

Editorial

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Volume 3 : Issue 1**Article Ref. #: 1000NPOJ3e009****Article History****Received:** October 16th, 2017**Accepted:** October 23rd, 2017**Published:** October 24th, 2017**Citation**

Berbari A, Daouk N. Hypertension-chronic kidney disease relationships. *Nephrol Open J.* 2017; 3(1): e18-e21.

doi: [10.17140/NPOJ-3-e009](http://dx.doi.org/10.17140/NPOJ-3-e009)

Hypertension-Chronic Kidney Disease Relationships

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A large number of epidemiologic, clinical and experimental studies indicate a strong association between hypertension (HT) and chronic kidney disease (CKD).¹ Further, this association portends an ominous prognosis. Patients with HT and CKD are at a much greater risk for cardiovascular disease as compared with those without chronic kidney disease.¹

Hypertension defined as office systolic and/or diastolic blood pressures (SBP/DBP) equal to or greater than 140/90 mmHg, and involving about 30-40% of the world population, is a major contributor to heart disease, stroke and renal disease.²

Chronic kidney disease, defined as a persistent kidney damage, as reflected either by reduced glomerular filtration rate (an estimated GFR <60/ml/min/1.73 m²) and/or increased urinary albumin excretion, is emerging as a major public health problem.³ The prevalence of CKD varies between 8-16% of the adult population.³ Although, severe kidney damage is associated with an increased risk of endstage renal disease (ESRD), a milder degree of kidney damage is a marker of cardiovascular disease (CVD).⁴

The hypertension-chronic kidney disease relationship is complex and appears to be dependent on several factors which include i) etiology of the hypertensive disorder; ii) level of BP; iii) type of the CKD; iv) BP phenotype.

Etiology of the Hypertensive Disorder

Hypertension is the second cause of end stage renal disease (ESRD) after diabetes mellitus.⁵ However, discrepant opinion exists regarding whether non-malignant essential (primary) hypertension can cause ESRD.⁶ Several epidemiologic studies reported low prevalence and incidence rates of renal failure among hypertension subjects.⁷ In one study, creatinine clearance, as a determinant of glomerular filtration rate (GFR), fell only by 0.92 ml/min per year in hypertensive subjects as compared to 0.75 ml/min per year in normotensive subjects.⁸ These observations have been attributed to mild renal vascular changes associated with non-malignant hypertension. It has been postulated that the progressive hyalinization and sclerosis of the preglomerular renal vasculature, frequently reported in patients with non-malignant essential hypertension, referred to as hypertensive nephrosclerosis and resulting from long-standing exposure to high blood pressure (BP) levels may not be severe enough to cause ESRD.⁹

The hypertension-related nephropathy has been termed hypertensive nephrosclerosis which includes two variants, benign (non malignant) and malignant nephrosclerosis.

The diagnosis of benign hypertensive nephrosclerosis is a diagnosis by exclusion.⁴ It is a clinical diagnosis based on history, physical examination, urinalysis and laboratory evaluation.⁴ Since kidney biopsy is rarely performed, the diagnosis is typically made in patients with chronic kidney disease (CKD) who have had a long-standing hypertension, subnephrotic range proteinuria without evidence of other kidney disease. Histopathologic lesions in benign hypertensive nephrosclerosis are characterized by vascular, glomerular and tubular changes.⁴ These changes have been attributed to loss of renal autoregulation and exposure of the intrarenal

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vasculature to long-standing elevated BP levels.⁴

LEVEL OF BLOOD PRESSURE

Several studies have also reported low incidence rates of ESRD in hypertensive patients with no evidence of underlying primary intrinsic renal disease.^{10,11} In both Multiple Risk Factor Intervention Trial (MRFIT) and Kaiser Permanente of Northern California, two large population studies, the incidence of nephropathy in hypertensive subjects with no evidence of primary renal disease was low at 15.6 and 14.3 cases per 100,000 persons-years respectively.^{10,11} Further, in both studies, the risk of ESRD was associated with increasing BP levels throughout the BP readings above the optimal level.^{10,11} The higher the BP levels the higher the risk of renal failure. In the Kaiser Permanente study, compared with subjects with a BP <120/80 mmHg, the adjusted relative risks for developing ESRD were 1.62 for BP=120-129/80-84 mmHg, 1.98 for BP=130-139/85-89 mmHg, 2.59 for BP=140-159/90-99 mmHg, 3.86 for BP=160-179/100-109 mmHg, 3.88 for BP=180-209/110-119 mmHg, and 4.25 for BP ≥210/120 mmHg.¹¹ The systolic BP component appears to be the stronger predictor of CKD.¹⁰ In the MRFIT, a systolic BP higher by 1 standard deviation (SD) was associated with doubling of risk of ESRD.¹⁰ In contrast, increasing diastolic blood pressure (DBP) levels may act as initiators of CKD when associated with systolic blood pressure (SBP) within the normotensive range.¹⁰ In the MRFIT, in subjects with stage 1 diastolic hypertension (DBP=90-99 mmHg), the incidence of ESRD rose sharply from 9.8 to 16.4 per 100,000 persons-years across categories of SBP within the normotensive range.¹⁰

Other risk factors have been reported to increase the susceptibility to renal failure in benign nephrosclerosis, including Afro-American race, obesity, glucose intolerance, high serum uric acid levels, albuminuria, and genetic factors.⁸

Several studies have indicated that genetic factors especially D allele of the ACE gene may be associated with increased susceptibility to CKD and ESRD in patients with primary hypertension.¹²

In contrast, if the BP becomes markedly elevated and exceeds a certain threshold, malignant hypertension and malignant nephrosclerosis, characterized by disruption of the intrarenal microvascular and glomerular structures, renal functional impairment, proteinuria and hematuria develop.⁹

TYPE OF THE CHRONIC KIDNEY DISEASE (CKD)

Hypertension is very frequent in patients with CKD with an estimated prevalence of about 60%, reaching about 95% in stages 3-5 CKD.⁸ This prevalence rate depends on the type of nephropathy and the degree of renal functional impairment.¹³

The prevalence of hypertension is highest in renal vascular disease (93%), in established diabetic nephropathy (87%), and in polycystic kidney disease (74%) compared to a lower prevalence in glomerulonephritis and tubular interstitial disease.¹³

The prevalence of hypertension increases with worsening renal function. An inverse relationship between renal functional impairment and prevalence of hypertension has been reported in the Chronic Renal Insufficiency Cohort (CRIC) study.¹⁴ About 92% of patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m² were hypertensive while 67% of those with eGFR >60 ml/min/1.73m² had elevated BP.¹⁴

Other factors increase the risk of hypertension in CKD such as urinary albumin excretion, obesity, and race.¹⁵ Pooled data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2005 revealed that albuminuria was an independent risk for hypertension in CKD.¹⁶ Urine albumin/creatinine ratio greater than 6.67 mg/g in men and greater than 15.27 mg/g in women was associated with doubling the risk of developing hypertension.¹⁷

Obesity is an important risk factor of hypertension in CKD. In the modification of diet in renal disease (MDRD) study, body mass index (BMI) was a strong predictor for hypertension in patients with eGFR= 25-55 ml/min/1.73m².¹⁸

The prevalence of hypertension in CKD reveals racial disparities, being higher among non Hispanic blacks than whites or Mexican Americans.¹⁸

BLOOD PRESSURE PHENOTYPE

Hypertension related nephropathy is dependent, not only on the level of BP, but also on BP patterns.^{19,20} Several recent studies indicate that among the various BP patterns elucidated by ambulatory BP monitoring, masked and nocturnal hypertension are associated with a greater risk of hypertensive nephropathy than diurnal and white-coat hypertension.^{19,20} In CKD hypertensive

patients, non-dipping and reverse dipping patterns were also associated with a greater risk of ESRD.¹⁹ Further, resistant hypertension is frequently observed in renal patients, at least partly due to inadequate treatment of the elevated BP states.²¹

In the light of these recent observations, recent guidelines recommend ambulatory BP monitoring in the management of patients with CKD.¹⁹

Inadequate BP control is a major cause for the development and progression to CKD and ESRD.²²

BP control in renal patients requires lifestyle modifications especially strict salt restriction, avoidance of weight gain, treatment of associated comorbid conditions and abnormal metabolic factors, and administration of antihypertensive medications. Combination therapy is usually required.⁴ Inhibitors of the renin-angiotensin system are recommended as primary agents, to reduce both BP and albuminuria.^{4,22,23} Changes in serum creatinine and potassium, possible complications of renin-angiotensin blockade should be carefully monitored.²³ Addition of a thiazide diuretic is advisable.²³

BP goals of <130/80 have been generally recommended in renal patients.²³ Intensive BP reduction may provide protection against progression to renal failure in patients with CKD.⁴

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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