Chapter 1
Epidemiology of Hypertension in Chronic Kidney Disease

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Prevalence of Chronic Kidney Disease and Its Determinants

Chronic kidney disease (CKD) is defined as persistent kidney damage, which is often reflected by either a reduction in glomerular filtration rate or increased urine albumin excretion, or both. CKD is now a worldwide public health challenge. According to the 2010 Global Burden of Disease study, CKD is ranked 18th in the list of causes of total number of global deaths with an estimated annual death rate of 16.3 per 100,000 [1]. The prevalence of CKD varies across different countries and regions and is estimated to range between 8 and 16 % of the adult population [2–9]. The prevalence of CKD has shown a steady global increase over the years. For example, in the USA, the prevalence of CKD was estimated to be around 10 % between 1988 and 1994 and it increased to 13.1 % between 1999 and 2004 [4]. The prevalence estimates of CKD differ slightly depending on the GFR estimating equations used [4, 10]. The rise in CKD prevalence and incidence has been attributed to an aging population as well as an increased prevalence of hypertension, diabetes, and obesity, all of which are recognized as important global health challenges [4, 11, 12].

According to the 2010 United States Renal Data System (USRDS) Annual Data Report, the leading causes of kidney failure in the USA are diabetes, hypertension, and glomerulonephritis. Hypertension and diabetes account for 99 and 153 per million population of incident cases of end-stage renal disease (ESRD), respectively [13]. The prevalence of stage 3 or higher CKD in diabetics in the USA exceeds 15 % [13]. Over 5 % of people with newly diagnosed type 2 diabetes already have CKD and an estimated 40 % of diabetics will develop CKD in their time course [14]. Data from World Health Organization showed that the number of individuals with diabetes is currently around 154 million globally and is projected to double within

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the next 20 years. The increase is most notable in less developed countries, where the number of diabetic patients could rise from 99 million to 286 million by 2025 [15]. China and India are projected to have 139 million people with diabetes in 2025 [16]. A parallel increase in the global incidence and prevalence of CKD due to diabetic nephropathy is therefore anticipated. CKD in diabetes is associated with an increased risk of progression to ESRD [17].

The aging population also in part explains an increase in the incidence of hypertension, diabetes, and CKD worldwide. The prevalence of CKD was reported to be 7.4 % among women aged 18–39 years and increased to 18.0 and 24.2 % among those aged 60–69 and 70 years or above, respectively, in the Chinese general population [2]. Similar parallel increase in CKD prevalence with aging was observed across the USA, Canada, and Europe although the absolute prevalence differed across countries [4, 8, 18]. Cardiovascular disease is also an important cause of CKD.
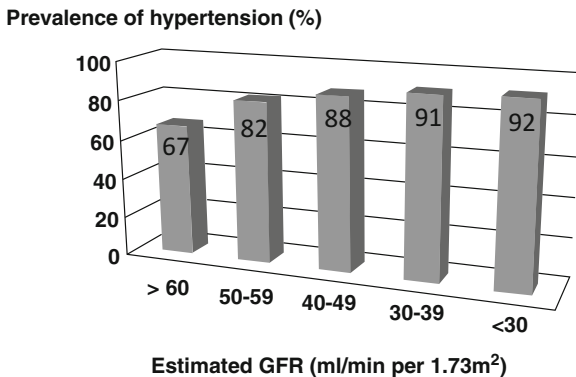
Definition of Hypertension

The American Heart Association defines hypertension as a blood pressure of 140/90 mmHg or more, measured in clinic setting, based on two readings, 5 min apart and sitting in chair and confirmed with elevated reading in contralateral arm.

Prevalence of Hypertension in CKD

Hypertension is very common in CKD, with a prevalence estimated around 60–95 % in CKD stage 3–5 [19–22]. Hypertension has a complex interrelationship with CKD. Hypertension is an important modifiable cause for CKD as well as a consequence of CKD. Nearly a billion of the adult population (around 26.4 %) in 2000 had hypertension (defined as >140/90 mmHg) and this proportion is projected to increase by about 60 % to 1.56 billion by 2025 (24 % in developed countries and 80 % in developing regions such as Africa and Latin America) [23]. A corresponding global increase in the prevalence of CKD is therefore anticipated. The Global Burden of Disease Study identified elevated blood pressure as the leading risk factor, among 67 studied, for death and disability-adjusted life years lost during 2010 [24]. According to the USRDS Annual Data report for 2014, up to 25 % of CKD was attributed to hypertension. Of the 10.7 % of Medicare patients diagnosed with CKD in 2013, nearly half also have diabetes, and over 92 % also have hypertension [25]. The rate of ESRD caused by hypertension has grown 8.1 % since 2000, to 99.1 per million population. In contrast, the incident rate of diabetic ESRD fell 1.5 % between 2007 and 2008, to 153 per million population—a rate nearly unchanged from that of 2000 while that of ESRD due to glomerulonephritis has fallen 23.4 %, to 23.7 per million population [25].

Fig. 1.1 Prevalence of hypertension in different CKD stages [27]

The prevalence of hypertension in CKD shows racial disparities in being higher among non-Hispanic blacks versus whites or Mexican Americans, as reported in several cohorts. In the Modification of Diet in Renal Disease (MDRD) study, the prevalence of hypertension was higher in blacks versus whites [93 % versus 81 %] [26]. Similarly, in Chronic Renal Insufficiency Cohort (CRIC) study, hypertension was reported in 93 % of African Americans versus 80 % of whites although Hispanics show a greater risk for CKD and ESRD compared to non-Hispanics [27]. Socioeconomic status and lifestyle also influence the prevalence of hypertension in CKD patients. Patients with poorer socioeconomic status, lower income, and education level showed a higher prevalence of hypertension [27].

The prevalence of hypertension increases with worsening estimated glomerular filtration rate (eGFR), as shown in CRIC study [27] (see Fig. 1.1). The prevalence of hypertension was 92 % for those with eGFR <30 ml/min per 1.73 m^2 and 67 % for those with eGFR >60ml/min per 1.73 m^2. The prevalence estimates for hypertension among CKD patients in China, India, and Mexico were similar to those reported in CRIC cohort [28–30].

The prevalence of hypertension varies by the etiology of CKD. CKD due to diabetic nephropathy showed the highest prevalence of hypertension independent of kidney function [27]. Hypertension was also more frequent among patients with polycystic kidney disease, renal artery stenosis when compared to glomerulonephritis, tubulointerstitial disease, or chronic pyelonephritis [31]. Albuminuria was an important, independent risk factor for hypertension as shown by pooled data from National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999–2005 [32, 33]. In the United States National Kidney Foundation's Kidney Early Evaluation Program (KEEP), decreasing GFR by 10 ml/min/1.73 m^2, increasing age, obesity, African American race, and microalbuminuria were all associated with an increased prevalence of hypertension [22]. Urine albumin to creatinine ratio greater than 6.67 mg/g in men and above 15.24 mg/g in women resulted in doubling the risk of developing hypertension when accounting for baseline blood pressure, body mass index, and creatinine [34]. Higher albumin/creatinine ratios, even within the normal range, are independently associated with increased risk for development

of hypertension in the general population [35]. Proteinuria was shown to be one of the most important correlates of systolic blood pressure in older men, especially with ambulatory and home systolic blood pressure [36]. The association between albuminuria and hypertension may be mediated via an increased inflammation, endothelial dysfunction, and renal sodium handling [37].

Obesity was an important predictor of hypertension among CKD patients. In the MDRD study, body mass index was a strong predictor of hypertension among patients with a GFR of 25–55 ml/min per 1.73 m^2 [26]. Likewise, both the KEEP (78.6 % versus 60.3 %) and NHANES study (52 % versus 30.8 %) showed a greater prevalence of hypertension among obese subjects as compared to non-obese subjects [22]. Obesity was also an independent risk factor for CKD [38].

Suboptimal blood pressure control was common in CKD, especially those at the highest risk of adverse outcomes due to diabetes or albuminuria [39]. The NHANES data showed that elevated serum creatinine level was strongly related to suboptimal treatment of high blood pressure [20]. Only 36 % of subjects met the blood pressure target of <140/90 while only 14 % of treated hypertensive individuals met the older blood pressure target of <130/85 proposed for individuals with kidney disease [20]. In the KEEP program for people at high risk for CKD, the prevalence (86 %), awareness (80 %), and treatment (70 %) of hypertension were high but good blood control was achieved in only 13 % [40]. Poor medication adherence was associated with 23 % increased risk of uncontrolled hypertension [41]. These data suggest poorly controlled hypertension is associated with much of the high burden of CKD and there is a need to improve blood pressure control in CKD.

Clinic Blood Pressure and Ambulatory Blood Pressure

The diagnosis and control of hypertension critically depend on accuracy of blood pressure measurements. Clinic blood pressure frequently overestimates and underestimates true blood pressure in hypertensive general population and this is also observed in patients with CKD. Misclassification of blood pressure control at the office was observed in 1 of 3 hypertensive patients with CKD, suggesting that ambulatory-based control rates were far better than office-based rates [42]. Using ambulatory blood pressure monitoring as the reference standard, home blood pressure monitoring showed the best diagnostic performance for hypertension compared with routine or standardized clinic measurements in CKD. One week-averaged home blood pressure >140/80 mmHg was associated with awake ambulatory blood pressure >130/80, a threshold considered as hypertensive in the CKD population [43]. White coat hypertension is defined as an elevated clinic blood pressure but controlled blood pressure out of clinics. Masked hypertension is defined as controlled blood pressure in clinic setting with elevated blood pressure out of clinics. According to a systematic analysis including six studies with 980 CKD subjects, the overall prevalence of white coat hypertension was 18.3 % (range, 10–28 %) and masked hypertension 8.3 % (range, 5–28 %). Notably, 40.4 % of subjects with CKD considered to have normal or

controlled blood pressure in fact had masked uncontrolled hypertension (range, 26–54 %) while 30 % of subjects with CKD that were thought to have hypertension had normotension at home [44]. Similarly, a high rate of masked hypertension was observed in the follow-up study of the African American Study of Kidney Disease (AASK) cohort; of the 61 % subjects with controlled clinic blood pressure, 70 % had masked hypertension [45]. This location-dependent hypertension, namely masked hypertension and white coat hypertension, has been shown to predict prognosis in patients with hypertension. Masked hypertension carries a risk equivalent to sustained hypertension, whereas white coat hypertension carries a risk almost equivalent to normotension [46]. In the general population, the risk of CKD was significantly increased in sustained hypertension, masked hypertension, and white coat hypertension [47]. The AASK study showed that target organ damage was more common in subjects with sustained or masked hypertension [45]. CKD patients with masked hypertension were more likely to progress to end-stage renal disease [48]. The prevalence rates of masked hypertension depend very much on the definitions used to define masked hypertension. Conventionally, masked uncontrolled hypertension was defined as clinic blood pressure >140/90 mmHg or daytime ambulatory blood pressure ≥135/85 mmHg. In a recent study of 333 veterans with CKD, the prevalence of masked uncontrolled hypertension was 26.7 % defined by daytime ambulatory blood pressure, 32.8 % by 24-hour ambulatory blood pressure and more than doubled to 56.1 % if defined by daytime or nighttime ambulatory blood pressure [49].

Ambulatory blood pressure was superior to clinic blood pressure measurements in correlating with end-organ damage [36]. Ambulatory blood pressure showed a stronger association with proteinuria [36] and echocardiographic left ventricular hypertrophy [50, 51] than clinic blood pressure in CKD population. In keeping with these observations, a prospective cohort study conducted in 217 veterans with CKD showed that 24 h ambulatory systolic blood pressure provided additional prognostic value for composite cardiovascular endpoint of myocardial infarction, stroke, and mortality beyond clinic blood pressure, indicating the importance of ambulatory blood pressure in predicting clinical outcomes in CKD (see Fig. 1.2) [48]. Clinic blood pressure above goal and ambulatory blood pressure at goal identify a low risk condition while clinic blood pressure at goal and ambulatory blood pressure above goal are both associated with higher cardio-renal risk similar to that observed in patients with both clinic and ambulatory blood pressure above goal [52]. Furthermore, the definitions used to classify patients as having hypertension or normotension can influence the risk for being classified as having masked hypertension in favor of white coat hypertension. A meta-analysis has shown that when the thresholds for classification of clinic and ambulatory blood pressure are equal, the risk for diagnosis of masked hypertension is less (risk ratio of 0.74). When the clinic blood pressure threshold is higher and home blood pressure threshold is lower, the risk (risk ratio of 1.36) for diagnosing masked hypertension is greater [44]. More recent analysis by Agarwal and co-workers showed that clinic blood pressure was a good determinant of masked uncontrolled hypertension with area under the receiver-operating characteristics curve of 0.82 (95 % confidence intervals, 0.76–0.87). Home blood pressure was no better than clinic blood pressure in
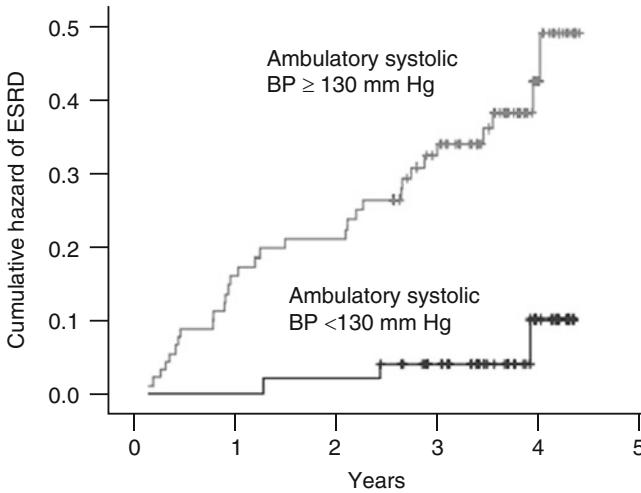
Fig. 1.2 Cumulative incidence of ESRD in patients with elevated systolic clinic blood pressure. Adapted from Agarwal R, et al. Prognostic importance of ambulatory blood pressure recordings in patients with chronic kidney disease. Kidney Int 2006;69:1175–80; used with permission

diagnosing masked uncontrolled hypertension in CKD. Thus, the use of home blood pressure to diagnose masked uncontrolled hypertension was not supported. Nevertheless, ambulatory blood pressure showed short-term reproducibility in diagnosing masked uncontrolled hypertension and may detect a phenotype with increased cardiovascular risk [49].

Hypertension and Kidney Outcomes in Chronic Kidney Disease

There are compelling data from observational studies that high blood pressure was associated with the development and progression of CKD [53–55]. Lowering blood pressure has also been a key treatment strategy in slowing the progression of CKD. However, the blood pressure threshold level of which this risk was increased remains controversial. The NHANES study showed an eightfold higher risk of an elevated serum creatinine among those with hypertension versus those with a normal blood pressure [20]. In the Multiple Risk Factor Intervention Trial, systolic and diastolic blood pressure was identified as strong risk factors for progression to ESRD, independent of age, race, income, use of medication for diabetes mellitus, history of myocardial infarction, serum cholesterol concentration, and cigarette smoking as well as baseline serum creatinine and proteinuria over an average follow-up duration of 16 years [53]. Those with blood pressure more than 210/120 mmHg showed at least a 20-fold increased risk of ESRD than those with blood pressure less than 120/80 mmHg. The estimated risk of ESRD associated with systolic blood pressure was also greater than that with diastolic blood pressure when both systolic and

diastolic blood pressure were considered together. The risk appeared to start at systolic blood pressure of 140 mmHg rather than 130 mmHg and was the highest among those with systolic blood pressure of 150 mmHg or above [53].

The KEEP cohort showed that high systolic blood pressure accounted for most of the risk of progression to ESRD [56]. There is also evidence that the risk of ESRD appeared to increase even with modest elevation of blood pressure and the observed relationship did not appear to be due to confounding by clinically evident baseline kidney disease. Notably, among subjects with eGFR over 60 ml/min per 1.73 m^2, those with blood pressure of 12–129/80–84 mmHg were 62 % more likely to develop ESRD while those with blood pressure of 130–139/85–89 mmHg were 98 % more likely to develop ESRD compared to those with blood pressure below 120/80 mmHg [57]. Several earlier clinical trials also established that lower blood pressure levels were associated with slower progression of CKD among subjects with proteinuria [55, 58].

On the other hand, post-hoc analysis from the Homocysteinemia in Kidney and ESRD (HOST) study, a double-blind randomized controlled trial in 2056 subjects with advanced CKD (mean eGFR 18 ml/min per 1.73 m^2) showed no graded association between systolic blood pressure and cardiovascular events or ESRD. However, those with systolic blood pressure >157 mmHg were associated with an increased risk of ESRD [59]. A systematic analysis putting together 11 randomized controlled trials of 9287 patients with CKD concluded that a more intensive blood pressure lowering reduced the risk of composite kidney failure events by 17 % and the risk of ESRD alone by 18 %, especially those with proteinuria. However, intensive blood pressure lowering appeared to have no effect on kidney failure among those who did not have proteinuria [60]. Another systematic review of three large trials in this field, namely the MDRD study [58, 61, 62], Ramipril Efficacy in Nephropathy-2 (REIN-2) study [63], and the AASK study [64–66] including 2272 CKD subjects failed to show any significant benefit by lowering blood pressure to less than 125/75 to 130/80 as compared to 140/90 mmHg. However, subgroup analysis suggested that a lower target may benefit in subjects with proteinuria [67].

These observations are in contrast to the Systolic Blood Pressure Intervention Trial (SPRINT) which is a randomized controlled trial that examined >9000 hypertensive subjects with an increased cardiovascular risk but without diabetes. Among those with baseline CKD, the number of subjects showing ≥50 % decline in GFR or ESRD did not differ between intensive treatment (target 120 mmHg) versus standard treatment (target 140 mmHg). However, among those with no CKD at baseline, those randomized to intensive treatment showed more adverse renal outcomes compared to standard treatment [68]. This finding adds to the growing uncertainties of target blood pressure for kidney protection in high risk subjects with and without CKD. Although the JNC 7 recommended a target blood pressure of less than 130/80 mmHg for CKD subjects [69], more recent recommendations from JNC 8 acknowledged the limitations of available evidence and suggest a target of less than 140/90 mmHg be used [70]. The CRIC study showed that having longitudinal blood pressure values and time-updated systolic blood pressure greater than 130 mmHg may be more strongly associated with CKD progression than analyses based on a

single baseline systolic blood pressure [71]. Given the clinical uncertainties and the potential for harm, it appears that a BP target of <140/90 mmHg in the clinic or <135/85 mmHg at home appears reasonable even among those with CKD.

Hypertension and Cardiovascular Outcomes in CKD

Blood pressure is an important determinant of cardiovascular risk in the general population [72] and lowering blood pressure reduces cardiovascular events in this population [73, 74]. A previous meta-analysis showed that lowering blood pressure was the main target to lower major cardiovascular event risk in hypertensive subjects [74]. Earlier study demonstrated the importance of blood pressure reduction in CKD. In the MDRD study, each 10 mmHg increase in follow-up systolic blood pressure increased the risk of hospitalization for cardiovascular and cerebrovascular disease by 35 % [61]. However, it remains controversial as to what ideal blood pressure target should be in terms of cardiovascular protection in CKD. A recent systematic analysis including 26 trials with 152,290 participants of which 30,295 subjects had CKD (defined as having eGFR <60 ml/min per 1.73 m^2) confirmed that blood pressure lowering significantly reduced the risk of major cardiovascular events by about one-sixth (for each 5 mmHg reduction in systolic blood pressure) in those with CKD (hazard ratio, 0.83, 95 % confidence intervals, 0.76–0.90) and the risk reduction was very comparable to those without CKD (hazard ratio, 0.83, 95 % confidence intervals, 0.79–0.88) [75]. Specifically, the systematic analysis showed that blood pressure lowering per se, rather than a particular anti-hypertensive drug class, was associated with cardiovascular risk reduction [75]. Notably, these observations are in keeping with the SPRINT trial showing that among adults with hypertension but without diabetes, lowering systolic blood pressure to a target goal of less than 120 mmHg significantly reduced the risk of fatal or non-fatal cardiovascular events and death from all causes as compared with the standard goal of less than 140 mmHg [68]. On the other hand, two retrospective cohort studies raised uncertainties with lower blood pressure targets [76, 77]. One study examined elderly veterans with CKD and initially uncontrolled hypertension and found higher mortality among subjects treated to a systolic blood pressure of less than 120 mmHg versus 120–139 mmHg (hazard ratio, 1.7, 95 % confidence intervals, 1.63–1.78) [77]. Another retrospective analysis of a large diverse cohort of hypertensive subjects observed a U-shaped curve for the risk associated with both achieved systolic and diastolic blood pressure in relation to a composite endpoint of all-cause mortality or ESRD [76]. Thus, while lowering blood pressure is recognized as one of the core strategies in reducing cardiovascular risk in CKD, the blood pressure target that confers the largest cardiovascular benefit has remained uncertain. Randomized trials rather than observational studies should inform clinical practice. Thus, guidelines such as the JNC 8 have taken the position that BP lowering to <140/90 mmHg measured in the clinic, even among those with CKD, appears reasonable.

Conclusions

Both hypertension and CKD are important global health problems and are strongly interrelated. Hypertension may cause CKD and modify the outcomes of CKD. On the other hand, hypertension may also result from CKD. High blood pressure increases the onset and progression of CKD and worsens the clinical outcomes of CKD patients. More attention is needed to raise awareness of hypertension and improve blood pressure control among CKD population.

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