. Data demonstrate that dietary sodium intake influences renal tissue oxygenation, low sodium intake leading to an increased renal medullary oxygenation both in normotensive and young hypertensive subjects (61). It has become clear that sodium and water dysregulation can exert profound effects on kidney and vascular health, far greater than previously recognized. Maladaptation to a combined high-salt and low-water intake can be linked to the growing epidemic of hypertension and chronic kidney disease (62). As we explained in the part about the relation between immunity disorders and elevated blood

pressure, auto-immune mediated renal diseases play an essential role in HTN/elevated blood pressure. An important role for inflammation and the immune system in promoting hypertension in general is now well recognized, including contributions of immune cells infiltrating the kidneys (63,64) as well as effects of inflammatory cytokines on renal function (63,65,66,67). Renovascular disease is a major cause of hypertension, and it accounts for 1 to 5% of all cases of hypertension in the general population (68).

5- Neurogenic HTN:

Neurogenic component contributes to the initiation, maintenance and progression of HTN (69). Increasing evidence also suggests that, coupled to autonomic dysfunction, treatment-resistant HTN is accompanied by a chronic low-grade inflammatory profile that facilitates end-organ damage and perpetuates the hypertensive state (69,70), suggesting a close link between SNS (Sympathetic Nervous System) and the IS (Inflammatory System) (69). The role of autonomic dysfunction in hypertension comes from the multiple lines of evidence showing that young hypertensive individuals and those in the early stages of hypertension also have an increased sympathetic and a reduced cardiac vagal drive (71). An increased sympathetic nerve traffic has been documented in young, middle-aged, and elderly hypertensives; in pregnancy-induced hypertension; and in systo-diastolic hypertension or an isolated elevation of systolic blood pressure (71,72). published studies have also shown that the adrenergic hyperactivity is detectable in a- HT affecting young, middle-age, and elderly people (73,74,75,76), systo-diastolic and isolated systolic HT (73,76), pregnancy-induced HT (73,77), white-coat and masked HT (73,78,79), and dipping, extreme dipping, non-dipping, and reverse dipping condition (73, 80,81). sympathetic dysregulation has been shown in the different stages of hypertension (mild, moderate, severe), in hypertensive forms of young, middle-aged and elderly patients, in white-coat hypertension, masked hypertension and pregnancy-induced high blood pressure [71,82,83]. Microneurography studies showed high sympathetic drive induced by hypoxia in hypertension (84). Psychosocial stress doubles the risk of HT, the most related factors being post-traumatic stress disorder, anxiety and work stress (85). Although the evidence for a link between anxiety and risk for incident hypertension is mixed, cross-sectional studies have found small to moderate associations between the 2, and a large NHANES study found a prospective association of anxiety/stress/worry/tension with incident hypertension in middle-aged adults (86,87). Anxious patients had higher rates of uncontrolled BP and moreover, Patients with anxiety

showed higher morning SBP than patients without anxiety (88). People with mental illness such as anxiety, depression and bipolar disorder have an increased Blood Pressure Variability regardless of age (89).

6- Immunity disorders and HTN (Inflammatory HTN):

The burden of hypertension globally suggests that there is a continued need to understand the underlying mechanisms that contribute to its development. Increases in blood pressure are primarily attributed to perturbations in the kidney, vasculature, and CNS, but both clinical and experimental evidence implicate the immune system in the pathogenesis of essential hypertension (90, 91). Many studies over a long period of time correlated between immunity disorders and elevated Blood Pressure and consequently HTN. Consistent with essential hypertension, a variety of inflammatory cytokines, including TNF-α and IL-6, have been implicated in the pathogenesis of autoimmune diseases (90,92). A direct blood pressure modulatory role for autoantibodies in humans was demonstrated by studies in patients with refractory hypertension in which immunoadsorption of α_1-adrenoceptor receptor autoantibodies was sufficient to lower mean arterial pressure (90,93). The potential importance of $CD8^+$ T cells was recently reported in a study of patients with essential hypertension. The authors concluded that hypertensive patients have more immuno-senescent $CD8^+$ T lymphocytes with increased expression of CXCR3, a receptor for chemokines, which recruit T cells to injured organs (90,94). Rheumatoid arthritis (RA) is frequently associated with hypertension (76% of patients with RA were diagnosed with HTN) and despite limited longitudinal studies exploring this topic, methotrexate and exercise were shown to protect against risk of hypertension in RA patients (95). The majority of SLE cases occur in women at an age in which the prevalence of hypertension and cardiovascular disease is typically low. However, women with SLE have a high prevalence of hypertension (96, 97) for reasons that remain unclear (the prevalence of hypertension in patients with SLE reaches as high as 74%) (96), but multiple factors contribute to the pathogenesis of hypertension, including increased risk of atherosclerosis (98,99) and cardiovascular events (99), the inflammatory cytokine, tumor necrosis factor (TNF)-α, oxidative stress, as well as B-cell hyperactivity and autoantibody production (101) where immune cells and chronic inflammation have been implicated in the pathogenesis of both hypertension and SLE (96).

7- Hormonal Hypertension:

The role of the hormonal and endocrine system as an etiology of elevated blood pressure is well known. As it was named as secondary HTN, hyperaldosteronism is one of the causes of elevated blood pressure (102). Recently, it was recognized that elevation of aldosterone is more common than it was thought to be previously. Although adrenal adenoma is a cause, but other causes should be sought.

Pheochromocytoma as well is a cause of elevated blood pressure where hyperexcretion of sympathetic mediators has been validated. More-over the role of sympathetic nervous system exceeds the presence of pheochromocytoma. Heightened sympathetic nervous system (SNS) activity, especially in the kidney and brain, increases BP in obese patients (34)

Cushing disease and hypercortisolism is also one of the mentioned causes of elevated blood pressure. In obese patients with elevated blood pressure, cortisol level should be measured during the routine workup.

Thyroid disorders also may play a direct or indirect role in the elevation of blood pressure. If symptoms or signs suggest the presence of hyperthyroidism in a patient with elevated blood pressure, then workup is recommended.

Renin is one of the important mediators that control the blood pressure. High blood levels have been also recognized in patients with elevated blood pressure, especially in obese patients. renal vascular inflammation may increase the levels of renin and play a role in addition to other factors in elevation of blood pressure. lack of intracellular NO bioavailability in the collecting duct increases CD-renin synthesis and secretion, thus leading to an inappropriate intratubular RAS activation, which may contribute to the development and progression of hypertension (103). In the kidney, the activation of the RAS results in sodium retention and hypertension, independent from the systemic RAS (103, 104,105). In adults, conditions such as chronic ischemia, prolonged adrenergic activation, and Na^+ depletion perturb blood pressure homeostasis and increase the number of renin-expressing cells along the afferent arteriole and kidney interstitium and inside the glomerulus, recapitulating the embryonic distribution of renin expression (106,107,108,109).

8- Nutritional HTN:

Nutrition, food components and herbal substances can cause frequent episodes of elevated blood pressure. Although they may not be a direct cause of HTN, they trigger elevation in blood pressure values in patients at risk for HTN. High salt intake is deleterious to the cardiovascular system both in normo- as well as in hypertensive individuals (110). Numerous studies have found high sodium intake to be associated with increased risks of cardiovascular disease (CVD) and all-cause mortality among patients with hypertension (111). High sodium intake increases blood pressure. In a review of 47 studies that was published in Journal of clinical Hypertension in 2018, there was a clear correlation between sodium intake and BP (112). Many mechanisms have been proposed for the etiology of correlation between high salt diet and elevated blood pressure, including endothelial dysfunction, activation of RAAS system, abnormal water retention and increase in intravascular volume and increase in cardiac output, activation in sympathetic system, and increase in glomerular perfusion pressure (110). High-salt food products, energy drinks, food products containing liquorice, and alcoholic beverages have hypertensinogenic properties (113). Furthermore, a positive association was found between the consumption of ultra-processed foods and blood pressure/arterial hypertension (114).

9- Drug-induced HTN:

Evidence that documents a correlation between the elevation in blood pressure and certain medication or drugs is well known. The elevation of blood pressure in drug-induced hypertension occurs through a variety of mechanisms, most notably, sodium and fluid retention, activation of the renin-angiotensin-aldosterone system, alteration of vascular tone, or a combination of these pathways (115). Systemic hypertension is one of the most frequently encountered vascular toxicities of many anticancer therapies and is a major risk factor for cardiovascular disease (CVD) (116). Recent studies define new connections between endothelial dysfunction and Vascular Endothelial Growth Factor Receptor-Inhibitors (VEGFRi)-induced hypertension, including the balance between nitric oxide, oxidative stress, endothelin signaling, and prostaglandins and the potential role of microparticles, vascular smooth muscle cells, vascular stiffness, and microvessel rarefaction (117). Mediated by a variety of molecules, there is an imbalance in the vascular tone favoring net vasoconstriction that mediates EPO-induced hypertension (118). Non-Steroidal Anti-Inflammatory Drugs

(NSAIDS), Glucocorticoids, Licorice, Highly active antiretroviral therapy (HAART), sex hormones, sodium-containing formulations, and herbals are linked to elevated blood pressure (119). Marijuana users had a higher risk of dying from hypertension. Compared to non-users, marijuana users had a 3.42-times higher risk of death from hypertension (120).

10- Pregnancy-induced hypertension:

Placental ischemia is also associated with increased release of bioactive factors (16). As we mentioned previously, MMPs are elevated in plasma and amniotic fluid of pregnant women who developed pre-eclampsia (121,122), where placental ischemia may play an essential role in hypertension. Placental ischemia induces the release of biologically active factors such as growth factor inhibitors, anti-angiogenic factors, inflammatory cytokines, reactive oxygen species, hypoxia-inducible factors, and antibodies to vascular angiotensin II (AngII) receptor (123). In the kidney this inactivation of free VEGF is believed to cause endotheliosis and proteinuria (124). In preeclampsia, increased placental production of a splice variant of VEGFR1 (soluble *fms*-like tyrosine kinase 1 (sFlt1)) sequesters VEGFs resulting in functionally impaired VEGFR signaling (117,125). Indeed, preeclamptic women and VEGFRi-treated cancer patients both develop hypertension, proteinuria, and renal endotheliosis (117, 126). Overall, placental ischemia/hypoxia is thought to lead to widespread activation of the maternal vascular endothelium, resulting in enhanced formation of endothelin and superoxide, increased vascular sensitivity to angiotensin II, and decreased formation of vasodilators such as nitric oxide. These endothelial abnormalities, in turn, cause generalized vasoconstriction throughout the body including the kidneys, which play a critical role in the long-term regulation of arterial pressure (127). These findings urge the need for early detection of blood pressure changes in the pregnant followed by early usage of vasodilators that counterbalance between placental perfusion and systemic vasoconstriction. Although this may not target the main pathophysiology, but this may reduce the risk of renal impairment and consequent elevated blood pressure post-partum. All risk factors that enhance placental hypoperfusion should be targeted to decrease the risk of further elevation in blood pressure.

11- Hyperuricemic HTN:

The association between increased serum urate and hypertension has been a subject of intense controversy. Nevertheless, experimental evidence strongly suggests that an increase in intracellular urate is a key factor in the pathogenesis of primary hypertension (128). Elevated uric acid levels are risk factors for gout, hypertension, and chronic kidney diseases (129). High level of uric acid indicated a higher likelihood of developing hypertension in both genders and metabolic syndrome in males after 10 years of follow-up (130). Clinical studies show that the serum uric acid value is closely associated with hypertension in hyperuricemic patients (cross-sectional study), and with the onset of hypertension (longitudinal study). Furthermore, one interesting report shows that treatment of hyperuricemia with allopurinol lowers blood pressure in juvenile essential hypertension patients with hyperuricemia (131). Thus, there are many mechanisms through which hyperuricemia can cause elevated blood pressure, ranging from the process of oxidative stress, the effect on renal impairment, enhanced inflammatory process and the consequent increased risk of atherosclerosis. Furthermore, there is a possible bidirectional association between nephrolithiasis and HTN (132), which warrants aggressive workup and management of nephrolithiasis as a possible cause of HTN in the future.

12- Cancer induced HTN:

The fact that cancer and hypertension frequently co-occur and share multiple risk factors suggests that overlapping pathophysiological mechanisms play prominent roles in both conditions. The search for overlapping mechanisms involved in the pathogenesis of both conditions has highlighted important processes, including inflammation and an increase in reactive oxygen species (ROS) and oxidative stress (116).

Conclusion:

As a Conclusion, there is no doubt that uncontrolled HTN or chronic elevation in Blood pressure stays a major risk factor for stroke, heart failure, renal failure and atherosclerosis (103), but this is a vicious circle with bidirectional relationship. Finally, there is no essential hypertension; Elevated blood pressure is always secondary, although the type of the cause and its advanced stage implement the management and the need for short or long-life medication.

True resistant hypertension (RH) is reported in 10.1% of patients treated for elevated BP (133) where cautious blood pressure control should be considered, and in all cases, there should be an equilibrium between controlling blood pressure and organ perfusion. This review opens the door for a new era in the approach of hypertensive patients where further evidence-based studies are needed.

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