Interplay of Hypertension and Chronic Kidney Disease: A Comprehensive Review on Pathophysiology, Risk Factors, Clinical Manifestations, Diagnosis, and Management Strategies

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Abstract

This literature review explores the intricate relationship between hypertension and chronic kidney disease (CKD), examining their pathophysiology, risk factors, clinical manifestations, diagnosis, and management strategies. Hypertension, defined by elevated blood pressure, is identified as a significant contributor to CKD. The review elucidates the complex mechanisms involving the sympathetic nervous system, vasomotor center, and hormonal pathways, contributing to heightened cardiovascular and cerebrovascular risks. Risk factors for hypertension are delineated into modifiable and non-modifiable categories, with lifestyle choices like smoking, obesity, and dietary patterns playing crucial roles. Clinical symptoms of hypertension, such as headaches, blurred vision, and renal complications, often manifest after prolonged elevated blood pressure. The diagnostic process involves standardized blood pressure measurements and comprehensive examinations to identify potential complications. In the context of CKD, hypertension emerges as both a cause and consequence, highlighting a bidirectional relationship. Management strategies encompass non-pharmacological interventions, including dietary sodium reduction and weight loss, as well as pharmacological approaches like diuretics and mineralocorticoid receptor antagonists. Positive outcomes are observed with multidisciplinary care and community involvement, particularly in achieving blood pressure goals. The review explores complications associated with hypertension, underscoring its major role as a risk factor for heart disease, stroke, vision impairment, and kidney disease. CKD, characterized by structural or functional kidney abnormalities lasting over three months, has a diverse etiology involving factors such as diabetes, hypertension, and glomerulonephritis. In conclusion, this review consolidates current knowledge on hypertension and CKD, providing a holistic understanding of their interconnectedness and offering insights into their clinical management.

Keywords: Chronic kidney disease, Hypertension, Treatment.

1. Introduction

Hypertension, characterized by elevated systolic blood pressure (SBP) exceeding 140 mmHg and diastolic blood pressure (DBP) equal to or surpassing 90 mmHg, stands as a pervasive global health concern. In concert with its well-established role as a precursor to cardiovascular diseases, emerging evidence underscores its intricate relationship with Chronic Kidney Disease (CKD). This comprehensive literature review endeavors to dissect the multifaceted interplay between hypertension and CKD, offering insights into

their shared pathophysiological mechanisms, risk factors, clinical manifestations, diagnostic intricacies, and the array of management strategies that navigate the complex landscape of these intertwined conditions.

Hypertension, often referred to as the "silent killer," is a prevalent medical condition that significantly contributes to the global burden of disease. According to Williams et al. (2018), the diagnosis of hypertension is established through repeated measurements of elevated blood pressure levels in clinical settings. However, recent paradigms have expanded to incorporate Home Blood Pressure Monitoring (HBPM) and Ambulatory Blood Pressure Monitoring (ABPM), recognizing the importance of comprehensive assessments beyond clinic-based measurements (Unger et al., 2020a). The pathophysiology of hypertension extends beyond the conventional understanding of elevated blood pressure, involving intricate mechanisms orchestrated by the sympathetic nervous system, vasomotor center, and hormonal pathways. These elements collectively contribute to increased cardiovascular and cerebrovascular risks, highlighting the complexity of the interactions at play (Kasper et al., 2005).

This review categorizes risk factors for hypertension into modifiable and non-modifiable factors. Lifestyle choices, including smoking, obesity, and dietary patterns, emerge as pivotal influencers, accentuating the dynamic nature of hypertension and its susceptibility to individual choices (Casey & Benson, 2006). Clinical manifestations of hypertension often remain latent for extended periods, with symptoms such as headaches, blurred vision, and renal complications surfacing after prolonged exposure to elevated blood pressure (Mansjoer et al., 2001). Intriguingly, the relationship between hypertension and CKD is not unidirectional; rather, it is characterized by bidirectional causality. CKD can both contribute to the development of hypertension and ensue as a consequence of prolonged hypertensive states. This bidirectional relationship accentuates the complexity of managing these conditions comprehensively (Hamrahian, 2016).

Management of hypertension in the context of CKD encompasses a spectrum of interventions. Non-pharmacological strategies, including dietary sodium reduction and weight loss, synergize with pharmacological approaches involving diuretics and mineralocorticoid receptor antagonists. The multidisciplinary nature of care, incorporating community involvement and healthcare professionals, has demonstrated positive outcomes in achieving blood pressure goals (Van Zuilen et al., 2008). The review delves into the complications associated with hypertension, emphasizing its pivotal role as a major risk factor for heart disease, stroke, vision impairment, and kidney disease. CKD, defined by structural or functional abnormalities lasting over three months, has diverse etiologies, with diabetes, hypertension, and glomerulonephritis being prominent contributors to its onset (KDIGO, 2012).

In conclusion, this review synthesizes the current understanding of the intricate relationship between hypertension and CKD, shedding light on their interconnectedness and providing a comprehensive foundation for understanding and managing these complex health conditions. The exploration of pathophysiological mechanisms, risk factors, clinical manifestations, diagnostic intricacies, and management strategies aims to equip healthcare professionals and researchers with a nuanced understanding to address the evolving landscape of hypertension and CKD.

2. Review Content

2.1 Hypertension

2.1.1 Definition and Classification

Hypertension is a condition where systolic blood pressure (SBP) is greater than 140 mmHg, and diastolic blood pressure (DBP) is equal to or greater than 90 mmHg in measurements at clinics or healthcare facilities

(Williams et al., 2018). According to most guidelines, hypertension is recommended to be diagnosed when both SBP and DBP consistently reach or exceed these limits after repeated examinations (Unger et al., 2020). While facility-based blood pressure measurement is the gold standard for diagnosing hypertension, Home Blood Pressure Monitoring (HBPM) and Ambulatory Blood Pressure Monitoring (ABPM) are increasingly promoted (Unger et al., 2020).

2.1.2 Pathophysiology

The mechanisms controlling blood vessel constriction and relaxation are located in the vasomotor center in the brainstem. The sympathetic nervous system originates from this center, extending down to the spinal cord and exiting from the spinal cord column to sympathetic ganglia in the thorax and abdomen. Stimulation of the vasomotor center results in impulses moving downward through the sympathetic nerves to the sympathetic ganglia. At this point, preganglionic neurons release acetylcholine, stimulating postganglionic nerve fibers to capillary blood vessels. The release of norepinephrine causes constriction of capillary blood vessels. Various factors, such as anxiety and fear, can influence blood vessel responses to vasoconstrictor stimuli. Individuals with hypertension are highly sensitive to norepinephrine, though the exact reasons are unclear. Simultaneously, when the sympathetic nervous system stimulates blood vessels in response to emotional stimuli, the adrenal glands are also activated, leading to additional vasoconstrictive activity. The adrenal medulla secretes epinephrine, causing vasoconstriction. The adrenal cortex secretes cortisol and other steroids, reinforcing the vasoconstrictive response of blood vessels. Vasoconstriction resulting in decreased blood flow to the kidneys triggers the release of renin. Renin stimulates the formation of angiotensin I, which is then converted into angiotensin II, a potent vasoconstrictor. This, in turn, stimulates aldosterone secretion by the adrenal cortex. This hormone causes sodium and water retention by renal tubules, leading to an increase in intravascular volume. All these factors tend to induce hypertension. Structural and functional changes in the peripheral blood vessel system account for the changes in blood pressure in the elderly. These changes include atherosclerosis, loss of elasticity in connective tissues, and a decrease in the relaxation of smooth muscle in blood vessels, which, in turn, reduces the ability of blood vessels to distend and contract. Consequently, the aorta and large arteries lose their ability to accommodate the volume of blood pumped by the heart (stroke volume), resulting in a decrease in cardiac output and an increase in peripheral resistance. Essentially, blood pressure is influenced by cardiac output and peripheral resistance. Various factors affecting cardiac output and peripheral resistance will influence blood pressure, such as high salt intake, genetic factors, stress, obesity, and endothelial factors (Kasper et al., 2005).

2.1.3 Risk Factors

Hypertension risk factors are divided into modifiable and non-modifiable factors. Genetics, gender, race, and age are non-modifiable risk factors. Modifiable risk factors include smoking, obesity, stress, dietary patterns, lack of exercise or physical activity, and high blood cholesterol levels (Casey & Benson, 2006). In summary, modifiable hypertension risk factors are closely related to unhealthy lifestyles, especially excessive salt consumption, frequent intake of saturated and trans fats leading to increased triglyceride, LDL, total cholesterol levels, and decreased HDL levels in the blood. Consequently, lipid accumulation in the blood occurs over time, blocking blood vessel lumens. Additionally, alcohol and tobacco consumption habits can increase the risk of hypertension (WHO, 2021).

2.1.4 Clinical Symptoms

Clinical manifestations of hypertension mostly occur after years of experiencing hypertension. Clinical features of hypertensive patients include headaches upon waking, sometimes accompanied by nausea and vomiting due to increased intracranial pressure, blurred vision caused by hypertensive damage to the retina, abnormal gait due to central nervous system damage, nocturia due to increased renal blood flow and

glomerular filtration, dependent edema, and swelling caused by increased capillary pressure. However, symptoms may also be limited to elevated blood pressure without other abnormalities (Mansjoer et al., 2001).

2.1.5 Diagnosis

Based on medical history, most hypertensive patients are asymptomatic. Some may complain of symptoms like headaches, dizziness, or blurred vision. Supporting suspicions of secondary hypertension includes the use of medications such as hormonal contraceptives, corticosteroids, decongestants, and NSAIDs, paroxysmal headaches, sweating, tachycardia, and a history of previous kidney disease. The medical history should also explore cardiovascular risk factors such as smoking, obesity, lack of physical activity, dyslipidemia, diabetes mellitus, microalbuminuria, decreased GFR, and family history (Kasper et al., 2005). Physical examination involves taking the average blood pressure values from two measurements during each doctor visit. If blood pressure is ≥ 140/90 mmHg on two or more visits, hypertension can be confirmed. Blood pressure measurements should be performed with a proper device, appropriate cuff size and positioning (at the level of the heart), and the correct technique. Additional tests are conducted to examine existing or ongoing complications, such as complete blood count, urea, creatinine, blood sugar, electrolytes, calcium, uric acid, and urinalysis. Other examinations include assessing cardiac function with electrocardiography, fundoscopy, kidney ultrasound, chest X-ray, and echocardiography. In cases suspecting secondary hypertension, tests are conducted based on indications and differential diagnoses. For hyper- or hypothyroidism, thyroid function tests (TSH, FT4, FT3) are performed, hyperparathyroidism (PTH level, Ca2+), primary hyperaldosteronism involves measuring plasma aldosterone, plasma renin, abdominal CT scan, increased serum Na levels, decreased K levels, and increased K excretion in urine causing metabolic alkalosis. For pheochromocytoma, metanephrine levels are measured, and an abdominal CT scan/MRI is conducted. In Cushing's syndrome, a 24-hour urine cortisol test is performed. In renovascular hypertension, CT angiography of renal arteries, kidney ultrasound, and Doppler sonography are conducted (Kasper et al., 2005). The five main classes of antihypertensive drugs routinely recommended are Angiotensin-converting Enzyme inhibitors (ACEi), Angiotensin II Receptor Blockers (ARBs), beta-blockers, calcium channel blockers (CCB), and diuretics (Williams et al., 2018).

2.1.6 Complications

Hypertension is a major risk factor for heart disease, congestive heart failure, stroke, vision impairment, and kidney disease. Elevated blood pressure generally increases the risk of these complications. Untreated hypertension affects all organ systems and ultimately shortens life expectancy by 10-20 years. Mortality in hypertensive patients occurs more rapidly if the condition is uncontrolled and has led to complications in several vital organs. The most common cause of death is heart disease, with or without stroke and kidney failure. Complications occurring in mild and moderate hypertension affect the eyes, kidneys, heart, and brain. In the eyes, there may be retinal bleeding and vision disturbances leading to blindness. Heart failure is a common disorder found in severe hypertension, along with coronary and myocardial abnormalities. Stroke frequently occurs in the brain, causing bleeding due to the rupture of microaneurysms that can result in death. Other abnormalities that may occur include thromboembolic processes and transient ischemic attacks (TIAs). Kidney failure is often encountered as a complication of long-term hypertension and in acute processes, such as malignant hypertension (Mansjoer et al., 2001).

2.2 Chronic Kidney Disease

2.2.1 Definition

Chronic Kidney Disease (CKD) is the presence of structural or functional kidney damage and/or a glomerular filtration rate (GFR) less than 60 mL/min/1.73m2 or albuminuria of at least 30 mg per 24 hours, with markers of kidney damage (e.g., hematuria or structural abnormalities like polycystic or dysplastic kidneys) lasting more than three months or having a history of kidney transplant (Chen, 2019). CKD results in a progressive

decline in kidney function and generally ends in kidney failure. Kidney failure is a clinical condition characterized by irreversible kidney function decline to a degree that requires ongoing kidney replacement therapy, such as kidney transplantation or dialysis. CKD is defined as structural or functional kidney abnormalities lasting more than 3 months with implications for health. CKD is classified based on causes, GFR categories, and albuminuria categories (KDIGO, 2012).

2.2.2 Etiology and Epidemiology

The leading causes of CKD are diabetic nephropathy, hypertension, glomerulonephritis, obstructive uropathy, and interstitial nephritis. In Indonesia, the most common causes of CKD are glomerulonephritis, urinary tract infections (UTIs), kidney stones, diabetic nephropathy, hypertension, and polycystic kidneys (Irwan, 2016). CKD is now recognized as a public health priority worldwide. The epidemic wave of CKD over this decade has resulted in an 82% increase from previous years, making CKD a disease with a burden comparable to diabetes mellitus (Jha et al., 2013). The World Health Organization (WHO) indicates that both acute and chronic kidney failure affects 50% of the population, with only 25% receiving treatment, and only 12.5% being well-treated. CKD worldwide is on the rise and has become a serious health problem. Global Burden of Disease research in 2010 showed that chronic kidney disease was the 27th leading cause of death in the world in 1990 and continued to rise, ranking 18th in 2010 (Kemenkes, 2018).

2.3 Hypertension in CKD

Chronic kidney disease (CKD) is a common cause of hypertension, and CKD is also a complication of uncontrolled hypertension. The interaction between hypertension and CKD is complex, increasing the risk of adverse cardiovascular and cerebrovascular outcomes. This is particularly important in managing resistant hypertension commonly seen in patients with CKD. Standardized blood pressure (BP) measurement is crucial in diagnosing and managing hypertension in CKD. (Hamrahian, 2016). In short, CKD interacts with hypertension on many levels. There is a two-way relationship between these two diseases. Hypertension, especially resistant hypertension, can occur not only as a result of CKD but is also a significant risk factor for CKD development. Resistant hypertension is prevalent among CKD patients, and its prevalence seems to be proportional to the level of kidney dysfunction (Tanner et al., 2013).

Common causes of uncontrolled BP in CKD patients include non-compliance with important lifestyle changes such as a low-salt diet, inadequate or suboptimal treatment regimens including diuretics, and poor compliance with antihypertensive therapy, sometimes due to drug intolerance (Yiannakopoulou et al., 2005). Other potential causes of uncontrolled BP include previously undiagnosed secondary hypertension that can be cured; psychiatric causes; disruptive substance use like non-steroidal anti-inflammatory drugs (NSAIDs) or amphetamines; and drug interactions. Besides preventing cardiovascular events (McCullough et al., 2011),

2.4 Management of Hypertension in CKD.

There are several non-pharmacological treatments for hypertension in the context of CKD. A study by Slagman et al. (2011) found that, in those already established on RAAS blockade, reducing dietary sodium intake to a target of <50 mmol/day (3 g/day salt) further lowers systolic BP by an additional 10 mmHg. Restriction to a target of <100 mmol/day (6 g/day salt) has also shown a 25% reduction in proteinuria, an effect unlikely to be explained solely by BP reduction (Vogt et al., 2008). There are instances where dietary sodium has little impact on BP. However, as GFR decreases, the sensitivity of BP to dietary sodium load increases. In practice, limiting dietary sodium can be challenging. Urinary sodium measurements by Slagman et al. (2011) showed that despite regular counseling sessions, the average dietary sodium intake in the <50 mmol/day target group was 106 mmol/day. In those without dietary restrictions, intake was 186 mmol/day. Recognizing personal dietary preferences and setting realistic goals (<100 mmol/day sodium) under the supervision of a nutrition expert can enhance the likelihood of achieving meaningful and sustainable dietary changes (McMahon et al., 2012).

Effective weight loss reduces BP and proteinuria and may slow the progression of CKD (Navaneethan et al., 2009). In overweight patients (body mass index [BMI] > 27 kg/m2) with CKD and proteinuria (>1 g/24 hours), an average weight loss of 4% can reduce proteinuria by 30% (Morales et al., 2003). The benefits of a multidisciplinary approach have also been demonstrated in CKD. A systematic review by Santschi and colleagues (Santschi et al., 2011) showed improved achievement of BP goals in hypertensive patients after the introduction of community pharmacists. In the MASTERPLAN study (Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of Nurse Practitioners) conducted in the Netherlands, specialized nursing care clearly improved the management of cardiovascular risk factors, including BP, at 1 and 2 years in patients with CKD stages 3-4 (Van Zuilen et al., 2008). Volume excess, often subclinical, affects up to 50% of people with CKD and is an independent risk factor for CVD (Hung et al., 2014). Diuretic therapy can reduce volume expansion and has been shown to improve left ventricular mass index and arterial stiffness in those with CKD (Zamboli et al., 2011; Edwards et al., 2009). Thus, diuretics are often used as part of combination drug therapy in CKD and offer antihypertensive and cardioprotective effects (Zamboli et al., 2011).

In non-proteinuric CKD, monotherapy with thiazide (such as bendroflumethiazide) or thiazide-like diuretics (such as indapamide) may have a role and should be considered as potential first-line therapy. Treatment with diuretics can also reverse the loss of physiological nocturnal BP reduction described in CKD. Loop diuretics (such as furosemide) are highly valuable, although higher doses are often needed in those with lower eGFR because the tubular action of these drugs depends primarily on glomerular filtration. The combination of loop and thiazide diuretics is very potent, and care should be taken to avoid fluid depletion. Diuretics should generally be avoided in patients with polycystic kidney disease due to accelerated cyst growth and the associated loss of excretory function related to their use. Mineralocorticoid receptor antagonists (such as spironolactone) effectively reduce BP in CKD but carry the risk of exacerbating hyperkalemia (Currie et al., 2016). These agents have been shown to improve systolic and diastolic function in early CKD and may therefore have value in patients with concurrent left ventricular dysfunction (Edwards et al., 2010). It is unclear whether this effect is solely due to BP reduction. To answer this question, a randomized study comparing spironolactone with the thiazide diuretic chlorthalidone in stage 3 CKD patients has been completed (SPIRO-CKD [Spironolactone in Chronic Kidney Disease]), and the results are awaited (Hayer et al., 2017). In hypertensive patients without CKD, spironolactone is more effective than bisoprolol or doxazosin in reducing BP when used as fourth-line add-on therapy.

3. Conclusion

In conclusion, this comprehensive review underscores the intricate interplay between hypertension and chronic kidney disease (CKD), emphasizing their bidirectional relationship and shared impact on cardiovascular health. By dissecting their pathophysiology, exploring risk factors, clinical manifestations, and delving into management strategies, this review contributes to a holistic understanding of these interconnected conditions. The recognition of hypertension as both a cause and consequence of CKD highlights the importance of integrated healthcare approaches. The multifaceted nature of their association necessitates ongoing research and a collaborative effort across disciplines to refine diagnostic and therapeutic interventions for improved patient outcomes in the complex landscape of hypertension and CKD.

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