Contribution of Hypertension to Chronic Kidney Disease
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Abstract
Hypertension is one of the most prevalent chronic diseases worldwide and is a major risk factor for a decline in kidney function in patients with diabetic and non-diabetic kidney diseases. Conversely, patients with chronic kidney disease (CKD) inevitably develop hypertension during the course of the disease. Hypertension causes loss of autoregulation of afferent arterioles which leads to transmission of high systemic blood pressure to the glomeruli resulting in glomerular ischemia and subsequently glomerulosclerosis. Achieving optimal blood pressure control remains an integral component in the care of managing patients with CKD and is relevant at all stages of the disease irrespective of the underlying etiology. Blood pressure targets should be individualized based on age, comorbidities, and presence of proteinuria. Lifestyle changes notably sodium restriction should be implemented in all patients in addition to the antihypertensive therapy. Blockers of the renin-angiotensin-aldosterone system should be the agents of choice in the treatment of hypertension in CKD because of their antiproteinuric and renoprotective effect.

Key words: Hypertension, chronic kidney disease, proteinuria, blood pressure monitoring, nephrosclerosis, cardiovascular diseases

Introduction
The incidence of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is on a rise worldwide.[1] The prevalence of CKD varies across countries in Asia but tends to be higher in rural areas.[2] In the COBRA-BPS trial, the overall prevalence of CKD was found to be highest in Sri Lanka (58.3%), followed by Bangladesh (36.4%) and Pakistan (16.9%).[2] One of the independent factors that was associated with the higher odds of developing CKD in this study included uncontrolled hypertension. A cross-sectional survey in China revealed that 71.2% of prevalent hypertensive patients have CKD and demonstrated the relationship between poor blood pressure control and worsening stages of CKD.[3] It is well established that hypertension is intimately associated with worsening kidney function in both diabetic and non-diabetic nephropathies.

Clinical Epidemiology of Hypertensive Kidney Disease
Estimating the true prevalence of CKD and eventually ESKD attributable to hypertension alone is difficult. First, the rate of progression of CKD secondary to hypertensive kidney disease is slow and decades-long of follow-up is required to appreciate the temporal evolution of kidney function.[4] Individuals with clinically presumed hypertensive kidney disease are rarely subjected to a kidney biopsy.[5] The 2017 US Renal Data System (USRDS) Annual Data Report alluded that the clinical judgment used by nephrologists on establishing the etiology of ESKD could be quite variable; only a small proportion of patients listed to have ESKD secondary to hypertensive nephrosclerosis on financing administrative forms fulfilled the clinical criteria established by Schlessinger and the ASSK trial investigators for hypertensive kidney disease.[6] The criteria require clinical evidence of end-organ damage from hypertension on cardiac imaging, urine protein studies, history of uncontrolled blood pressure preceding kidney dysfunction, and absence of immune-mediated diseases or diabetes mellitus. In yet another study, <1/5 of patients clinically diagnosed with hypertensive nephrosclerosis were found to have histological evidence of nephrosclerosis on their kidney biopsies.[7] Nephrosclerosis is also a non-specific finding on kidney biopsies which can be caused by pathologies other
than hypertension.\(^4\) Moreover, these older patients often have concomitant diabetes mellitus contributing to cardiovascular diseases, and etiology of ESKD is multifactorial.\(^6\) Hypertension is cited as the third most common etiology of ESKD locally, after diabetes mellitus and glomerulonephritis.\(^9\)

Regardless of adjudication bias in kidney disease causation, the connection between blood pressure control and the risk of worsening nephropathy has been demonstrated in multiple studies. In a 15-year follow-up study of approximately 12,000 hypertensive individuals at Multiple Veteran Affairs centers in the USA, the odds for CKD were incremental from 2.8 for pre-treatment systolic blood pressure (SBP) of 166–180 mmHg and 7.6 for pre-treatment SBP of >180 mmHg\(^{10}\) compared to a pre-treatment SBP of >140 mmHg. Importantly, a decrease in SBP by >2 mmHg after treatment was associated with a marked relative risk reduction (RR) in developing ESKD (RR of 0.65 for a decrease in SBP level 2–15 mmHg, RR 0.56 for a decrease of 15–20 mmHg, and 0.39 for a decrease >20 mmHg); findings consistent with that from the multiple risk factor intervention trial involving 12,000 patients which was conducted a year later.\(^{11}\) Despite individuals with baseline CKD being excluded from the trial, the investigators found that elevation of either systolic or diastolic blood pressure one standard deviation above the range in the lowest group was associated with a 1.7-fold increased risk of developing ESKD.

**Pathophysiology of Nephropathy Contributed by Hypertension**

The pathogenic determinants of hypertensive kidney damage include systemic blood pressure “load,” the degree to which it is transmitted to the renal microvasculature, and the local tissue susceptibility to any given degree of barotrauma.\(^{12}\)

**Systemic BP Load and its Transmission to Renal Microvasculature**

Chronic hypertension contributes to loss of afferent arteriolar autoregulation with subsequent transmission of high systemic blood pressure to the glomeruli. Under normal conditions, renal blood flow varies minimally within a broad range of systemic mean arterial pressure (MAP) (80–160 mmHg).\(^{13}\) Increase in blood pressure within this range leads to proportionate autoregulatory vasoconstriction of the preglomerular vasculature, thereby maintaining the renal blood flow and glomerular hydrostatic pressure relatively constant. This serves as a protective adaptation in chronic hypertension, and hence, in a vast majority of patients with hypertension, the glomerular capillaries are still protected from barotrauma and significant proteinuria is not seen.\(^{14,15}\) In contrast, when blood pressure exceeds a critical threshold as in the case of malignant hypertension, there is acute vascular injury which compromises the autoregulatory response of glomerular vasculature, further amplifying the degree of kidney damage.\(^{16,17}\) Proteinuria, hematuria, and rapid loss of kidney function ensue.\(^{15}\)

Kidney damage can also occur with blunting of the autoregulatory mechanism of glomerular blunting. This leads to enhanced transmission of elevated systemic pressures to the renal microvasculature.\(^{12}\) Significant preglomerular vasodilatation, as observed after a unilateral nephrectomy or in early type 1 diabetes, results in a greater fractional transmission of the ambient systemic pressures.\(^{18}\) If the renal autoregulation is intact, only a modest increase in the vulnerability to hypertensive injury is expected and a benign course of nephropathy follows.\(^{18}\) However, if renal autoregulation is additionally impaired, the susceptibility to hypertensive injury is markedly enhanced with a greatly reduced BP threshold for damage primarily, leading to accelerated glomerulosclerosis.\(^{14,15}\) This phenomenon is seen in the rat 5/6 ablation model which mimics the progressive kidney failure after loss of renal mass in humans.\(^{20}\) Brenner et al. used this model to formulate the concept of glomerular hyperfiltration injury which is caused by increase in the glomerular capillary plasma flow rate and mean capillary hydraulic pressure, secondary to the adaptive reduction in pre- and post-glomerular arteriolar resistances.\(^{15}\)

**Genetic Determinants of Tissue Susceptibility**

The theory on the genetic variants of APOL1 being strongly associated with kidney disease including hypertension-attributed CKD has received much emphasis recently.\(^{21}\) In African-Americans, the rate of CKD progression to ESKD secondary to hypertensive nephrosclerosis, focal segmental glomerulosclerosis (FSGS), and HIV-associated nephropathy (HIVAN) is higher compared to European-Americans.\(^{22}\) This can be attributable to the two protein-changing alleles of the APOL1 gene, namely the APOL1 G1 allele and APOL1 G2 allele. APOL1 high-risk genotypes are defined as two risk alleles in any combination (homozygous G1/G1, homozygous G2/G2, or compound heterozygous G1/G2).\(^{23}\) More than 50% of African-Americans carry at least one risk allele.\(^{21}\) High-risk genotypes were found in African-Americans with FSGS and HIVAN (72%) and hypertension-associated ESKD (44%) compared to 12–14% in healthy controls.\(^{23}\) Compared to individuals carrying APOL1 low-risk genotypes (0 or 1 risk allele), the odds ratio for these diseases in carriers of high-risk genotypes is 17 for FSGS, 29 for HIVAN, and seven for hypertensive nephrosclerosis.\(^{24}\) The APOL1 protein is expressed within the glomerular podocytes and arteriolar endothelial cells in normal kidney and within glomerular arterioles and interlobular arteries in FSGS and HIVAN.\(^{24}\) It has been speculated that APOL1 expression in the arterial wall could have a biologic role in the pathogenesis of hypertensive kidney disease by altering cellular physiology promoting arteriosclerosis as it is a lipid-binding protein.\(^{21}\)

**Blood Pressure Control and Progression of CKD**

The kidneys play a key role in long-term blood pressure regulation. In his seminal experiments using isolated perfused kidneys, Guyton demonstrated that an acute rise in blood
pressure results in a brisk increase in renal sodium excretion and subsequent loss of extracellular fluid and overall blood pressure reduction.\(^{(30)}\) Due to a decrease in the number of viable nephrons and abnormal kidney tubular function in CKD, sodium excretion is affected, and hence, the usual diuretic response seen in pressure natriuresis is blunted. This leads to worsening hypertension in CKD and observation of increasing prevalence of salt-sensitive hypertension as kidney function declines. Salt sensitivity is an inability of the kidney to respond appropriately to high sodium load and often results in uncontrolled hypertension.\(^{(27)}\) It is observed more frequently in the elderly, patients with progressive CKD, certain genetic abnormalities, and African-Americans.\(^{(24)}\)

The second key player in CKD-related hypertension is the increased activity of the renin-angiotensin-aldosterone system (RAAS).\(^{(29)}\) The kidneys secrete renin in response to decreased renal perfusion, leading to an increase in angiotensin-2 which causes a host of vascular responses including direct vasoconstriction, aldosterone secretion, and increase in sympathetic activity. In polycystic kidney disease, the compression of renal vasculature by enlarging cysts causes the activation of the RAAS system resulting in hypertension.\(^{(30)}\)

Treatment of such cases with bilateral nephrectomy or inhibitors of RAAS has been shown to result in control of blood pressure, suggesting failing kidneys as the source of excess renin.\(^{(31)}\)

Other factors proposed to explain increased vascular resistance in CKD include the increased production of endothelin and endogenous digitals-like substance, reduced generation of vasodilators such as nitric oxide and kinins, and imbalance between the vasodilator and vasoconstrictor prostaglandins.\(^{(29)}\) Lastly, medications used commonly in CKD, in particular, erythropoiesis-stimulating agents have been associated with the long-term side effect of hypertension, possibly the result of increased hematocrit and blood viscosity. There has also been some evidence that it is in part due to vascular production of thromboxane, a vasoconstricting prostaglandin.\(^{(29)}\) Normal physiology allows nitric oxide vasodilation to offset prostaglandin-induced hypertension.\(^{(29)}\) However, this response is impaired in CKD.

**Management of Hypertension in CKD**

**General Rules**

The latest guideline from the Joint National Commission VIII on management of hypertension recommends a blood pressure goal of <140/90 mmHg for patients with CKD aged between 18 and 60 years.\(^{(32,33)}\) However, it is questionable as to whether this target is applicable to all patients with CKD.\(^{(27)}\) The safety of intensive blood pressure lowering in CKD patients older than 70 years, who have been largely excluded from clinical trials examining the benefit of blood pressure control, is not yet established.\(^{(27)}\) The systolic hypertension in the elderly program has shown that the treatment of systolic hypertension to a mean target of 143 mmHg as achieved in the active treatment group, reduced morbidity and mortality. However, this trial excluded patients with renal dysfunction. It has been recognized that target SBPs are harder to attain in older participants in whom widening of pulse pressure may occur when diastolic blood pressure levels are lowered in the course of treatment.\(^{(34)}\) Since patients with CKD tend to be older and have more cardiovascular risk factors, it is advisable to individualize treatment in patients according to their age and comorbidities.

SPRINT trial investigated the effect of two different SBP treatment goals (target SBP <120 mmHg in the intervention arm vs. <140 mmHg in controls). The primary outcome was a composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes.\(^{(35)}\) There was a significant improvement in the primary composite outcome with more aggressive blood pressure control. However, this was at the expense of a higher incidence of acute kidney injury with electrolyte abnormalities, syncope, and bradycardia. In a subgroup analysis of patients with CKD, there was no significant difference in incident albuminuria or the rate of CKD progression between the two groups. Several limitations of the SPRINT trial have been identified. Patients of East Asian ethnicity contributed to only a minority of study subjects (<2%). This limits the applicability of trial results to the Asia-Pacific region. The baseline blood pressure for the participants in both the intensive treatment and standard treatment groups was approximately 139/78 mmHg. The blood pressure in the trial was also measured using the automatic oscillometric method which is usually lower than the auscultatory SBP measurement by 5–10 mmHg. Hence, a target of an SBP of <120 mmHg was easily attained.

Non-pharmacologic (lifestyle changes) and combined pharmacologic treatments are both necessary to achieve the target blood pressure.\(^{(36)}\) Sodium restriction is an important adjunct to all medication regimens for CKD patients with hypertension. In a randomized trial involving patients with CKD Stages 3–4 and poorly controlled hypertension, a low-sodium diet (100 mmol/day that translates to 2.4 g sodium per day or 6 g of salt per day) was associated with substantial reductions in BP (decrease in SBP by 9.7 mmHg and diastolic BP by 3.9 mmHg), the need for antihypertensive medications, and extracellular volume.\(^{(37)}\) The magnitude of change was more pronounced compared to patients without CKD, suggesting that patients with CKD are particularly salt sensitive. The KDOQI guideline on hypertension in patients with CKD in 2004 recommends limiting sodium intake to 2.4 g/day (i.e., 6 g of salt) in patients not on dialysis.\(^{(33)}\) This recommendation is a notable dietary restriction, as a no-added-salt diet already contains roughly 4 g sodium which exceeds the amount that a patient with CKD can excrete irrespective of diuretic administration. Sodium intake is reduced in a low-protein diet as a consequence of the selection of low-sodium foods, which results in a better-controlled BP; however, this has to be balanced against the risk of malnutrition in CKD patients.

Blockers of the RAAS system are preferred for their antiproteinuric effect as a result of decreasing systemic and intraglomerular pressure. Dual blockade with ACE inhibitors...
(ACEI) and angiotensin receptor blockers (ARB) reduces the proteinuria to a greater degree than either class alone but has not been proven to preserve renal function or improve cardiovascular outcome.\(^{38}\) Of note is the increased risk of syncope, hyperkalemia and acute kidney injury observed in the 2008 Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET).\(^{39}\) In a meta-analysis that included 11 randomized clinical trials in adult CKD patients, the addition of non-selective aldosterone antagonists together with ACEi or ARB significantly reduced proteinuria, but this did not translate into a longitudinal improvement in kidney function and there was a significantly higher risk of hyperkalemia.\(^{40}\)

Diuretic therapy combined with RAAS blockade is preferred in CKD with manifest edema.\(^{36}\) Thiazide diuretics may lose their effectiveness with advanced CKD and can be replaced by loop diuretics in the latter. The primary site of action for thiazides is the Na\(^+/\)Cl\(^-\) cotransporter in the distal convoluted tubule of the nephron, which is responsible for only 5% of total filtered sodium reabsorption. With impaired glomerular filtration and reduced filtration of sodium, it is presumed that distal diuretic therapy alone becomes insufficient. Potassium-sparing diuretics including aldosterone receptor antagonists such as spironolactone and eplerenone typically maintain their therapeutic effectiveness in the more advanced stages of CKD because their effect does not require tubular entry and, hence, independent of glomerular filtration and tubular secretion.\(^{36}\) However, they should be used with caution due to hyperkalemic risk in advanced CKD.

**CKD with Proteinuria**

The KDIGO 2012 guidelines recommend a target blood pressure of <130/80 mmHg for patients with albuminuria.\(^{34}\) In post hoc and subgroup analyses of the modification of diet in renal disease (MDRD) and The African-American Study of Kidney Disease and Hypertension (AASK) studies, a target MAP of 92 mmHg was associated with a slower decline in kidney function in patients with proteinuria of >0.3–1 g/day.\(^{35,36}\) The Steno-2 study showed a reduced risk of cardiovascular disease with a blood pressure target of 130/80 mmHg compared to 135/85 mmHg in patients with Type 2 diabetes and microalbuminuria.\(^{37}\)

Most clinical trials have established the renoprotective impact of ACE inhibitors and angiotensin receptor blocker blockade in the management of patients with proteinuria, especially in diabetic kidney disease. Treatment with captopril was shown to retard the progression of microalbuminuria to overt proteinuria and of overt nephropathy to ESKD in patients with Type 1 diabetes mellitus.\(^{41,42}\) Irbesartan and losartan have been demonstrated to reduce the risk of progression of kidney disease in patients with type 2 diabetes mellitus.\(^{43,44}\) The Irbesartan in Diabetic Nephropathy Trial assessed the renoprotective effects of adding irbesartan, amlopidine, or placebo to standard blood pressure-lowering regimen in type 2 diabetes with proteinuria. The primary composite end point was a doubling of the baseline serum creatinine concentration, the development of end-stage renal disease, or death from any cause. Treatment with irbesartan was associated with a significantly lower risk of primary composite end point, despite comparable blood pressure attainment in all arms.

**CKD without Proteinuria**

The benefit of tighter blood pressure control (<140/90 mmHg) and the use of RAAS blockade in non-proteinuric nephropathy are not well established.\(^{27}\) The AASK trial was a randomized trial comparing the effects of two levels of blood pressure control and three antihypertensive drug classes on the kidney function decline in hypertension.\(^{45}\) The average blood pressure achieved in the low blood pressure group and usual blood pressure group was 128/78 mmHg and 141/85, respectively. Ramipril appeared to be more effective than amlopidine or metoprolol in decreasing the composite secondary outcome of worsening kidney function. The trial also showed that in patients with negligible proteinuria, a usual blood pressure goal had a more favourable effect toward the change in eGFR from baseline compared with a lower blood pressure goal. This is consistent with the findings from the MDRD study that largely involved non-diabetic patients and compared the effect of intensive (MAP 92 mmHg) versus usual blood pressure (MAP of 107 mmHg) control in eGFR decline.\(^{46}\) There was no difference seen between these two groups. In summary, current available evidence is inconclusive with regard to the benefit of aggressive BP lowering in the treatment of non-proteinuric kidney disease.

**Conclusion**

Hypertension can be both a cause and consequence of CKD. Understanding the factors that are involved in the pathogenesis of hypertension-induced renal damage forms the platform for targeted therapy to retard the progression of kidney disease. Blood pressure goals and treatment therapy should be individualized with respect to the age group of patients, severity of proteinuria, and presence of cardiovascular comorbidities. The benefits of RAAS blockade agents in CKD with overt proteinuria have been widely demonstrated. These agents should be the treatment of choice for hypertension in patients with proteinuric kidney disease, with caution exercised in cases of more advanced CKD due to competing risks of hyperkalemia and acute kidney injury.

**References**


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