Hypertension in Chronic Kidney Disease

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Abstract

Hypertension, a global public health problem, is currently the leading factor in the global burden of disease. It is the major modifiable risk factor for heart disease, stroke and kidney failure. Chronic kidney disease (CKD) is both a common cause of hypertension and CKD is also a complication of uncontrolled hypertension. The interaction between hypertension and CKD is complex and increases the risk of adverse cardiovascular and cerebrovascular outcomes. This is particularly significant in the setting of resistant hypertension commonly seen in patient with CKD. The pathophysiology of CKD associated hypertension is multi-factorial with different mechanisms contributing to hypertension. These pathogenic mechanisms include sodium dysregulation, increased sympathetic nervous system and alterations in renin angiotensin aldosterone system activity. Standardized blood pressure (BP) measurement is essential in establishing the diagnosis and management of hypertension in CKD. Use of ambulatory blood pressure monitoring provides an additional assessment of diurnal variation in BP commonly seen in CKD patients. The optimal BP target in the treatment of hypertension in general and CKD population remains a matter of debate and controversial despite recent guidelines and clinical trial data. Medical therapy of patients with CKD associated hypertension can be difficult and challenging. Additional evaluation by a hypertension specialist may be required in the setting of treatment resistant hypertension by excluding pseudo-resistance and treatable secondary causes. Treatment with a combination of antihypertensive drugs, including appropriate diuretic choice, based on estimated glomerular filtration rate, is a key component of hypertension management in

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CKD patients. In addition to drug treatment non-pharmacological approaches including life style modification, most important of which is dietary salt restriction, should be included in the management of hypertension in CKD patients.

1 Introduction and Epidemiology

Hypertension is a global public health issue and the major risk factor for heart disease, stroke and kidney failure resulting in premature death and disability (World Health Organization 2013). Over the last decade, hypertension has become the number one factor in the global burden of disease. Concurrently, there has been an increasing number of deaths and disability-adjusted life years related to poorly controlled blood pressure (BP) (Murray and Lopez 2013). Despite increased awareness and improved treatment of hypertension, the prevalence of hypertension is rising. Review of the 2011–2014 National Health and Nutrition Examination Survey (NHANES) data shows that nearly one-half (47 %) of adults aged 20 and over with hypertension had uncontrolled high BP in the United States (Yoon et al. 2015). These data include individuals with true resistant hypertension – defined as BP that remains above goal despite the concurrent use of three antihypertensive agents of different classes, including a diuretic, prescribed at optimal doses (Calhoun et al. 2008) without a secondary cause.

Chronic kidney disease (CKD) is another common and growing problem. CKD is defined as kidney damage for ≥ 3 months, due to structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR) or GFR <60 mL/min/1.73 m^2 for ≥ 3 months, with or without kidney damage. Renal parenchymal disease is both a common cause and complication of uncontrolled

hypertension (Peralta et al. 2012). In other words hypertension is the most common comorbidity seen in patients with CKD. And its prevalence increases with declining renal function (Muntner et al. 2010). Additionally, CKD is recognized as a risk factor for cardiovascular disease, which makes treatment of hypertension even more important for CKD patients. Along the same line individuals with CKD are more likely to have resistant hypertension. The prevalence of resistant hypertension increases as GFR decreases, with resistant hypertension rates of >20 % described based on ambulatory blood pressure monitoring (ABPM) (De Nicola et al. 2013; Sakhuja et al. 2015).

In summary CKD interacts with hypertension on many levels. There is a bidirectional relationship between the two diseases. Hypertension, particularly resistant hypertension, can not only occur as the result of CKD, but it is also an important risk factor for CKD progression. Resistant hypertension is very common amongst patients with CKD and the prevalence appears to be proportional to the degree of renal dysfunction (Tanner et al. 2013). At some point it becomes difficult to determine which disease process precedes the other, as both diseases share similar risk factors including age, obesity, minority descent and comorbidities like diabetes or cardiovascular disease (Table 1). The interaction between hypertension and CKD is complex and increases the risk of adverse cardiovascular and cerebrovascular outcomes particularly in the setting of resistant hypertension.

Table 1 Patient's characteristic and risk factors for hypertension in CKD

Older age
High baseline BP
Obesity
Obstructive sleep apnea
Ethnic minorities
Diabetes
Excessive dietary salt ingestion
Heavy alcohol consumption
Smoking
Vascular atherosclerosis

2 Blood Pressure Measurement and Role of Ambulatory Blood Pressure Monitoring

Accurate BP measurement is an important factor in establishing the diagnosis and management of hypertension. A standardized approach to measuring BP improves the consistency and accuracy of the recorded readings. Inaccurate BP measurement techniques such as measuring the BP before the patient rests quietly for 5 min and use of inappropriately small cuff are the most common causes of falsely elevated BP readings (Pickering et al. 2005). Multiple readings taken at intervals of at least 1–2 min and then averaged is a better representation of a patient's BP. The BP should be measured in both arms to check for any major reading discrepancies, as between-arm BP differences are common even in healthy people. In hypertensive patients, a difference of 4–5 mmHg is not uncommon. A difference in systolic BP of over 10 mmHg requires vascular assessment, as heavily calcified or arteriosclerotic arteries, seen more commonly in patients with CKD, cannot be compressed fully for accurate BP readings. BP values between arms that are different by over 15 mmHg could indicate a heightened risk for vascular disease and death (Clark et al. 2012). In general, for management purposes it is recommended that the higher BP of the two arms be used.

Major causes of uncontrolled BP in patients with CKD include non-adherence to important lifestyle changes such as low salt diet, an inadequate or suboptimal treatment regimen including diuretics, and poor adherence to antihypertensive therapy, sometimes due to medication intolerance (Yiannakopoulou et al. 2005). Other possible causes of uncontrolled BP are previously undiagnosed but curable secondary hypertension; psychiatric causes; use of an interfering substance such as non-steroidal anti-inflammatory drugs (NSAIDs) or amphetamines; and drug interactions.

In general clinic BP measurements are the most common method of assessment to evaluate hypertension. Ambulatory blood pressure monitoring (ABPM) is a useful tool that adds additional clinical information on a patient's BP pattern including an assessment of nighttime BP and diurnal variation in BP. ABPM may also provide additional diagnostic information, such as white-coat hypertension and masked hypertension (Drawz et al. 2012). White-coat hypertension is defined as persistently elevated clinic BP readings while out-of-office BP values measured by 24-h ABPM are normal. This condition is a common cause of apparent resistant hypertension and should be ruled out to avoid over treatment with antihypertensive drugs (de la Sierra et al. 2011). Patients with CKD and white-coat effect have a much lower cumulative risk of progressing to end stage renal disease (ESRD), highlighting the importance of ABPM in CKD patients (Agarwal and Andersen 2006). Alternatively, masked hypertension is defined as normal, or near normal, office BP levels but out-of-office hypertension. Masked hypertension appears to be remarkably prevalent in CKD patients (Agarwal et al. 2016). Patients with masked hypertension are at increased risk for target organ damage and cardiovascular events (Fagard and Cornelissen 2007). CKD patients with this condition appear to have a higher cumulative risk of end stage renal disease (ESRD) compared to those with controlled ambulatory pressures (Agarwal 2006). ABPM provides additional information compared to home and office recordings with measures of BP variability and nocturnal BP measurements. The circadian BP rhythm and nocturnal BP are often abnormal in patients with CKD. Patients with CKD often

loose the physiologic nocturnal 10–20 % fall in systolic and diastolic BP level. Patients with advanced CKD might even exhibit a rise in nocturnal BP, a phenomena called riser. The absence of nocturnal dip has been linked to increased risk of cardiovascular disease and target organ damage including progression of CKD (Kanno et al. 2013)' (Muxfeldt et al. 2009). Similarly there is a positive association between BP variability and the progression of renal damage and cardiovascular events (Ciobanu et al. 2013). When ABPM is not available, home BP measurement can provide some information on possible presence of white coat, masked, or resistant hypertension. Population studies both in general and in CKD (Cohen et al. 2014) demonstrate that home-measured BP is prognostically superior to office BP readings, correlates more closely with ABPM than office BP measurements, and is more predictive of adverse cardiovascular outcomes (Dolan et al. 2005; Niiranen et al. 2010). Therefore, out-of-office BP readings, ABPM or home BP measurement, should be used in management of hypertension.

3 Target Blood Pressure in Chronic Kidney Disease

The optimal BP level, whether systolic or diastolic, in the treatment of hypertension in general and CKD population remains a matter of debate and has become controversial despite recent guidelines and clinical trial data (James et al. 2014; SPRINT Research Group et al. 2015). In addition to prevention of cardiovascular events (McCullough et al. 2011), the goal in patients with CKD is to delay progression to ESRD with need for renal transplant or renal replacement therapy (Whaley-Connell et al. 2008).

Multiple trials in non-diabetics, including MDRD (Klahr et al. 1994), AASK (Wright et al. 2002), and REIN-2 (Ruggenenti et al. 2005) failed to show benefit from lower BP targets of <130/80 mmHg compared to <140/90 mmHg in slowing the progression of CKD to ESRD. A clinical trial on type 2 diabetics, that include a large number of diabetics with CKD, detected a small but statistically insignificant reduction in cardiovascular events among diabetics treated to the intensive systolic BP goal of <120 mmHg compared to goal BP of <140 mmHg (Cushman et al. 2010). In contrast, data from SPRINT (SPRINT Research Group et al. 2015) which excluded diabetics, but included 28 % of participants with reduced estimated GFR of 20–60 ml/min/1.73 m^2 showed a 25 % relative risk reduction in the cardiovascular events. There was no difference in rates of 50 % reduction of estimated GFR or ESRD between the intensive-BP treated group compared to standard-BP group. More patients without incident CKD had >30 % decline in estimated GFR with intensive treatment. Both ACCORD and SPRINT trials showed an increase in the risk of serious adverse events with the more intensive BP–lowering strategy. The benefit of BP target of less than 130/80 mm Hg in patients with CKD and proteinuria is supported based on post hoc analyses (Upadhyay et al. 2011). Hence, as depicted in Table 2, based on the limited clinical trial evidence almost all of the clinical practice guidelines for the management of BP in CKD without albuminuria or proteinuria recommend a goal BP of <140/90 mm Hg. The recommendation, based on expert opinion, is a lower BP target of <130/80 mm Hg for CKD patients with albuminuria or proteinuria.

The foundation of antihypertensive therapy in CKD patients should be based on the evidence-based strategy of using inhibitors of the renin angiotensin aldosterone system (RAAS) with diuretics, either thiazide or thiazide–type agents in the absence of significantly low GFR (<30 mL/min/1.73 m^2). Addition of other agents such as calcium channel blockers, or other drug classes should be considered as necessary to achieve a lower systolic BP level. It is important to balance the anticipated cardiovascular benefits of therapy in patients with higher cardiovascular risk with possible serious adverse effects of intensive targeted BP.

Table 2 Blood pressure targets and treatment recommendations in CKD

Guideline	BP target in CKD without Albuminuria or Proteinuria	BP target in CKD with Albuminuria or Proteinuria
JNC8 (James et al. 2014)	<140/90 mmHg	<140/90 mmHg
KDIGO (2012)	<140/90 mmHg	<130/80 mmHg
NICE (National Institute for Health and Care Excellence Hypertension clinical management of primary hypertension in adults; National Institute for Health and Care Excellence Chronic kidney disease)	<140/90 mmHg	<130/80 mmHg
CHEP (Dasgupta et al. 2014)	<140/90 mmHg	<140/90 mmHg
ESC/ESH (Mancia et al. 2013)	<140 mmHg	<130 mmHg
ASH/ISH (Weber et al. 2014b)	<140/90 mmHg	<140/90 mmHg
ISHIB (Flack et al. 2010)	<130/80 mmHg	<130/80 mmHg
ADA (American Diabetes Association 2013)	<140/80 mmHg	

Abbreviations: *ADA* American Diabetes Association, *ASH/ISH* American Society of Hypertension/International Society of Hypertension, *CHEP* Canadian Hypertension Education Program, *ESC/ESH* European Society of Cardiology/European Society of Hypertension, *ISHIB* International Society of Hypertension in Blacks, *KDIGO* Kidney Disease: Improving Global Outcomes, *NICE* National Institute for Heath and Care Excellence, *JNC8* USA Eighth Joint National Committee

4 Pathophysiology of Blood Pressure Regulation and Pathogenesis of Hypertension in Chronic Kidney Disease

The pathophysiology of CKD associated hypertension is complex because the kidney is not only the contributing organ, but is also a target organ of the hypertensive processes. Multiple mechanisms contribute to hypertension in CKD and their contributions might differ between patients.

Blood pressure is mainly regulated by four pathways. These include the sodium regulation, sympathetic nervous system (SNS) activity, humoral system – Renin Angiotensin Aldosterone System (RAAS), and auto-regulatory system. These pathways could have independent or interdependent effect on BP regulation. The pathological activity of one or multiple factors plus additional exogenous factors can influence BP and its management in patients with CKD. The endogenous pathologic factors in CKD include increased SNS (Klein et al. 2003) and RAAS activity plus endothelial dysfunction. Hypertension can cause and accelerate renal injury when impaired auto-regulation allows the transmission of high systemic pressures to the glomeruli, resulting in glomerulosclerosis (Bidani et al. 2013). Renal injury and loss of GFR in turn can cause hypertension due to impairment in sodium excretion and increased salt sensitivity (Koomans et al. 1982; Pimenta et al. 2009). Respectively, exogenous factors including high dietary sodium intake, and intervening medications like over-the-counters, such as NSAID (LeLorier et al. 2002) add to this complexity.

In general, GFR decreases with age and CKD accelerates the vascular ageing and atherosclerosis. This leads to increased arterial stiffness and increased risk of development of systolic hypertension in elderly patients with CKD (Briet et al. 2012). Similarly CKD is more common in patients with obesity and metabolic syndrome. The relationship between obesity and hypertension is well described (Hall 2003). However, the pathophysiology of obesity-induced hypertension is complex and not fully understood. Plausible mechanistic pathways of hypertension in CKD patients that are similar to obesity associated hypertension include impaired sodium excretion, increased SNS activity, and activation of the RAAS. There is also a high prevalence of obstructive sleep apnea (OSA) in CKD patients (Nicholl et al. 2012) and in patients with resistant

hypertension, indicative of considerable overlap in these conditions. Although the exact unifying pathologic mechanism of this relationship is unclear, it appears to be linked with hyperaldosteronism and salt and volume retention (Gonzaga et al. 2010).

5 Sodium Regulation

The kidneys filter over 25,000 mmol of sodium per day excreting only less than 1 % of the filtered sodium load. Mismatch of input and output as the result of inadequate sodium excretion in the setting of CKD over time can result in volume mediated hypertension. Initial volume expansion increases cardiac filling and cardiac output; leading to a decrease in RAAS activation and results in increased sodium excretion. Loss of sodium regulation in the setting of CKD and low GFR is associated with a greater sensitivity of BP to salt. This leads to the increased prevalence of salt-sensitive hypertension seen in CKD. In addition increased sodium intake results in arterial vessel stiffness, decreased nitric oxide release, and the promotion of inflammatory processes all of which contribute to BP elevation (Hovater and Sanders 2012). Excessive salt intake also blunts the BP lowering effect of most classes of antihypertensive agents thus favoring development of resistant hypertension (Luft and Weinberger 1988). These effects are more pronounced in salt-sensitive patients, including the elderly, African Americans, and patients with CKD (Boudville et al. 2005). The American Heart Association recommends a sodium intake of 1500 mg per day in patients at high risk, including those with hypertension, diabetes, African descent, and CKD (American Heart Association Shaking the salt habit). Patients with CKD usually have co-morbidities and polypharmacy is not an unusual scenario. Several medications, some commonly used by this patient population, interfere with BP control and can contribute to treatment resistance (Grossman and Messerli 2012). Consequently, there can be blunting of the BP lowering effect of several antihypertensive drug classes,

Table 3 Pharmacological agents that can increase blood pressure

Nonsteroidal anti-inflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Glucocorticoids with greater mineralocorticoid effect
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

including diuretics, angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARBs), and beta blockers (Conlin et al. 2000) (Table 3).

Non-steroidal anti-inflammatory drugs (NSAIDs) have an inhibitory effect on renal prostaglandin production, especially prostaglandin E2 and prostaglandin I2. This effect can lead to sodium and fluid retention. These adverse effects are especially manifested in elderly patients, diabetics, and patients with CKD (Johnson et al. 1994). Use of immunosuppressive agents in patients with CKD as a result of primary glomerulopathy or tubule-interstitial disease is common and associated with adverse effects including hypertension. Glucocorticoids with greater mineralocorticoid effect (e.g. cortisol) can cause significant increases in BP by inducing sodium and fluid retention. In such cases, use of a mineralocorticoid receptor antagonist (spironolactone or eplerenone) can be an effective strategy to lower BP. Similarly, drugs like Calcineurin inhibitors induce a salt sensitive hypertension as a result of increased renal expression of the phosphorylated (active) form of the thiazide-sensitive NaCl co-transporter (NCC) (Hoorn et al. 2011). This phenotype is similar to familial hyperkalemic hypertension (also known as pseudo-hypoaldosteronism type II or Gordon's syndrome), which presents as hypertension, renal sodium and potassium retention, and renal tubular acidosis. Other agents that can add difficulty in BP management include decongestant and diet pills

that contain sympathomimetic, amphetamine-like stimulants, oral contraceptives, and herbal preparations containing ephedra (or ma huang) (Mansoor 2001).

6 Sympathetic Nervous System Regulation

SNS activity is increased in CKD (Klein et al. 2003). Assessment of SNS activity and its contribution to BP regulation is imprecise, as circulating catecholamine levels provide only a rough estimate of SNS activity. Measurement of muscle sympathetic nerve activity is more precise, but remains a limited available diagnostic tool. The renal artery is highly innervated, with efferent renal nerves that originate from the central nervous system, and afferent renal nerves that originate from the kidneys. Stimulation of efferent renal nerves via β-1 adrenoreceptor stimulates renin secretion and activates the RAAS resulting in decreased urinary sodium excretion. Maximal stimulation of the efferent nerves can lead to an increase in renal vascular resistance (DiBona and Kopp 1997). Another well-described pathophysiology is the hypoxemia induced sustained increase in SNS activity seen in obstructive sleep apnea (OSA), which in turn raises BP through an increase in cardiac output, increase in peripheral resistance, and fluid retention (Somers et al. 1995). Accordingly, β-1 adrenergic blockers, ACE inhibitors, and ARBs are among the most effective antihypertensive agents in conditions with high SNS activity status including CKD and OSA.

7 Humoral System – Renin Angiotensin Aldosterone Regulation

Renin is secreted from the juxtaglomerular apparatus, which is the nephron site wherein there is contact between the afferent arteriole, and the distal convoluted tubule. While SNS stimulation induces renin secretion through the efferent renal nerves, renin secretion is also highly volume regulated (Davis and Freeman 1976). Volume depletion leads to renin secretion whereas volume overload and increased afferent arteriolar stretch suppress the renin secretion. In response to renin secretion, subsequent activation of RAAS causes vasoconstriction via angiotensin II effect. RAAS activation also increases sodium reabsorption by both angiotensin II in the proximal tubule and aldosterone in the distal nephron in exchange for the secretion of potassium. In addition to mineralocorticoid receptor stimulation aldosterone has a direct effect on the vasculature (Briet and Schiffrin 2013). Other factors like endothelins, oxidative stressors, and inflammatory mediators may also contribute to hypertension in CKD. Endothelins, such as ET-1, are potent vasoconstrictors. Oxidative stressors such as reactive oxygen species promote vasoconstriction, the release of renin, and increased urinary protein excretion (Araujo and Wilcox 2014). Inflammatory mediators or cytokines, such as TNF and IFNγ, further impair endothelial function (Crowley 2014). In addition, patients with CKD are at increased risk of vascular calcification and arterial stiffness which promote hypertension.

8 Chronic Kidney Disease and Resistant Hypertension

There is a strong association of CKD with greater prevalence of resistant hypertension, and greater risk of end-organ damage. Among CKD patients the severity of hypertension increases as GFR declines and sodium excretion decreases. Excess salt intake and subclinical volume overload are important contributors to the increased prevalence of resistant hypertension (Pimenta et al. 2009). As discussed earlier, a high dietary salt intake amplifies the consequences of impaired sodium excretion on BP. Therefore, a reduction in salt intake can have a synergistic effect on the actions of antihypertensive drugs that block the renin angiotensin aldosterone system in control of BP (Kwakernaak et al. 2014). Presence of significant proteinuria, commonly seen in CKD, may have an accentuating effect.

Aberrant filtration of plasminogen and its conversion within the urinary space to plasmin by urokinase-type plasminogen activator may increase sodium retention by activating the epithelial sodium channel (ENaC) and contributing further to volume overload status (Svenningsen et al. 2013). Similar results have been observed in patients with preeclampsia (Buhl et al. 2012). Overall, these findings stress the possible important role of amiloride use in the management of salt-sensitive hypertension associated with proteinuria or nephrotic syndrome.

The epidemic of obesity, a common finding in patients with CKD, with angiotensin-II independent release of aldosterone by adipocytes could be a reason for the increased occurrence of aldosterone mediated resistant hypertension (Ehrhart-Bornstein et al. 2003). Along the same line patients with CKD and Obesity are at high risk of developing OSA. The pathophysiology of OSA associated hypertension has not been fully elucidated, but in patients with resistant hypertension, it has been shown that aldosterone levels correlate with severity of OSA (Dudenbostel and Calhoun 2012). Blockade of aldosterone by mineralocorticoid receptor blockers reduces the severity of OSA and is an effective treatment strategy in the many patients who continue to have uncontrolled BP levels while taking three antihypertensive agents (Ziegler et al. 2011).

Patients with CKD have high prevalence of a blunted nocturnal BP decline and loss of the circadian BP pattern. During sleep in healthy individuals, there is a physiological BP decrease of 10–20 % of the average awake BP level. Patients with CKD often fail to show this nocturnal BP dip during the sleep period. These patients are referred to as non-dippers. In addition to the non-dipping phenomena as determined by ABPM, there may also be an increase in the sleep period BP levels, a pattern referred to as a riser. Other factors independently associated with elevated nighttime BP are proteinuria, older age, black race, and presence of diabetes (Drawz et al. 2016). There is a strong association between elevated nighttime BP and masked hypertension. Masked hypertension appears to have the same risk for cardiovascular events as

sustained hypertension and is a well-established risk factor for target organ damage, such as LVH, vascular stiffness, and cardiovascular events (Hänninen et al. 2013). The loss of circadian rhythm and increased prevalence of the riser BP pattern, is associated with highest cardiovascular events risk among all possible BP patterns, and is 2.5-fold more prevalent in CKD, and up to five-fold more prevalent in end-stage renal disease (Mojón et al. 2013). The high prevalence of non dipping BP, rising BP at night and/or masked hypertension in patients with CKD reinforces the need to measure out-of-office BP for a full characterization of the burden of Hypertension. Hence, ABPM is an important useful tool in assessing the overall 24-h BP pattern and contributes substantially to the risk stratification of cardiovascular outcomes in the high risk CKD population.

9 Evaluation of Hypertension in Chronic Kidney Disease

Patients with CKD and hypertension have complex hypertension. Achieving optimal BP control is frequently challenging even for nephrologists or hypertension specialists.

The first step in evaluation of a patient with CKD and difficult to treat hypertension is to confirm the diagnosis of true treatment resistance hypertension and exclude pseudo-resistance due to inaccurate blood pressure measurement technique and treatment non-adherence (Burnier et al. 2013) (Fig. 1). Barriers to successful medication adherence include polypharmacy, drug costs, dosing inconvenience and adverse effects of drugs. Once the diagnosis is confirmed, possible factors that can contribute to treatment resistance should be considered.. These include life style factors such as obesity, physical inactivity, high dietary salt intake, excessive alcohol ingestion and use of substances with potential interference with antihypertensive medications such as over the counter medications or herbs. It is important to consider and screen for overlapping conditions such as obstructive sleep apnea and possibly hyperaldosteronism.
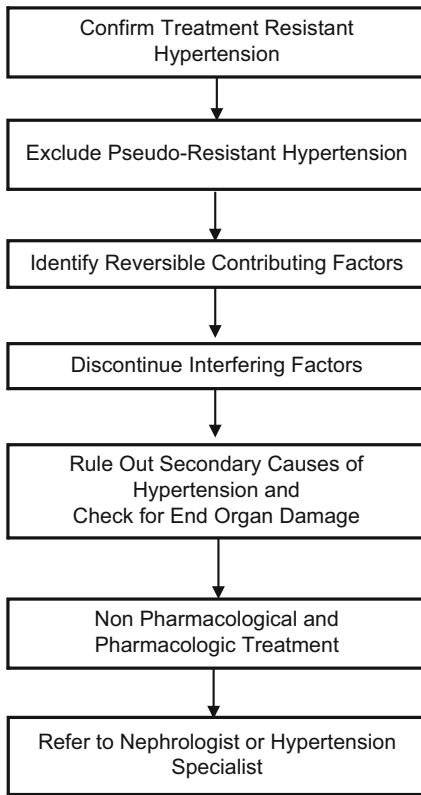
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AU1 **Fig. 1** A stepped sequence in evaluation and management of hypertension in patients with chronic kidney disease (See text for details for each step)

The medical history and physical examination should include information on duration, course, severity of the hypertension and if possible the chronologic relation to the established CKD diagnosis. It is important to inquire about presence of orthostatic complications (i.e. dizziness, fatigue, and vision blurring), prior regimens used, and any experienced side effect. History of snoring, witnessed apnea, and excessive daytime sleepiness indicates further evaluation for OSA. Presence of abdominal bruits in young female or carotid bruits in an elderly patient with known atherosclerotic disease increases the possibility of renal artery stenosis. Discrepancy between arm and thigh blood pressure readings is suggestive of aortic coarctation and features of Cushing's disease are suggested by central obesity, abdominal striae, moon face or prominent interscapular fat deposition.

Screening for target-organ damage including left ventricular hypertrophy (LVH $\geq$115 g/m^2 for men and $\geq$95 g/m^2 for women), retinopathy, microalbuminuria (increased urinary albumin excretion of $\geq$30–299 mg/g of creatinine), macroalbuminuria (increased urinary albumin excretion of $\geq$300 mg/g of creatinine), and degree of CKD by estimated GFR are essential to assess the overall increased risk of cardiovascular complications such as myocardial infarction, heart failure, stroke and further deterioration of renal function. The risk increases both with the degree and the duration of uncontrolled BP and CKD. The relationship between cardiovascular disease and target organ damage including CKD can be bidirectional. Uncontrolled BP can cause cardiovascular and renal structural and functional alterations, and contribute to development of LVH, aortic stiffness, microvascular disease. Overall, CKD can render hypertension more difficult to control (Muiesan et al. 2013).

Alternatively, the clinical findings of great discrepancy between higher clinic BP measurements and lower out-of office BP measurements particularly in a patient with orthostatic symptoms and no sign of target organ damage requires investigation for possible white-coat hypertension and overtreatment. Out-of-office BP measurements done by the patient, using a manual or automated blood pressure monitor, or the use of 24-h ABPM, as a more accurate alternative, can be used to document the presence and/or significance of any white-coat effect. 24-h ABPM also allows the assessment for absence of a nocturnal dipping, presence of a riser pattern, or significantly increased pulse pressure suggestive of vascular remodeling and vascular stiffness (Muxfeldt and Salles 2008). Hence, in accordance with the recent U.S. Preventive Services Task Force statement (Siu 2015) and evidence based data (Persu et al. 2014) it is recommended to confirm a diagnosis of hypertension or resistant hypertension with ABPM.

Basic laboratory evaluation of a hypertensive individual with CKD includes a routine metabolic profile, and urinalysis. Evaluation for a

renal vascular lesion should be considered, particularly in a young female patient, whose presentation may suggest the presence of fibromuscular dysplasia or an older patient at increased risk of atherosclerotic disease in whom there has been a recent deterioration in renal function following therapy with ACE-inhibitors or ARBs, or history of flash pulmonary edema. When a renal vascular lesion is suspected, a duplex ultrasound study is required to rule out renal artery stenosis (Rimoldi et al. 2014). Although duplex ultrasound results depend on the level of training and experience of operator, they are preferred modality over computer tomographic angiography in patients with CKD in view of increased risk of contrast induced acute kidney injury. The gold standard diagnostic renal arteriograms in the absence of suspicious noninvasive imaging are not recommended. The presence of persistent and otherwise unexplained hypokalemia requires measurement of both plasma renin activity and aldosterone concentration to rule out hyperaldosteronism. However, with low GFR and reduced potassium excretion, hypokalemia may be absent. In patients already taking antihypertensive drugs it can be difficult to interpret renin and aldosterone levels. Suppressed renin level without elevated aldosterone concentration is suggestive of inappropriate volume expansion commonly seen in patients with CKD.

10   Non-pharmacologic Therapy

Treatment of hypertension in patients with CKD starts with non-pharmacological approaches. The modification of lifestyle factors – restriction of dietary salt, weight loss, regular exercise, and decreased alcohol ingestion, factors that contribute to treatment resistance is of high importance. Also included in this approach in CKD patients is discontinuation of any potentially interfering substances, like NSAIDs, as clinically allowable. Although the benefit of dietary modification interventions has not been extensively studied in patients with hypertension and CKD, the data

on their benefits in general hypertensive population is compelling.

Compliance in adhering to a low salt diet in hypertensive patients, particularly in salt sensitive patients like African-Americans, elderly, and individuals with CKD is associated with significant reductions in systolic and diastolic BP (Vollmer et al. 2001). High salt diet blunts the effect of ACE inhibitors (Singer et al. 1991) and sodium reduction enhances the antiproteinuric effect of ARBs (Kwakernaak et al. 2014) which is an important renal protective effect of RAAS blockaders. Accordingly, dietary salt restriction to less than 100 mEq (2300 mg) of sodium/24-h is recommended by most clinical practice guidelines. Additionally ingestion of a diet rich in fruits and vegetables, with close monitoring of the potassium levels in CKD patients, reduces systolic and diastolic BP compared to a usual diet in hypertensive patients (Appel et al. 1997).

Long-term weight loss, although difficult to achieve and to maintain, is clearly associated with modest improvement of BP level. Successful reduction in excess body weight may also lead to a reduction in the number of antihypertensive medications (Aucott et al. 2005). Similarly, data from meta-analysis including both normotensive and hypertensive cohorts show regular aerobic exercise results in mild reduction of both systolic and diastolic BP (Whelton et al. 2002). Based on these observational data, patients should be encouraged to maintain an ideal weight and exercise for at least a minimum of 30 min on most days of the week.

High alcohol consumption is associated with increased risk of treatment resistant hypertension (Wildman et al. 2005; Aguilera et al. 1999). Alcohol intake should be limited to no more than 28 g of ethanol per day for men and 14 g per day for women as moderation in alcohol intake significantly improves BP control.

To improve and maximize patient adherence to prescribed medication, it is important to avoid complex dosing regimens and high out-of-pocket costs. The medication regimen should be simplified by using long-acting drugs, if

possible, and include antihypertensive drugs from different classes in order to provide a combination of pharmacological effects. A treatment strategy that reduces the number of tablets taken per day and the number of doses per day, as well as minimizing adverse effects facilitate drug treatment adherence. Encouraging patient involvement in their care by requesting frequent home BP measurements also can enhance medication adherence (Ogedegbe and Schoenthaler 2006).

11 Pharmacologic Therapy

The goal of pharmacologic therapy should be to achieve and maintain BP control using the least number of medications with minimal adverse effects. Individualization of treatment should consider etiologies and comorbidities that commonly co-exist among subgroups of patients. It is also important to consider the high cardiovascular disease risk status, age, sex, ethnicity, any disease associated target organ damage, and risk of drug–drug interactions. As an example, RAAS activation is often absent in elderly patients and in patients of African origin. For these patient sub-groups RAAS blockade for the treatment of treatment resistant hypertension may be less effective.

The standard recommended medical treatment regimen for hypertension is A + C + D. A = angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker; C = calcium channel blocker; D = thiazide-like diuretic (James et al. 2014; Weber et al. 2014a). The 'A + C + D' combination is well tolerated and acts on different BP regulatory systems with increased renal sodium excretion and inhibition of both the RAAS and the SNS activity. There is strong evidence that combination regimens reduce cardiovascular events in hypertensive individuals (Dahlof et al. 2005; Patel et al. 2007; Chalmers et al. 2014).

Resistant hypertension is commonly present in patients with CKD, especially with advanced CKD. Therefore a combination drug regimen that blocks different regulatory pathways is necessary to reduce BP level. Loss of GFR is associated with a slower rate of sodium excretion. The subsequent development of volume overload status plays a key factor in the pathogenesis of resistant hypertension in CKD, and diuretics are essential in achieving BP control. When sodium excretion cannot keep pace with constant sodium intake in patients with CKD, dietary salt restriction in conjunction with diuretics is required to maintain euvolemia. Lack of or underuse of diuretics in patients with CKD is a common cause of treatment resistant hypertension. Appropriate diuretic choice, based on estimated GFR, is a crucial component in hypertension management in CKD patients (Sica 2008).

Modification of an antihypertensive regimen by adding a diuretic, increasing the dose of the diuretic, or changing the class of prescribed diuretic based on GFR can significantly improve BP control (Tamargo et al. 2014a, b). Thiazides, unlike the thiazide-like compound indapamide, appear to have a small vasodilatory effect at high concentrations (Pickkers et al. 1998). In general the long-acting thiazide-like diuretic chlorthalidone (Ernst et al. 2006) is the most potent thiazide diuretic and can be used unless the GFR is very low. With a GFR less than 30 ml/min/1.73 m^2 loop diuretics should be used. Loop diuretics are more potent natriuretic agents. KDIGO guideline (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group 2013) recommends a switch from thiazide diuretic to loop diuretic at CKD Stage 4 (<30 mL/min/1.73 m^2). This recommendation however has been challenged recently, based on few small studies that reported efficacy of thiazide – type diuretics at GRF below 30 ml/min/1.73 m^2 (Cirillo et al. 2014). However, individuals with advanced CKD with or without albuminuria may require even higher doses of loop diuretics to achieve natriuresis and BP reduction. To avoid counter-regulatory rebound sodium reabsorption and volume retention in patients with CKD the diuretics should be dosed more frequently if short acting drugs are used (Shankar and Brater 2003). Use of long acting diuretics such as chlorthalidone or

Table 4 Properties of common diuretics

Drug class	Site of action	Drugs	Usual PO dose – mg	Dosing interval
Thiazide-type	Na-Cl cotransporter in distal convoluted tubule	HCTZ	12.5–50	Daily
		Chlorothalidone	6.25–25	
		Metolazone	2.5–10	
		Indapamide	1.25–5	
Loop agents	Na-K-2Cl cotransporter in thick ascending limb of the loop of Henle	Furosemide	20–80	Twice a day
		Bumetanide	0.5–2.0	Twice a day
		Torsemide	5–20	Daily
		Ethacrynic acid[a]	25	
Aldosterone antagonists	Cortical collecting tubule	Spironolactone	25–50	Daily
		Eplerenone	50	
Epithelial Na-Channel Blocker	Cortical collecting tubule	Amiloride	5–10	Daily

[a]Management of edema associated with renal disease in the setting of sulfa allergy

torsemide can avoid the rebound sodium absorption seen in patients using diuretics with short half-life. Moreover, the sequential blockade of sodium channels along the nephron with both a thiazide and loop diuretic is very effective, but this combination of diuretics requires frequent serum creatinine and electrolytes monitoring (Izzo 2012). In addition use of diuretics might correct the non-dipping BP during sleep, a phenomena commonly seen in patient with CKD (Uzu and Kimura 1999) (Table 4).

ACE inhibitors or ARBs if tolerated, are the important classes of drugs that are recommended in many guidelines for use in hypertensive CKD patients with or without proteinuria. Both ACE inhibitors and ARBs are recommended for CKD patients because of their efficacy, relatively low side effect profile, reno-protective effects and reduced risk for cardiovascular and renal events (Maione et al. 2011). RAAS blockers exert their reno-protective effect by reducing the intraglomerular pressure and thereby decreasing proteinuria (Anderson and Brenner 1988). A concurrent reduction in GFR and associated rise in serum creatinine of up to 30 % is physiologic and is associated with a better renal outcome (Holtkamp et al. 2011). The physiologic GFR drop is not an indication for drug cessation, unless there is complication of persistent hyperkalemia refractory to treatment. A greater increase in serum creatinine, if observed following initiation of ACE-inhibition or ARB therapy, could be due to volume contraction, use of nephrotoxic agents such as NSAIDs, or bilateral renal artery stenosis, which would require further investigation. Although a combination of an ACE inhibitor with an ARB could improve BP control in difficult to treat hypertension, this combination is associated with significant adverse effects (ONTARGET Investigators et al. 2008) including risk of severe hyperkalemia, hypotension and acute renal failure (Fried et al. 2013). Similar findings are seen with aliskiren, a direct renin inhibitor used with ACE inhibitor or ARB (Parving et al. 2012). Therefore a combination of RAAS agents should be avoided.

Dihydropyridine calcium channel blockers (CCBs) in contrast to non-dihydropyridine CCBs that have an antiproteinuric effect are very effective antihypertensive drugs (Bakris et al. 2004). Due to the higher precapillary arterial dilatation effect of the drug, patients may experience lower extremity edema that is refractory to diuretics, but improves or resolves with the use of an ACE inhibitor or ARB. The combination of CCB with an ACEI might be more effective in slowing the progression of CKD, particularly in black patients (Bakris et al. 2010; Weir et al. 2012).

Uncontrolled BP despite use of combination regimen of A + C + D (i.e. office BP > 140/90 mmHg and/or 24 h ABPM > 130/80 mmHg) requires search for pathogenic mechanism and possibly additional antihypertensive agent. Mineralocorticoid receptor antagonist (MRA) or aldosterone antagonists are the most important drug of choice for patients uncontrolled on multidrug regimens and low-renin status as the result of volume expansion or possible aldosterone escape phenomenon (Eide et al. 2004). Addition of low dose spironolactone of 12.5–50 mg daily is suggested as the fourth line of therapy and could effectively lower both systolic and diastolic BP (Williams et al. 2015). The MRA effect is independent of patient's baseline plasma aldosterone or 24-h urinary aldosterone level, plasma renin activity, or plasma aldosterone/renin ratio (Nishizaka et al. 2003). The most common adverse effect of spironolactone, the breast tenderness with or without breast enlargement, is particularly seen in men and at higher doses of 50–100 mg/day. Use of an aldosterone antagonist combined with an ACE inhibitor or ARB though not contraindicated requires careful monitoring of serum potassium and creatinine levels. Similarly, the risk of hyperkalemia is increased in patients taking NSAIDs, or with co-morbidities particularly like diabetes and/or CKD. Use of MRA should be restricted to patients with GFR > 30 mL/min/1.73 m^2 and plasma potassium concentrations of <4.5 mmol/L.

Amiloride is a diuretic that functions as an indirect aldosterone antagonist by blocking the epithelial sodium channel in the distal collecting duct of the kidney. Amiloride has been shown to be an effective add-on therapy in patients with uncontrolled hypertension or patients with significant proteinuria (Muxfeldt and Salles 2008). Beta-Blockers, as the fifth drug of choice, are more often used when there is a coexisting cardiac disease such as ischemic heart disease or heart failure (Rosendorff et al. 2015). If indicated, the more effective beta-blocking drugs are the drugs with combined alpha and beta antagonist activity. However, in a clinical condition of increased SNS activity and/or arterial stiffness, use of an alpha-blocker like doxazosin may have a favorable effect on BP and vascular remodeling. The main side effect of this drug is dizziness. Centrally acting agent, clonidine, can be very effective, but requires frequent dosing. The drug has a significant adverse effect profile and using a dose of over 0.6 mg per day is associated with rebound hypertension if doses are frequently missed. Potent vasodilators such as hydralazine or minoxidil have a higher incidence of adverse effects including lower extremity edema, and tachycardia.

Finally, an important factor in management of hypertension in CKD is the concept of chronotherapy. Intake of at least one of the hypertensive agents at bedtime is associated with a better 24-h mean BP control and, in particular, could induce the desired nocturnal dip in non-dippers, which could be beneficial in reducing cardiovascular event risk (Hermida et al. 2011a, b).

12 Device Interventions

Device-based interventions like carotid baroreceptor stimulation and renal denervation (RDN) have been used for the treatment of drug resistant hypertension with high SNS activity. Carotid baroreceptor stimulation decreases central neural sympathetic outflow through electrical activation of the sympatho-inhibitory area thus lowering arterial pressure (Lohmeier and Iliescu 2015). Baroreceptor stimulation requires surgical implantation and the BP-lowering effect may be attenuated if the hypertension is associated with hyperaldosteronism (Lohmeier et al. 2015) and angiotensin II-induced hypertension.

In contrast the renal arteries are highly innervated with both afferent and efferent nerves. Denervation of the renal arteries as a potential treatment for patients with resistant hypertension has been investigated. Using a catheter-based radiofrequency method, renal denervation may become a plausible treatment option in management of difficult to control resistant hypertension. However, to date, the RDN studies have had conflicting results (Krum et al. 2009; Esler et al. 2010; Bhatt et al. 2014).

Although the intervention in patients with CKD at baseline has shown positive results and the procedure is safe and well tolerated (Hering et al. 2012; Ott et al. 2015), subsequent studies are needed to determine the effectiveness of RDN for hypertension management.

13   Prognosis

The long-term prognosis of individuals with difficult to treat hypertension compared to patients with controlled hypertension has not been adequately determined. Patients with resistant hypertension are more likely to have target-organ damage, including carotid intima–media thickening, LVH, impaired renal function and microalbuminuria (Cuspidi et al. 2001). Respectively these patients have an unfavorable prognosis and are more likely to experience the combined outcome of death, myocardial infarction, congestive heart failure, stroke or CKD over time compared to those who have achieved goal blood pressure (Daugherty et al. 2012). Furthermore this risk increases if patients have CKD (De Nicola et al. 2013).

14   Summary

Hypertension is a global public health problem and is currently the number one factor in the global burden of disease. It is the major modifiable risk factor for heart disease, stroke and kidney failure. Renal parenchymal disease is both a common cause and also a complication of uncontrolled hypertension. The interaction between hypertension and CKD is complex and increases the risk of adverse cardiovascular and cerebrovascular outcomes. This is particularly significant in the setting of resistant hypertension commonly seen in patient with CKD. The pathophysiology of CKD associated hypertension is multi-factorial with different mechanisms contributing to hypertension. These include sodium dysregulation, increased sympathetic nervous system and renin angiotensin aldosterone system activity plus disturbance in auto-

regulatory system. Standardized blood pressure measurement is an important factor in establishing the diagnosis and management of hypertension in CKD. Use of ambulatory blood pressure monitoring provides an assessment of diurnal variation in BP commonly seen in CKD patients. The optimal BP target in the treatment of hypertension in general and CKD population remains a matter of debate and controversial despite recent guidelines and clinical trial data. Medical therapy of patients with CKD associated hypertension can be difficult, challenging, and even frustrating. Evaluation by a hypertension specialist may be required in the setting of commonly seen treatment resistant hypertension by excluding pseudo-resistance and treatable secondary causes. Use of combination regimen including appropriate diuretic choice, based on estimated glomerular filtration rate, is a crucial and key component of hypertension management in CKD patients. In addition to drug treatment non-pharmacological approaches including life style modification, most important of which is dietary salt restriction, should be included in the management of hypertension in CKD patients.

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