Hypertension and Chronic Kidney Disease in Asians

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14.1 Introduction

Chronic kidney disease (CKD) and hypertension can cause, and are known for their associations with one another. In adults with hypertension and CKD, the KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease made several new recommendations including method of blood pressure (BP) measurement, lifestyle interventions, BP targets (SBP <120 mmHg when tolerated), and choice of antihypertensive drugs [1]. As such, blood pressure control is imperative to retard CKD progression and to avoid complications associated with hypertension. For this chapter, focusing on countries in Asia, we review the following: (1) epidemiology of hypertension and CKD; (2) relationship of hypertension, and CKD, with clinical outcomes; (3) genetics associated with hypertension and CKD; (4) impact of sodium and dietary patterns; and (5) antihypertensives prescription patterns.

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14.2 Epidemiology

The prevalence of CKD in hypertensive patients, hypertension among CKD patients, and end-stage kidney disease (ESKD) caused by hypertension of various Asian countries are presented in Tables 14.1 and 14.2 [2]. The types and proportions of ethnic groups differ among countries, which in turn may contribute to differences in dietary habits, cultural beliefs and practices as well as socioeconomic status. These will be discussed in the later part of the chapter. As the sampling methodologies differ with each country or study, it is difficult and therefore, not recommended to perform direct comparisons with one another.

Knowledge on various international clinical practices in BP control remains limited. Alencar de Pinho et al. analyzed data from independent CKD cohort studies (internal Network of Chronic Kidney Disease, iNET-CKD) to compare the prevalence of uncontrolled BP in adults with CKD, as well as to illustrate prescription patterns of antihypertensives. The study observed lower prevalence ratios of uncontrolled BP in cohorts from North America and high-income Asian countries like Japan and Korea, while higher prevalence ratios in cohorts from European countries, India, and Uruguay [22].

Table 14.1 Prevalence of hypertension and CKD [2]

Area	Population	Hypertension (%)	CKD in hypertensive patients (%)	Hypertension in CKD patients (%)
China	General	35.4 [3]	61.2 [3]	79.8 [4]
Hong Kong	General	27.7 [5]	–	–
India	Opportunistic	43.1 [6]	–	64.5 [7]
Japan	General	60.0 (Male) [8] 41.0 (Female)	–	–
Malaysia	CKD (subgroup)	30.3 [9]	–	38.4 [10]
Singapore	General	23.5 [9]	7.6 [11]	–
South Korea	General	29.1 [12]	19.6 [13]	–
Taiwan	General	24.5 [14]	–	–

Table 14.2 Prevalence of ESKD caused by hypertension [2]

Area	ESKD due to hypertension (%)
China	10.5 [15]
Hong Kong	9.6 [16]
India	12.8 [17]
Japan	9.9 [18]
Singapore	5 [19]
South Korea	20 [20]
Taiwan	8.3 [21]

The prevalence of hypertension and CKD can differ among ethnic groups in countries with multi-ethnic populations, like Singapore [23]. In a cross-sectional study, varying patterns of association between individual BP components and CKD were found among Chinese, Malay, and Indians in Singapore [24]. Among Malays, higher prevalence of hypertension and CKD, and higher levels of SBP and DBP were observed [24]. Similar findings of association between Malays for hypertension and CKD were identified in another two cross-sectional studies conducted in Singapore [25, 26].

14.3 Relationship Between Hypertension and CKD

Association between hypertension and increased risk of developing CKD and cardiovascular disease have been established by several studies [27, 28]. A post-hoc analysis of the China Stroke Primary Prevention Trial (CSPPT) by Jiang et al. observed a U-shaped association between serum albumin levels and the risk of developing CKD among hypertensive patients with normal renal function [29]. In a Japanese prospective cohort study, incident hypertension was also associated with a higher risk of new-onset proteinuria [30].

Associations between hypertension and CKD have been demonstrated in studies performed in South Korea, Malaysia, Singapore, and Thailand [25, 31–34]. In the C-STRIDE study of hypertensive CKD Chinese patients, uncontrolled hypertension was associated with decreased estimated GFR, albuminuria, and higher cardiovascular risk [35, 36]. Several studies in India have also demonstrated hypertension to be a risk factor of CKD including the Screening and Early Evaluation of Kidney Disease (SEEK) [7, 37]. There are also studies evaluating the relationship of hypertension with progression of CKD. Inaguma et al. showed that elevated SBP and increased albuminuria were risk factors of CKD progression in Japan [38].

Visit-to-visit BP variability has been evaluated against various clinical outcomes. The post-hoc analysis of CSPPT study by Li et al. demonstrated SBP variability was associated with development of CKD in hypertensive patients with normal renal function [39]. Li et al. also showed significant association between visit-to-visit BP variability with the risk of subsequent first stroke in hypertensive patients with mild-to-moderate CKD [40]. In Japan, SBP variability was demonstrated to be associated with eGFR decline, particularly in those with proteinuria [41]. Among Malaysian hypertensive patients, visit-to-visit variability was shown to be a determinant of renal function decline [42].

In addition to BP variability, associations of non-dipping, reverse-dipping BP patterns were observed in hypertensive Korean patients with CKD [43]. Within-visit BP variability has also been evaluated. Azushima et al. demonstrated among Japanese CKD patients with hypertension, within-BP visit variability to be a risk factor of cardiovascular disease and use of RAAS inhibitors or alpha-blockers improved variability [44].

14.4 Genetics Associated with Hypertension and CKD

Studies have identified several genetic loci associated with blood pressure and kidney diseases through genome-wide association studies based on various types of ancestries [45, 46]. Within Asia, limited studies have been conducted but several gene polymorphisms have been identified to be associated with hypertension in patients with CKD.

Non-muscle myosin heavy chain 9 (MYH9) is a major susceptibility gene for end-stage renal disease, of which its single nucleotide polymorphisms (SNPs) are associated with hypertension and end-stage renal disease [47]. In a China case-control study by Liu et al., rs3752462 TT genotype of MYH9 was associated with higher risk of concurrent high SBP ≥140 mmHg in patients with CKD [47].

Angiotensin converting enzyme-1 (ACE) is a key player in the renin-angiotensin system that maintains BP and fluid homeostasis. The insertion (I) or absence (D, or deletion) polymorphism of ACE gene is associated with hypertensive renal damage [48]. Another case-control study evaluating ACE gene polymorphism in north Indians, demonstrated strong association of ACE DD genotype with hypertensive state and end-stage renal disease [49].

Apart from ACE, genes of other components of the renin-angiotensin system have been explored. ACE, AGT, and AGTR1 gene polymorphisms were examined by Su et al. on their associations with CKD susceptibility among Chinese in Taiwan [50]. *ACE*-A2350G AA genotype and *AGTR1*-C573T CT genotype were found to be risk factors for CKD [50].

Blood pressure increase after sodium loading is known as salt sensitivity and has been regarded as a potential blood pressure control target. The impact of sodium on hypertension and CKD will be discussed in the next section. Many SNPs have been identified to be associated with salt sensitivity in Asian populations including Chinese, Koreans, and Japanese, that are known to have high-sodium dietary habits [51–57]. As such, sodium restricted diets is a strategy to alleviate hypertension in patients with these polymorphisms.

14.5 Impact of Sodium and Dietary Patterns

In adults with pre-dialysis CKD, a recommended limit of sodium intake of <100 mmol/day or <2.3 g/day (by KDOQI Clinical Practice Guideline for Nutrition in CKD 2020 Update), and <90 mmol/day (<2 g/day) or <5 g of sodium chloride/day (by KDIGO 2021 Clinical Practice Guideline for Management of Blood Pressure in Chronic Kidney Disease) can improve volume control, and reduce blood pressure control or proteinuria [58, 59]. The renin-angiotensin-aldosterone system achieves fluid homeostasis through balancing of sodium excretion, extracellular fluid volume, and arterial BP [60]. In CKD, insufficient sodium excretion affects fluid and BP balance [61]. Through various mechanisms such as oxidative stress, inflammation, and endothelial dysfunction, excessive sodium intake has adverse effects on blood vessels, heart, kidneys and sympathetic nervous systems [62].

Table 14.3 Sodium intake by country and region

Country	Sodium intake, g/day (95% uncertainty intervals)[a] [69, 70]
China	4.83 (4.62–5.05)
India	3.72 (3.63–3.82)
Indonesia	3.36 (3.02–3.76)
Japan	4.89 (4.71–5.08)
Korea	5.21 (4.98–5.48)
Malaysia	3.57 (3.25–3.93)
Philippines	4.29 (3.65–5.10)
Singapore	5.14 (4.36–6.02)
Taiwan	3.92 (3.66–4.17)
Thailand	5.31 (4.88–5.75)

[a] Age-standardized estimated sodium intakes (g/day) in 2010

There are several major studies including Intersalt, DASH, ONTARGET, LowSALT CKD and HEMO, evaluating dietary sodium intake and its effects on various outcomes such as BP, proteinuria, cardiovascular events, and mortality [63].

A summary of sodium intake in several Asian countries is shown in Table 14.3. Quantity of salt intake can vary according to countries, regions, and ethnicity, as a result of different socio-economic-cultural factors. The INTERMAP study by China used 24-h urinary sodium excretion method and demonstrated an average sodium intake of 3990 mg/day, while the 2002 Chinese Nutrition and Health Condition Survey used 3-day dietary record and showed that the nationwide salt intake was 10.7 g/day [64–66]. A more recent 2010 China Health and Nutrition Survey revealed a decline in sodium consumption from 6.8 g/day in 1991 to 4.3 g/day in 2011 [66, 67]. In a Singapore National Nutrition Survey, the mean urinary sodium excretion was 142.2 mmol/24 h and estimated mean salt intake was 8.3 g/day [68]. Powles et al. analyzed sodium intake in adults, revealing a global mean of sodium intake of 3.95 g/day. Countries within Asia had the highest mean sodium intakes, with 4.8 g/day in East Asia countries, 5 g/day in Asia Pacific High-Income countries (Japan and South Korea), and 5.51 g/day in Central Asia [69].

He et al. showed salt reduction to 100 mmol/day led to SBP (5.8 mmHg) and DBP (2.82 mmHg) reduction in the general population [71]. For CKD, the evidence of sodium intake reductions is derived from short-term randomized controlled trials or crossover studies, and observational studies for clinical endpoints such as CKD progression, mortality, and cardiovascular events [58]. The evidence demonstrating benefits of sodium reduction on BP reduction in CKD were derived from short-term randomized trials that were mostly conducted in the United Kingdom, Netherlands, Australia, Japan, and USA [72–78].

Within Asia, the effects of lowering blood pressure and proteinuria via sodium restriction in Japanese patients with IgA nephropathy were demonstrated by Konishi et al. [73]. In China, Xu et al. demonstrated association of elevated BP and risk of hypertension with higher sodium intakes in adults in Shandong and Jiangsu [66, 79]. Another cluster-randomized trial conducted in China demonstrated a sodium reduction program involving health education and access to potassium-based salt substitute resulted in lower urinary albumin-creatinine ratio and lower odds of

albuminuria [80]. A case-control study on rural population in southern India showed high serum sodium-potassium ratio excretion. Hypertension was associated with lower serum potassium levels and a lower intake of vegetables was reported by participants with hypertension [81]. Loh et al. evaluated Malaysian patients with CKD to undergo 1-month salt restricting diet prospectively. Salt intake was estimated using 24-h urinary sodium and potassium levels. With salt reduction, improvement in BP and proteinuria were observed [82].

Differences in socio-cultural beliefs and practices contribute to different dietary habits too. A cross-sectional study on adults of Sado city in Japan demonstrated associations between the intake of miso soup and Japanese pickles, with daily salt intake of 9.4 g/day based on estimated 24-h urine sodium excretion [83]. Cultural differences within Indonesia with high-fat and high-salt dietary habits in several Indonesian provinces were shown to contribute to the difference in prevalence of hypertension among the provinces [84]. Teo et al. evaluated 24-h urinary sodium excretion in Singaporean patients with CKD and found dietary sodium intake was high among those in earlier stages of CKD, of which many had declined dietician counselling [85].

Twenty-four-hour urinary excretion has been established as a method to estimate daily sodium intake. Amano et al. measured daily sodium excretion using 24-h urine collection and compared with estimated sodium excretion from a spot urine sample in Japanese patients with chronic kidney disease, using a formula by Tanaka et al. [86, 87]. The study showed a significant difference in readings when compared. In a multi-ethnic Singaporean cohort, a 5-variable equation, which included spot urine sodium, age, gender, ethnicity, and weight, was formed to predict 24-h urine sodium excretion [11].

Apart from sodium, emphasis has been placed on dietary potassium and Dietary Approaches to Stop Hypertension (DASH) diet in patients with hypertension and CKD. Mun et al. studied dietary potassium patterns in adults with stage 2 CKD in Korean rural populations and observed high dietary potassium was associated with slower CKD progression in those with hypertension [88]. Furthermore, the HEXA study found association between low potassium intake with increased odds of advanced stage CKD in hypertensive participants in South Korea [89]. The DASH diet comprises of vegetables, fruits, low-fat dairy products, whole grain, fish, poultry and nuts, with low proportions of red meat, and sugary food. Two studies revealed DASH diet when combined with low sodium intake, effectively lowered BP [90, 91]. Only one study by Lee et al. had observed low odds of developing CKD in elderly adults with greater adherence to DASH-style diet [92]. The risk of incident CKD and components of DASH diet have been evaluated in several Asian studies. Firstly, fruits and vegetable-rich diets with lower dietary acid load, were associated with lower risk of incident CKD and proteinuria in a South Korean prospective study [93]. Secondly, red meat consumption was also associated with end-stage kidney disease in a prospective study in Singapore Chinese population, and not consumption of fish, eggs, or poultry [94]. While there has been no other studies evaluating DASH diet with progression or complications of CKD, studies on effects of components of DASH diets in Asian patients with CKD have been conducted but these are beyond the scope of this chapter [95].

14.6 Prescribing Patterns of Antihypertensives in CKD

The prevalence of uncontrolled hypertension differed by regions and countries; hence, approaches to managing hypertension were likely to be heterogeneous too [22]. The study conducted by Alencar de Pinho et al. analyzed prescribing patterns of antihypertensives. The highest number of antihypertensive drug classes (3 or more) was observed in cohorts from North America while lowest number was observed in the Chinese cohort study (only 1) [22]. Across the cohorts, renin-angiotensin-aldosterone system (RAAS) inhibitors was mostly prescribed and the preferred agent for monotherapy too. In comparison to cohorts from Brazil, Europe, and North America, diuretics were less frequently prescribed in Asian cohorts, in which calcium channel blockers (CCB) were most frequently prescribed [22].

The C-STRIDE cohort study in China observed that more than half of hypertensive CKD patients were on 2 or more antihypertensives. Among them, RAAS inhibitors and CCB were prescribed the most [35]. Similar findings were demonstrated by another study in China by Zhang et al. [96]. A prospective study on patients with CKD was conducted in Singapore by Teo et al. The study described the prescribing pattern of antihypertensives within a tertiary hospital. RAAS inhibitors were observed to be commonest antihypertensive prescribed, particularly in patients with diabetes mellitus [97]. Higher frequency of diuretics, beta-blockers, or dihydropyridine CCB were prescribed at higher stages of CKD and in patients aged >65 years [97]. On the other hand, a cross-sectional study evaluating CKD patients in Pakistan, among which 74.4% had hypertension, revealed that only 48.7% of them were on antihypertensives [98]. Only 17% of patients were on RAAS inhibitors as monotherapy or in combination with other antihypertensives. Among those on monotherapy, beta-blockers were mostly commonly prescribed [98]. In the CKD-JAC study, 91.9% of Japanese CKD patients had hypertension among which RAAS inhibitors were most frequently used, followed by CCB. Between two RAAS inhibitors, angiotensin receptor blockers were commonly prescribed than ACE-inhibitors [99].

14.7 Conclusion

Among different Asian populations, this chapter has (1) illustrated the epidemiology of hypertension and CKD, (2) explored the relationship of hypertension and CKD against renal outcomes, and (3) discussed how factors including genetics, dietary choices, and varying pharmacological treatments can play powerful roles in management of blood pressure and curbing CKD progression. Taken together, it remains important to review prevalence of uncontrolled hypertension and BP management practices, to identify gaps in knowledge and implement tailored national strategies to optimize BP control. And it would add to the overall armamentarium in the prevention of chronic kidney diseases in Asia and worldwide [100].

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