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Hypertension in Renal Disease: Pathogenesis and Management

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Abstract
Hypertension occurs in more than 80% of patients with chronic renal failure. The role of kidney in renal disease-related hypertension is very complex. Exogenous and endogenous factors may affect blood pressure in patients with renal disease, including high sodium intake, increased sympathetic nervous system activity, increased renin-angiotensin-aldosterone system activity, and endothelial dysfunction. In some cases, it becomes difficult to determine whether hypertension or renal disease is the underlying disorder. In addition to lifestyle and dietary modifications, pharmacological therapy is an important component in controlling and achieving blood pressure targets. The overall goal of hypertension therapy in renal disease is to prevent extrarenal complications from hypertension, such as heart disease and stroke. In all patients with renal disease, blood pressure should be controlled at the recommended level. Some guidelines for chronic renal disease patients recommend to start the therapy using ACE-I or ARB, or adding ACE-I or ARB to the patient's drug regimen.

Keywords: *Hypertension, Renal Disease, Hypertension Management*

I. INTRODUCTION

Hypertension is a major and independent risk factor for cardiovascular disease in the world. It is the second leading cause of end-stage renal disease (Singapuri & Lea, 2010). Hypertension is often found in acute and chronic kidney disease with glomerular or vascular disorders. The pathogenesis and type of therapy chosen for hypertension varies according to the patient's renal disease conditions (Mann, 2016). In this review, we outline the pathogenesis and treatment of hypertension in patient with chronic kidney disease.

II. SYSTEMIC HYPERTENSION

Systemic hypertension is defined as a chronic increase in systemic arterial pressure (Widmaier, Raff, & Strang, 2014). Hypertensive clinical criteria are based on the average of two or more systolic and diastolic blood pressure readings (Kotchen, 2015). Hypertension can be classified based on patient's blood measurements, including:

Table 1 Essentials of Dignosis (Vongpatanasin, 2014)

Prehypertension: systolic pressure of 120 – 139 mmHg or diastolic pressure of 80 – 89 mmHg
Stage 1 hypertension: systolic pressure of 140 – 159 mmHg or diastolic pressure of 90 – 99 mmHg
Stage 2 hypertension: systolic pressure of at least 160 mmHg or diastolic pressure of at least 100 mmHg

Hypertension also can be classified according to the cause. Hypertension caused by several factors that are not necessary is called Primary / Essential Hypertension. As for hypertension that the cause has been identified / known is called Secondary Hypertension (Widmaier, Raff, & Strang, 2014).

A. Primary / Essential Hypertension: Primary hypertension occurs in more than 90% of hypertension cases. The cause of this type of hypertension is not certainly known, although a number of genetic and environmental factors are suspected to be involved as the cause (Widmaier, Raff, & Strang, 2014). The prevalence of primary hypertension increases with age. In individuals with relative high blood pressure at a young age will increase the risk of subsequent hypertension (Kotchen, 2015).

B. Secondary Hypertension: Approximately 5% of patients have secondary hypertension with specific causes which have been identified. Almost all renal impairment can cause hypertension, and renal disease is the most common cause of secondary hypertension which is directly related to increased intravascular volume or increased activity of Renin-Angiotensin-Aldosteron System (RAAS) (Sutter, 2016). Hypertension occurs in more than 80% of patients with chronic renal failure. In general, the more severe hypertension occurs in patient with glomerular disease than in patient interstitial disease such as chronic pyelonephritis. Hypertension can also cause nephrosclerosis, and in some cases, it becomes difficult to determine whether hypertension or renal

disease is the initial disorder. The goal of hypertension therapy in renal disease is to control blood pressure and inhibit the rate of development of renal dysfunction (Kotchen, 2015).

III. RENAL FUNCTION, ANATOMY, AND PHYSIOLOGY

a. ***Renal Function:*** Kidney processes part of the blood plasma by removing the substances contained in it or by adding certain substances into it (Widmaier, Raff, & Strang, 2014).

Table 2. Functions of The Renal (Widmaier, Raff, & Strang, 2014)

Regulation of water, inorganic ion balance, and acid-base balance (in cooperation with the lungs)
Removal of foreign chemicals from the blood and their excretion in the urine
Removal of metabolic waste products from the blood and their excretion in the urine
Production of hormones/enzymes: • Erythropoietin, which controls erythrocyte production • Renin, an enzyme that controls the formation of angiotensin, which influences blood pressure and sodium balance • Conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which influences calcium balance

b. Renal Anatomy and Physiology

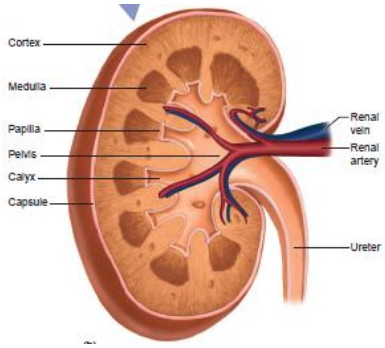

Figure 1 The Main Structure Component of the Kidney
(Widmaier, Raff, & Strang, 2014)

The bending surface of the kidney is called hilus, which has arterial and venous blood vessels of the kidney. The nerves initiating kidney to secrete urine through the ureter are also located in the hilus. Kidney is surrounded by protective capsule composed of fibrous tissue. Kidneys is divided into two parts, called the outer renal cortex and the inner renal medulla (Widmaier, Raff, & Strang, 2014). Each kidney consists of approximately 1 million similar subunits, called nephron. Each nephron consists of a glomerulus which is responsible for blood ultrafiltration, a proximal tubule, a loop of Henle, a distal tubule, and a collecting duct. Together, they are responsible for the selective reabsorption of the water and the electrolyte which have been filtered by glomerulus (Goddard & Turner, 2014)

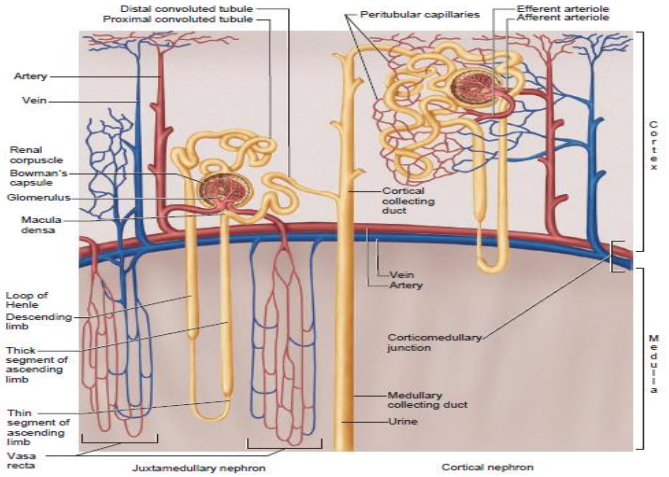

Figure 2 Nefron Basic Structure (Widmaier, Raff, & Strang, 2014)

Filtration pressure in the glomerulus is usually maintained at a constant level to face a number of variations in systemic blood pressure and cardiac output, by changing afferent and efferent arteriolar muscle tone. This stage is called autoregulation (Goddard & Turner, 2014)**.** The afferent and efferent arteriolar muscle tone is controlled by three main factors, including autonomic vasoreactive reflexes in afferent arterioles, tubuloglomerular feedback, and angiotensin-mediated vasoconstriction in efferent arterioles (George & Neilson, 2015). When there is a decrease in renal perfusion pressure, renin is released by special smooth muscle cells in the juxtaglomerular apparatus. Renin will break down angiotensinogen to release angiotensin I, which is further broken down by angiotensin-converting enzyme (ACE) to produce angiotensin II. This will restore the pressure of glomerular perfusion in short term by causing the efferent arteriolar vasoconstriction in kidney and by inducing systemic vasoconstriction to increase blood pressure resulting in increased renal perfusion pressure. In the long term, angiotensin II will increase plasma volume by stimulating the release of aldosterone, which can increase the reabsorption of sodium by renal tubules (Goddard & Turner, 2014).

IV. PATHOGENESIS OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

Chronic Kidney Disease (CKD) includes a spectrum of different pathophysiology associated with abnormal kidney function and a progressive decline of Glomerular Filtration Rate (GFR). The pathophysiology of CKD involves two broad set of mechanism of damage, initiating mechanism spesific to the underlying etiology (e.g., genetically determined abnormalitied in kidney development or integrity, immune complex deposition and inflammation in certain types of glomerulonephritis, or toxin exposure in certain disease of the renal tubule and interstitium) and a set of progressive mechanisms, involving hyperfiltration and hypertrophy of the remaining viable nephron, that are a common consequence following long-term reduction of renal mass, irrespective of underlying etiology (Goddard & Turner, 2014). Hypertension is the most common complication of CKD. (George & Neilson, 2015).

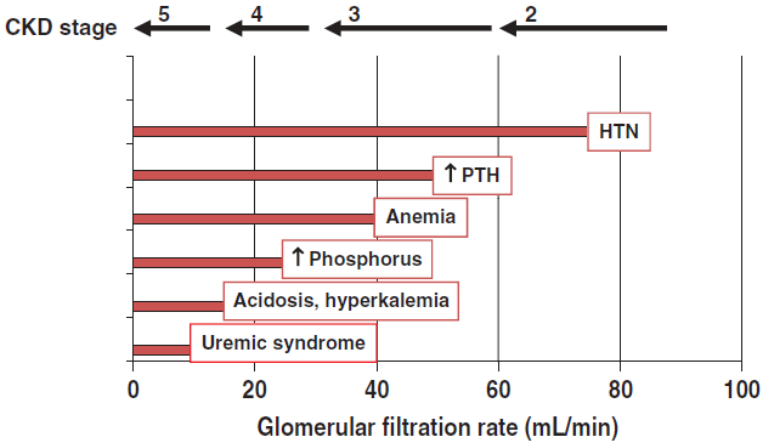

Figure 3 Complication of chronic kidney disease by stage and glomerular filtration rate (Watnick & Dirkx, 2016)

The role of kidney in CKD-related hypertension is very complex. Exogenous and endogenous factors may affect blood pressure in CKD patients, including high sodium intake, increased sympathetic nervous system activity, increased RAAS, and endothelial dysfunction (Townsend & Taler, 2015).

a. ***Role of Sodium and Volume:*** The excretion regulation of sodium is basic function of the kidney. Incompatibility between input and output amount for months or years can lead to volume-mediated hypertension or devastating volume depletion. NaCl intake through food or parenteral causes volume expansion and increased heart filling (preload), which further leads to increased cardiac output (Townsend & Taler, 2015).

b. ***Role of Increased Sympathetic Nervous System Activity:*** *The* kidney is not just a complicated filtering organ but also an organ that is rich in sensory nerves. The kidneys can be targeted by sympathetic nervous activity but also can be modulator of this activity (Campese, 2014). There are two main types of sensory receptors of the kidney and the afferent nerve, baroreceptor and chemoreceptor. Baroreceptor activity will be increased in responses of change in renal perfusion pressure. The change of chemoreceptor is stimulated by ischemic metabolites or uremic toxins. These two receptors, through the renal afferent nerve, can form connection with the integrative nucleus of the sympathetic nervous system in the Central Nervous System (CNS). Acute stimulation of the afferent nerve by an ischemic metabolite, such as adenosine or urea, will lead to increased reflexes on the efferent nerve activity and increased blood pressure. Chronic

stimulation of the afferent nerve by renal ischemia or other factors may lead to increased activity of the sympathetic nervous system and hypertension (Campese, 2014). At the beginning of impaired renal function, increased sympathetic nerve activity in the muscle may occurs. At a low level of stimulation, the renal efferent nerve will trigger renin secretion in the kidney. Stimulation of these efferent nerves results in decreased urinary sodium excretion (anti-natriuresis). While maximal nerve stimulation will initiate increased vascular resistance in the kidney (Townsend & Taler, 2015).

c. Role of Humoral System

i. ***Plasma Renin Activity:*** The relationship between the afferent arteriole, the distal tubule, and the base of the glomerulus forms a unity called the juxtaglomerular apparatus. When afferent arteriolar strains decrease for several reasons, RAAS in the juxtaglomerular apparatus is activated, and plasma renin activity increases. Sympathetic nerve activation will lead to activation of β1-adrenoreceptor, which will further stimulate renin secretion. When there is excessive sodium intake or increased intravascular volume, afferent arteriolar strain will increase and renin activity is suppressed. The mechanism above is different in CKD patients. In this patients, the renin system is more active at increased volume. In addition, the presence of angiotensin II, which is the final product of activation of this system, will not only gives vasoconstriction effect but can also trigger sodium reabsorption, increases neurotransmitter release in the sympathetic innervation system, and stimulates aldosterone release (Townsend & Taler, 2015).

ii. ***Aldosterone:*** Aldosterone triggers reabsorption of sodium in the distal tubule of the nephron during an exchange with potassium ions. The excess effect of aldosterone is known as a potential cause of hypertension (Townsend & Taler, 2015).

iii. ***Other Factors:*** Several other factors are known as mediators of increased blood pressure in CKD patients. These factors include endothelin, oxidative stressors, and inflammatory mediators. Endothelin, such as ET-1, is a vasoconstrictor that can cause inflammation and fibrosis (Townsend & Taler, 2015). ET-1 is involved in development and progression of CKD (Campese, 2014). Oxidative stressors including ROS (Reactive Oxygen Species), can trigger vasoconstriction, renin release, and increase urinary protein excretion. Inflammatory mediators including cytokines, such as TNF and IFNγ, may impair endothelial function

d. ***Role of Vascular Endothelium:*** The blood pressure regulation system is directly related to the endothelium and blood vessel walls. Nitric Oxides (NO) release disorders from endothelium leads to decreased bioavailability of NO, either by restricting the substrate (arginine) or by oxidizing the NO in the cell before it is released, may damage important response in vasodilation (Townsend & Taler, 2015). Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor that inhibits NO synthesis and causes endothelial dysfunction, vasoconstriction, elevated blood pressure, and progression of atherosclerosis. ADMA level is increase significantly in patients with CKD and End Stage Renal Disease (ESRD), which is contributes to hypertension, severity of atherosclerosis, and mortality of patients (Campese, 2014)

e. Role of Arterial Structural Changes: The integrity and distensibility of the arterial structure have been known for a long time as a factor contributing to the incidence of hypertension and cardiovascular disease (Campese, 2014). The processes that can make arterial or arteriolar walls become stiff, such as vascular calcification or excessive accumulation of collagen, are both known to be more active in CKD patients and cause increased blood pressure (Townsend & Taler, 2015).

V. PHARMACOLOGIC THERAPY OF HYPERTENSION IN RENAL DISEASE

Management of hypertension therapy in CKD requires a variety of approaches. In addition to lifestyle and dietary modifications, pharmacological therapy is an important component in controlling and achieving blood pressure targets (Chaturvedy, 2014). The overall goal of hypertension therapy in CKD is to prevent extrarenal complications from hypertension, such as heart disease and stroke. In all patients with CKD, blood pressure should be controlled at the recommended level (George & Neilson, 2015). Some guidelines for CKD patients recommend to start the therapy with ACE-I or ARB, or adding ACE-I or ARB to the patient's drug regimen (Townsend & Taler, 2015).

a. ACE Inhibitors (ACE-I) and Angiotensin Receptor Blockers (ARB): *ACE-I decrease the production of angiotensin II, increase bradykininlevels*, and reduce sympathetic nervous system activity. While ARB provide selective blockade of AT1 receptors, and the effect of angiotensin II unblocked AT2 receptors may augment their hypotensive effect (Vongpatanasin, 2014). ACE-I and ARB are the first choice in

hypertension patients with CKD. ACE-I and ARB are given to slow the rate of decline in renal function by decreasing systemic arterial pressure and improving intraglomerular hyperfiltration. ACE-I and ARB inhibit angiotensin II-induced vasoconstriction in efferent arterioles in glomerular microcirculation. This inhibition causes a decrease in intraglomerular filtration pressure and proteinuria (George & Neilson, 2015). Hyperkalemia is a side effect that needs to be watched on the administration of ACE-I or ARB. Combination with potassium-sparing diuretics should be controlled even must be avoided in some patients (George & Neilson, 2015).

b. Aldosteron Blockers: Aldosterone blockers (mineralocorticoid antagonist) be an important fourth-line blood pressure agent in the treatment of resistant hypertension (Judd & Calhoun, 2015). Aldosterone receptors antagonist block the effect of aldosterone, therefore decrease sodium reabsorption and water retention by the kidney. Aldosterone blockers have been used to lower blood pressure and have an effect on reducing proteinuria in CKD patients (Chaturvedy, 2014). Patients in later stages of CKD are likely to meet the classification of resistant hypertension, however, risks of hyperkalemia and acute kidney injury have limited aldosterone blockers use in advanced CKD (Judd & Calhoun, 2015).

c. Calcium Channel Blockers (CCB): Drugs of this class lower blood pressure by inhibiting vascular smooth muscle contractions associated with blockade of calcium channel and decreased peripheral resistance. However, in some cases, reflexes can stimulate the sympathetic nervous system and trigger tachycardia (Chaturvedy, 2014). Non-dihydropyridine CCB (Diltiazem, Verapamil) has antiproteinuria effects, whereas dihydropyridine CCB is more effective in lowering blood pressure and can be combined with ACE-I or ARB without a negative effect on proteinuria (Townsend & Taler, 2015).

d. β-blockers: β-blockers are often indicated in patients with cardiovascular complications, such as CHF, post MI, or tachyarrhythmias (Chaturvedy, 2014).

e. *Diuretics:* In CKD patients, diuretics are used to reduce excess of salt and volume, in patients whose blood pressure remains high during the therapy (Chaturvedy, 2014). In general, as GFR falls, higher doses of diuretics are needed to achieve a natriuretic response (Judd & Calhoun, 2015). Loop diuretics are indicated for CKD when eGFR patients is less than 30 ml/min/1.73 m^2. It is expected that this therapy can provide diuresis effects on low GFR (Chaturvedy, 2014).

VI. CONCLUSION

The role of kidney in CKD-associated hypertension is complex because the kidney contributes to and is damaged by the hypertension processes. Numerous exogenous and endogenous factors can influence blood pressure in patients with CKD, including increased activity of the renin – angiotensin system, high sodium dietary intake, enhanced activity of the sympathetic nervous system, impaired nitric oxide synthesis and endothelium – mediated vasodilatation. ACE-I and ARBs appear to slow the rate of decline of kidney function by reducing intraglomerular pressure by preferential dilatation of efferent arterioles that can prevent glomerular sclerosis and reduce proteinuria.

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