A REVIEW ARTICLE: FACTORS CONTRIBUTING TO RESISTANT HYPERTENSION IN CKD PATIENTS

S.V. N. Vyshnavi, P. Vardhani, D. Sirisha, G. Sadasiva Rao

INTRODUCTION

Hypertension, or high blood pressure, is a serious medical condition on its own, but resistant hypertension poses an even greater threat to health. Resistant hypertension is defined as blood pressure that remains elevated despite the use of three different antihypertensive medications, one of which is typically a diuretic. This condition is challenging to manage and control, and it requires close monitoring and specialized treatment. (1)

If left uncontrolled, resistant hypertension can lead to severe complications, including:

- **Cardiovascular Diseases:** Uncontrolled high blood pressure puts a strain on the heart and blood vessels, increasing the risk of heart attack, stroke, and other cardiovascular problems.
- **Kidney Damage:** Hypertension can damage the blood vessels in the kidneys, leading to impaired kidney function and potentially chronic kidney disease.
- **Aneurysm:** Persistent high blood pressure weakens blood vessel walls, making them susceptible to bulging and potentially rupturing, causing a life-threatening situation.
- **Vision Problems:** Uncontrolled hypertension can lead to eye damage, retinopathy, and vision loss.
- **Cognitive Decline:** Chronic hypertension is associated with an increased risk of cognitive impairment and dementia.
- **Heart Failure:** The heart has to work harder to pump blood against elevated pressure, which can lead to heart muscle weakening and heart failure.
- **Peripheral Artery Disease:** Hypertension can cause narrowed and damaged blood vessels in the legs and arms, leading to reduced blood flow and potential tissue damage.
- **Atrial Fibrillation:** Resistant hypertension may increase the risk of abnormal heart rhythm, particularly atrial fibrillation. (1)

Abstract- Resistance hypertension is one of the complications where blood pressure remains elevated despite the use of three antihypertensive which includes a diuretic. If it is left untreated it can lead to severe complications which includes CVS diseases, kidney diseases. This review article focused on factors that leads to resistant hypertension in Chronic Kidney disease patients. The factors include pseudo resistance, life style factors, drug related causes, secondary causes and genetic causes. Pseudo resistance means high blood pressure that seems to be resistance to treatment, but other factors are actually interfering with proper treatment or measurement. Pseudo resistance occurs due to poor blood pressure monitoring technique, poor medication adherence, white coat effect and life style factors include obesity, excessive salt intake, and alcohol consumption. Excessive salt intake is the leading cause of resistant hypertension in CKD patients and the mechanism includes volume retention, Vascular dysfunction, arterial stiffness and sympathetic activation and mineralocorticoid receptor activation. Drugs that leads to resistance hypertension include NSAIDS, cyclosporine, Glucocorticoids and mineral corticoids. Obstructive sleep apnea is the most common factor which leads to resistance hypertension in chronic kidney patients.

Index Terms: Resistant hypertension, chronic kidney patients, excessive dietary sodium intake, Obstructive sleep apnea

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Fig 1: JNC 8 GUIDELINES (2)

Factors contributing to Resistant Hypertension:
1. Pseudo Resistance
2. Life style Factors
3. Drug Related Causes
4. Secondary Causes
5. Genetical Causes.

PSEUDO RESISTANCE:
Pseudo-resistance, as mentioned in your question, refers to a situation where it appears that a patient's blood pressure is resistant to treatment, but in reality, it is due to factors other than true treatment resistance. These factors include poor blood pressure monitoring technique, poor medication adherence, and the white coat effect.

- Poor Blood Pressure Monitoring Technique (PBPM): Poor blood pressure monitoring technique can lead to inaccurate blood pressure readings, which may incorrectly suggest treatment resistance. Some common mistakes that can cause inaccurate readings include:
  1. Measuring Blood Pressure Too Quickly: Blood pressure readings should be taken after the patient has been sitting quietly for a few minutes to allow their body to relax. Rushing the measurement can lead to higher readings due to temporary stress or activity.
  2. Incorrect Cuff Size: Using a cuff that is too small or too large for the patient's arm can also result in inaccurate readings. The cuff should fit snugly around the upper arm with room for one finger to fit between the cuff and the arm.
  3. Improper Cuff Positioning: The cuff should be placed at heart level to ensure accurate measurements. Placing it too high or too low can lead to incorrect readings.
  4. Failure to Rest Between Measurements: Taking multiple blood pressure readings too quickly without allowing the patient to rest can result in artificially elevated readings.

- Poor Medication Adherence: Sometimes, patients may not take their prescribed blood pressure medications consistently or as directed by their healthcare provider. Non-adherence to medication regimens can lead to ineffective control of blood pressure and may mistakenly be interpreted as treatment resistance.

- White Coat Effect: The white coat effect refers to the phenomenon where a patient's blood pressure is elevated in a clinical setting (such as a doctor's office or hospital) due to the anxiety or stress associated with the medical environment. This temporary increase in blood pressure can give a false impression of treatment resistance. (1) (3)

LIFE STYLE FACTORS:
Lifestyle factors play a significant role in the development of hypertension (high blood pressure). Among these factors, obesity, excess dietary sodium intake, and alcohol consumption have been identified as important contributors to hypertension.
Obesity: Obesity is a condition characterized by excessive body fat accumulation, and it is a well-known risk factor for hypertension. The higher the body mass index (BMI), the greater the risk of developing high blood pressure. Obesity leads to various physiological changes that contribute to hypertension. Some mechanisms include: (1) (4)

1. Sympathetic Nervous System (SNS) over activation: In obesity, there is an increased activation of the sympathetic nervous system, which regulates the "fight-or-flight" response. This heightened SNS activity results in increased heart rate and constriction of blood vessels, leading to elevated blood pressure.

2. Stimulation of the Renin-Angiotensin-Aldosterone System (RAAS): The RAAS plays a critical role in blood pressure regulation. In obesity, there is often an overstimulation of this system, leading to vasoconstriction and fluid retention, both of which raise blood pressure.

3. Adipose-derived cytokines and insulin resistance: Adipose tissue (fat cells) produces various cytokines, such as leptin, which can affect blood pressure regulation. In obesity, there may be alterations in these cytokines, leading to increased blood pressure. Additionally, insulin resistance, commonly associated with obesity, can also contribute to hypertension. (1) (4)

4. Structural and functional renal changes: Obesity can cause changes in the kidneys, leading to impaired renal function, altered sodium handling, and fluid retention, all of which can raise blood pressure. (5)
• **Excess Dietary Sodium Intake:** High dietary sodium intake has been linked to increased blood pressure in some individuals. However, the relationship between sodium intake and hypertension is complex and can vary from person to person. Some mechanisms by which excess dietary sodium may contribute to hypertension include:
  1. Volume retention: High sodium intake can lead to fluid retention in the body, increasing blood volume and subsequently raising blood pressure.
  2. Vascular dysfunction: Excess sodium consumption may negatively affect the function and health of blood vessels, leading to elevated blood pressure.
  3. Arterial stiffness: High sodium levels can contribute to arterial stiffness, which can impair blood flow and raise blood pressure.
  4. Sympathetic activation and mineralocorticoid receptor activation: These mechanisms, similar to those seen in obesity, can be involved in the blood pressure-raising effects of excess sodium intake. (1)

• **Alcohol Consumption:** Alcohol intake, especially in excessive amounts, can lead to hypertension through various pathways. Some mechanisms include:
  1. Diminished baroreceptor reflex: Alcohol interacts with receptors in the brainstem, affecting the baroreceptor reflex, which plays a role in blood pressure regulation.
  2. Increased plasma cortisol levels: Alcohol consumption can lead to increased levels of the stress hormone cortisol, which may contribute to elevated blood pressure.
  3. Imbalance between CNS factors and peripheral vascular effects: Alcohol can disrupt the balance between factors that influence heart rate and cardiac output, as well as the effects on blood vessels, leading to changes in blood pressure.
  4. Increased plasma renin activity: Similar to obesity, alcohol can stimulate the RAAS, leading to elevated blood pressure. (6)

**DRUG RELATED CAUSES:**

- **Glucocorticoid and mineralocorticoid:** They have intense effect on hemodynamics, such as increasing stroke volume, increasing blood pressure and enhancing the press effect of noradrenaline. However, glucocorticoids also stimulate extensive activity of Na-K-ATPase and increase the synthesis of its subunits. Although glucocorticoid is an important transport enzyme in the renal tubule (primarily the cortical collecting duct), it increases renal potassium secretion and decreases urinary sodium excretion (2). And drugs such as prednisone can cause sodium and water retention but the mechanism for rise in blood pressure is still un known on the other hand mineralocorticoid causes significant fluid retention and it may worsen hypertension in susceptible individuals. *shisha*, a common ingredient in oral tobacco products, can raise blood pressure by inhibiting cortisol metabolism via beta-hydroxysteroid dehydrogenase, resulting in an increase in mineralocorticoid receptor stimulation. (7)

- **NSAIDS:** Non steroidal anti-inflammatory drugs (NSAIDs) can raise blood pressure by inhibiting the production of prostaglandins E2 and I2, which reduces vasodilation and sodium excretion. In case of selective COX-2 (cyclooxygenase-2) inhibitors such as celecoxib having less BP effect than traditional NSAIDs [1].

- **Cyclosporin:** Cyclosporin administration in patients can cause a decrease in glomerular filtration, which leads to an increase in filtration fraction, fractional proximal reabsorption of sodium chloride and water, and a decrease in sodium filtered excretion fraction. Cyclosporine causes severe renal vasoconstriction in patients by activating endothelial vasoconstrictors (thromboxane endothelin), the sympathetic nervous system, and cytosol calcium. Finally, hypertension is caused by sodium chloride retention. [9]

- **Erythropoietin:** Erythropoietin administration leads to an increase in hematocrit and erythrocyte mass thus causing changes in vascular smooth muscle ionic milieu and that in turn results in arterial remodelling by activation of vascular cell growth leading to rise blood pressure caused by increase in vascular resistance. In renal failure patients erythropoietin causes rise in plasma aldosterone level. [5] Erythropoietin can induce anti-natriuretic effect thus causing changes in sodium levels excretion leading to hypertension in patients [11]

- **Cocaine:** Cocaine consumption leads to inhibition reuptake of catecholamines like norepinephrine and dopamine and acts on both central and peripheral nervous system [7]. Due to increased sympathetic outflow and blockage of norepinephrine reuptake thus resulting in intense sympathetic activation leading to increase in blood pressure [1]

**SECONDARY CAUSES**

- **Obstructive sleep apnea** - It is a condition which is characterized by recurrent obstructive breathing events caused by upper airway obstruction during sleep accompanied by daytime symptoms and sleep hypoventilation syndrome. These changes in breathing patterns may influence blood pressure regulation mechanisms. OSA events at night cause changes in autonomic and hemodynamic parameters, leading to increased night time blood pressure [14]. The mechanism related to hypertension is not completely explained. However elevated sympathetic tone, intermittent hypoxia, endothelin – and hypoxia mediated vasoconstriction and obesity may contribute to etiology but hyperaldosteronism may be main pathogenic mechanism combining resistant hypertension with obstructive sleep apnea. In addition increase in sympathetic activity may cause changes in blood pressure and in turn increases cardiac output peripheral resistance as well as increase in fluid retention causing high blood pressure. [13]

- **Primary aldosteronism:** Aldosterone promotes sodium reabsorption, potassium and sodium secretion and thus increases blood pressure through reabsorption of sodium and mineralocorticoid receptor activation. [16]

- **Hyperparathyroidism:** The parathyroid glands control levels of calcium and phosphorus in your body. If the gland releases too much parathyroid hormones then the amount of calcium in your blood rises by which it triggers a rise in blood pressure [17].

- **Pheochromocytoma:** Pheochromocytoma is a type of neuroendocrine tumor that grows from cells called chromaffin cells.
These cells produce hormones needed for the body and are found in the adrenal glands. The adrenal glands are small organs located in the upper region of the abdomen on top of the kidney. Pheochromocytomas produce high levels of chemicals called catechol amines which are strong hormones associated with stress and they act on the cardiovascular system to increase heart rate, blood pressure, and blood flow. [18]

GENETICAL REASONS:
- As resistant hypertension represents as an extreme phenotype, it seems reasonable to predict that genetic factors may play a greater role than in the general hypertensive population.
- In one of the few genetic evaluations of patients with resistant hypertension, investigators in Finland screened 347 patients with resistant hypertension for mutations of the β and γ subunits of the epithelial sodium channel (ENaC).
- Mutations of these subunits can cause Liddle’s syndrome which is a rare monogenic form of hypertension.
- Compared with normotensive controls, 2 β ENaC and γ ENaC gene variants were significantly more prevalent in the patients with resistant hypertension. The presence of the γ gene variants was associated with increased urinary potassium excretion relative to plasma renin levels but was not related to baseline plasma aldosterone or plasma renin activity.[1]

CONCLUSION
This review focuses primarily on resistant hypertension by investigating different factors that causes blood pressure variability. The risk factors such as Pseudo resistance, Lifestyle factors, Drug related, secondary causes, genetical reasons along with their mechanism are explained briefly. The most common factors that contribute to resistant hypertension is usually excess sodium intake and obstructive sleep apnea even in non-CKD patients. We can also observe that patients suffering with multiple risk factors are immune to antihypertensive drugs leading to greater incidence of resistant hypertension in those patients. Finally by understanding these factors we can identify the risk factors and take necessary measure if required to prevent the prevalence of resistant hypertension in CKD patients.

REFERENCES:


