Pathophysiology of Hypertension in Chronic Kidney Disease

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Abstract
There are a multitude of mechanism of pathogenesis of hypertension in CKD. The most important is the rennin angiotensin axis and the renal autoregulation. However the role of other mechanism like the sympathetic nervous system overactivity, drugs, endothelial dysfunction, genetics and oxidative stress cannot be ignored. In this article, we present a detailed description of the various mechanism involved in the pathogenesis of hypertension in CKD.

Key words: CKD, pathophysiology, hypertension, Renin angiotensin axis.

Introduction
Chronic kidney disease (CKD) is the most common cause of secondary hypertension.1 CKD contributes to around 50% of secondary hypertension and 5% of all-cause hypertension. The higher prevalence of hypertension in this population increases the cardiovascular morbidity and mortality. The complex interplay of factors leads to the development and persistence of hypertension in CKD. The major players are extracellular volume (ECV) overload, increased renin-angiotensin-aldosterone axis (RAAS) activation, enhanced endothelin-1 release, and sympathetic nervous system (SNS) activation.2 The dietary and lifestyle factors also have some contributory roles. The prevalence of hypertension is higher among patients with CKD when compared to the general population (64.5% vs. 41%).3 Based on a national survey of representative sample of non-institutionalized adults in the USA, it is estimated that hypertension occurs in 23.3% of individuals without CKD, and 35.8% of Stage 1, 48.1% of Stage 2, 59.9% of Stage 3, and 84.1% of Stage 4–5 CKD patients.4 Almost 85–90% of the incident dialysis patients will have hypertension. The prevalence of hypertension also varies with the etiology of CKD. A strong association with hypertension was found in patients with renal artery stenosis (93%), diabetic nephropathy (87%), and polycystic kidney disease (74%).5

Pathophysiological Mechanisms
Hypertension in CKD can be broadly classified into two categories: Volume-mediated hypertension and renin-mediated hypertension. Hypertension in CKD is primarily an imbalance in the renal autoregulatory mechanisms due to the impaired renal functions [Figures 1 and 2].

Impaired renal sodium handling and volume overload
The kidneys play such a vital role in long-term blood pressure regulation that Guyton et al. argued that sustained hypertension could not occur in the absence of the impairment of renal handling of sodium.7 Guyton et al. proposed that sodium balance after salt intake is regulated by the pressure-natriuresis mechanism. Sodium loading is associated with a transient increase in blood pressure which returns to primary values after pressure-natriuresis and regulation of ECV. Some individuals have impairments of sodium elimination mechanisms, and for the same sodium natriuresis effect, they need to have higher blood pressure. Thus, sodium retention causes expansion of ECV, causing higher cardiac output with tissue perfusion that exceeds metabolic needs. Peripheral tissue vasculature responds by activating autoregulatory vasoconstriction, causing further increases in peripheral resistance. All these facts, as well as studies performed on transplanted kidney patients, place the kidney in a central position in the regulation of blood pressure.

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Received 01-03-2018; Accepted 4-04-2018
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Hence, impaired renal functions in CKD patients cause more abnormal sodium handling, increased total body sodium, and hence, impaired water excretion leading to a volume overloaded status. The abnormal renal sodium handling happens much before the drop in glomerular filtration rate. The renal autoregulation could be responsible for the secondary increase of the peripheral resistance in the presence of blood volume expansion, as it occurs in CKD.\[6\]

It was demonstrated in Sprague-Dawley rats\[8\] that hypertension can be induced by a prolonged high-salt diet and that it is associated with increased renal injury and significant changes in renal cytokine gene expression profiles that are closely related to the pro-inflammatory response, pro-matrix formation and endothelial dysfunction, and attenuated cell survival and differentiation. They found that a high-salt diet decreases renal expression of vascular endothelial growth factor, whereas a subsequent study revealed that inhibition of the vascular endothelial growth factor receptor enhances dietary salt-induced hypertension. The salt sensitivity (effects on BP in relation to the sodium intake) is augmented in renal disease.\[9\] Hence, the need for diuretics and volume control even in dialysis patients is self-explanatory.

The Dietary Approach to Stop Hypertension (DASH) diet for the control of hypertension further stresses the role of salt in the pathogenesis of hypertension. It includes a diet low on salt, high fruits, vegetable and whole grain intake, less animal and dairy fat, less saturated fats, and plenty of fluids. It was proven in the DASH trial that the participants who followed the DASH diet had a significantly lower systolic blood pressures and also there were no episodes of accelerated hypertension.\[10\]

RAAS

The intrarenal and circulating RAAS which are interdependent systems control the systemic blood pressure. The intrarenal RAAS is also involved in renal autoregulation. Activation of the RAAS axis is well documented in CKD and dialysis patients. In addition to its direct vasoconstrictor effects, it also activates the SNS which contributes to the hypertension. In patients with CKD, vascular disease or areas of local ischemia and renal injury may activate the local RAAS which, in turn, increases the hypertension in CKD.\[11\] The role of RAAS blockade in CKD in the treatment of hypertension in CKD is quite beneficial. [Figure 3].

SNS

The SNS activity is enhanced in CKD. In health, SNS is also one of the arms of the renal autoregulation. The kidney has both baroreceptors

Figure 1: Pathogenesis of hypertension in chronic kidney disease

Figure 2: Factors and mechanisms of hypertension in chronic kidney disease\[6\]

Figure 3: Circulating and tissue renin-angiotensin system
and chemoreceptors, and the signals of which are conveyed to the vasomotor centre of the brain. Increased SNS activity leads to an increased renal tubular sodium reabsorption, hence contributing to the volume overload. In addition, it also increases the peripheral vascular resistance by its vasoconstrictor effects.[12]

**Oxidative Stress and Nitric Oxide Antagonism in CKD**

Oxidative stress occurs due an overplay of the oxidants as compared to the antioxidants in CKD. The oxidant excess of molecules such as superoxide and hydrogen peroxide in CKD causes an antagonism of endothelial nitric oxide,[13] vasoconstriction and increased peripheral vascular resistance. And hence the causal association of oxidative stress with hypertension in CKD is proven through a lot of experiments on animal models.

**Exogenous Drugs**

The above-mentioned drugs also form an important part of the pathogenesis of hypertension as many of these drugs such as cyclosporine and tacrolimus in transplant patients and erythropoietins form an inseparable part of the medication list in CKD patients [Figure 4].

**Smoking and Alcohol**

It is recognized that cigarette smoking is accompanied by an acute increase in blood pressure and heart rate. One of the first studies conducted on this regard, evaluating the effects of heavy smoking (one cigarette every 15 min for 1 h) on blood pressure and heart rate in a group of normotensive smokers, documented that, in resting conditions, the first cigarette caused an immediate and marked increase in blood pressure and heart rate, with the values achieved similar for the remaining three cigarettes. The hemodynamic effects were so prolonged that, throughout the smoking hour, blood pressure and heart rate were persistently higher than during the non-smoking hour, indicating that heavy smoking is associated with a rise in blood pressure, persisting for more than 15 min after smoking one cigarette and with also an increase in blood pressure variability. Through a mechanism which involves the stimulation of the sympathetic nervous system mainly at nerve endings, smoking is responsible for a marked and prolonged increase in plasma catecholamines parallel to the blood pressure increase [Figure 5].[15]

Recent epidemiological and clinical studies have demonstrated that chronic ethanol consumption (more than three drinks per day, 30 g ethanol) is associated with an increased incidence of hypertension and an increased risk of cardiovascular disease. The magnitude of the increase in blood pressure in heavy drinkers averages about 5–10 mmHg, with systolic increases nearly always greater than diastolic increases. Similar changes in blood pressure were also reported in preclinical studies. In the Framingham cohort, there was an increase of 7 mmHg in mean arterial pressure when heavy alcohol users were compared with all others. In some epidemiological studies, a linear dose-response relationship has been established, sometimes starting with a consumption threshold of three drinks per day (30 g of ethanol) [Figure 6].[16]

**Others**

Role of a potent vasoconstrictor endothelin-1 cannot be overemphasized. In CKD, endothelin levels are increased. It binds to endothelin A receptor and causes vasoconstriction. Antagonism of endothelin A causes a reduction in blood pressure.[17] The role of parathormone is still controversial.

Other factors such as vascular stiffness in CKD, renal artery stenosis, genetic factors such as family history, age, and ethnicity, vascular endothelial dysfunction in CKD due to ADMA, high levels of endogenous digitalis-like factors in CKD,[18] high arginine vasopressin levels, and reduced vasodilatory prostaglandins may also contribute to the hypertension in CKD.
Genetics

Heritability studies and genome-wide association studies have established that hypertension, a prevalent cardiovascular disease, has a genetic component that may be modulated by the environment (such as lifestyle factors). In BP, family and twin studies have yielded heritability estimates in the ranges of 48–60% (systolic BP) and 34–67% (diastolic BP). It has a polygenic inheritance pattern.[19]

With specific reference to CKD, an association of APO L1 gene and kidney disease and in turn hypertension was found in African populations.

Conclusion

There is a multitude of mechanisms of hypertension in CKD including the abnormal renal sodium handling to the numerous vasoconstrictor mechanisms. A better understanding of these concepts has helped us to develop a targeted therapeutic approach to the management of hypertension in CKD. The ACE inhibitors and ARBs (RAAS blockade), beta-blockers (SNS blockade), and diuretics form the mainstay of management. The dietary modifications in terms of salt reduction also play a major role due to the salt-sensitive hypertension in CKD. Lifestyle modifications in the form of regular physical exercise may improve the control of blood pressure and endothelial function and decrease inflammation and insulin resistance.[20] Moreover, physical exercise has no untoward effect on the progression of CKD. In short, the 6’s of metabolic syndrome such as sugars, spirits, smoking, salt, stress, and sedentary lifestyle should be handled accordingly for a healthy living.

References


How to cite this article: Rashmi SR, Vishwanath S. Pathophysiology of Hypertension in Chronic Kidney Disease. Hypertens 2018;4(3):166-169.

Source of support: Nil, Conflict of interest: None

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