SEMINARS IN
NEPHROLOGY

Treatment of Hypertension in Chronic Kidney Disease

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Chronic kidney disease (CKD) is a major public health problem in the United States. It is estimated that nearly 20 million Americans have some degree of chronic kidney disease defined as an estimated glomerular filtration rate of less than sixty milliliters per minute or evidence of kidney damage by imaging study, biopsy, biochemical testing or urine tests with an estimated glomerular filtration rate more than sixty milliliters per minute. Hypertension is present in more than 80% of patients with CKD and contributes to progression of kidney disease toward end stage (ESRD) as well as to cardiovascular events such as heart attack and stroke. In fact the risk for cardiovascular death in this patient population is greater than the risk for progression to ESRD. Proteinuria is an important co-morbidity in hypertensives with CKD and increase risk of disease progression and cardiovascular events. Treatment of hypertension is therefore imperative. The National Kidney Foundation clinical practice guidelines recommend a blood pressure goal of <130 mmHg systolic and <80 mmHg diastolic for all CKD patients. Recent post-hoc analyses of the Modification of Diet in Renal Disease study indicate that lower blood pressure may provide long-term kidney protection in patients with nondiabetic kidney disease. Specifically a mean arterial pressure <92 mmHg (e.g. 120/80 mmHg) as compared to 102-107 mmHg (e.g. 140/90 mmHg) is associated with reduced risk for ESRD. In most cases achieving this goal requires both non-pharmacologic and pharmacologic intervention. Dietary sodium restriction to no more than 2 grams daily is important. In addition, moderate alcohol intake, regular exercise, weight loss in those with a body mass index greater than 25 kg/M^2 and reduced amount of saturated fat help to reduce blood pressure. The first line pharmacologic intervention should be an angiotensin converting enzyme inhibitor or angiotensin II type 1 receptor blocker in those with diabetes or non-diabetics with more than 200 mg protein/gram creatinine on a random urine sample. For non-diabetics with less than 200 mg protein/gram creatinine on a random urine sample, no specific first-line drug class is recommended. After initial dosing with an ACEi, ARB or other drug, a diuretic should be added to the regimen. Thereafter, beta-blockers, calcium channel blockers, apha blockers and alpha 2 agonists (e.g. clonidine) and finally vasodilators (e.g. minoxidil) should be added to achieve blood pressure goal. Combinations of ACEi and ARB are helpful in reducing proteinuria and may also lower blood pressure further in some some cases. Blood pressure should be monitored closely in hypertensive patients with CKD and both clinic and home blood pressure measurements may help the clinician adjust treatment.

KEYWORDS hypertension, chronic kidney disease, proteinuria, cardiovascular disease

More than 80% of patients with chronic kidney disease (CKD) have hypertension. Hypertension is an important risk factor not only for renal disease progression but also for cardiovascular events including myocardial infarction and stroke in those with CKD. Moreover, many studies have shown that the normal circadian rhythm of blood pressure is disrupted in patients with CKD. In particular, the normal nocturnal decrease in blood pressure is reduced or obliterated in patients with CKD. Lack of such a decrease in blood pressure has been linked to a higher likelihood of development of microalbuminuria, left ventricular hypertrophy, and, probably, progression of CKD.[1-4]

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However, there are no prospective studies of renal or cardiovascular outcomes in which blood pressure control was titrated to 24-hour ambulatory blood pressure measurement or aimed specifically at ameliorating nocturnal hypertension. Therefore, one must remember that treatment regimens are based mostly on repeated measures of blood pressure over time, performed during daytime hours (in a clinic or physician's office). Moreover, it should be noted that few randomized clinical trials have measured the impact of different levels of blood pressure lowering on renal outcomes, in particular, slowing the decrease in the glomerular filtration rate (GFR) and cardiovascular events. Studies that randomly assigned participants to different levels of blood pressure control did not show significant differences in progression of established nephropathy.[5-7] However, the United Kingdom Prospective Diabetes Study and the Appropriate Blood Pressure Control in Diabetes trial both showed a reduction in risk for onset or worsening of albuminuria in type 2 diabetic patients without established diabetic nephropathy.[7-9] Nevertheless, several studies have indicated that lower blood pressure in both diabetic and nondiabetic patients with nephropathy generally is associated with a slower decrease in GFR and/or a lower albumin excretion rate. However, there are no studies that have focused on controlling nocturnal blood pressure or used ambulatory blood pressure monitoring. For example, nocturnal lowering of blood pressure in CKD is a major goal of therapy for preventing renal disease progression and cardiovascular complications. Several key questions regarding blood pressure control in CKD remain to be answered. This article discusses the current treatment of hypertension in patients with CKD. An important principle in this discussion is that hypertension in CKD often is associated with other cardiovascular risk factors and treatment of hypertension should include assessing and, when possible, managing these factors.

Comorbid Factors Influence Progression of Hypertensive CKD

Several factors that are present in hypertensive patients with CKD should be kept in mind when treating hypertension. First, several studies indicate that lower GFR is a risk factor for subsequent development of end-stage renal disease (ESRD) and the rate of decrease in GFR is faster among those with lower GFR levels.[10-12] Second, approximately 60% of hypertensive patients have dyslipidemia and 40% of dyslipidemic individuals are hypertensive. Hypertriglyceridemia and low plasma levels of high-density lipoprotein are associated with onset of hypertensive renal disease.[13] Also, hypercholesterolemia correlates with global glomerulosclerosis in patients with biopsy examination–proven hypertensive nephrosclerosis.[14] Third, cigarette smoking has been associated with an increased rate of decrease in renal function in diabetic patients and those with hypertensive nephrosclerosis[15,16] Cigarette smokers with hypertensive nephrosclerosis and CKD have a markedly increased rate of progression of kidney disease despite similar levels of blood pressure control compared with nonsmokers.[17]

Cardiovascular Disease Risk

It is important to note that those with hypertension and CKD are at high risk for cardiovascular morbidity and mortality.[18] For example, long-term follow-up evaluation of patients with hypertensive CKD indicates that systolic blood pressure increase is a strong predictor of development of heart failure.[19] Hypertensive patients with CKD are far more likely to have a myocardial infarction, stroke, or cardiovascular death than those without CKD.[20] Importantly, after controlling for blood pressure level, those with kidney disease are at higher risk for these complications. Therefore, in addition to blood pressure control, treatment should include identification and management of other cardiovascular risk factors in hypertensive nephrosclerosis.

Treatment

Assessment and Management Guidelines

Assessment of patients with hypertensive kidney disease should include complete medical history, physical examination, hemoglobin A1C level, routine chemistries and urinalysis, urine protein/creatinine ratio renal sonogram, and appropriate serologic testing to look for mimics. This evaluation is aimed at identifying other causes of kidney disease such as familial diseases (eg, Alport's syndrome, Fabry's disease, focal segmental glomerulosclerosis) of the kidney as well as systemic lupus erythematosus, atheroembolic renal disease, multiple myeloma, systemic necrotizing vasculitides, hepatitis-associated glomerulonephritides, and cryoglobulinemia. Data from the African American Study of Kidney Disease and Hypertension (AASK) kidney biopsy examination pilot study indicate that these criteria correctly will identify patients with a pathologic picture consistent with hypertensive nephrosclerosis.[14] Further evaluation for causes other than hypertension including renal biopsy examination may be necessary in some cases depending on the results of serologic or renal imaging studies. The history and examination should include assessment of lifestyle and diet with particular attention to smoking, exercise, and overweight stature. For example, the presence of metabolic syndrome may confer increased risk for CKD.[21] In addition, a lipid panel and measurement of blood hemoglobin level are important because both dyslipidemia and anemia may increase risk for kidney disease progression in some patients.[13,22]

Treatment Goals

The National Kidney Foundation Clinical Practice Guidelines for Hypertension recommend a goal blood pressure for all hypertensive patients with CKD of less than 130 mm Hg systolic and less than 80 mm Hg diastolic. There is an important interaction between blood pressure, proteinuria, and kidney outcomes in patients with hypertension and CKD. There are 2 main treatment goals for those with hypertensive CKD: (1) lower the blood pressure and (2) block the renin-angiotensin-aldosterone system with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor

Table 1 Recommended BP Goal and Specific Agents for Treatment of CKD

Type of CKD	BP Goal	Preferred Agents for CKD, ± Hypertension	Other Agents to Reduce Cardiovascular Disease Risk and Reach BP Goal
Diabetic	<130/80	ACE inhibitor or ARB	Diuretic preferred, then β-blocker or CCB
Nondiabetic with spot urine total Protein-to-Creatinine ratio ≥200 mg/g	<130/80	ACE inhibitor or ARB	Diuretic preferred, then β-blocker or CCB
Nondiabetic with spot urine total Protein-to-Creatinine ratio ≤200 mg/g	<130/80	None preferred	Diuretic preferred, then ACE inhibitor ARB, β-blocker, or CCB
Transplanted CKD	<130/80	None preferred	CCB, diuretic, β-blocker, ACE inhibitor, ARB

ARB, Angiotensin II type I receptor blocker; CCB, calcium channel blocker.

blocker. The most important aspect of management of hypertensive CKD is to decrease blood pressure. An ACE inhibitor or angiotensin II type 1–receptor antagonist is recommended as the drug of first choice for decreasing blood pressure in all diabetic and in nondiabetic patients with urine total protein/creatinine ratio of more than 200 mg/g creatinine. However, other first-line agents are considered acceptable for those nondiabetic CKD and urine protein/creatinine ratios of less than 200 mg/g creatinine.[23] The choice of an ACE inhibitor or an angiotensin-receptor blocker as first-line treatment is based on results of the AASK and other studies in hypertensive patients with nondiabetic kidney disease.[5,24-27]

In the AASK study, nearly 1,100 African Americans with hypertensive nephrosclerosis and decreased GFR were randomized to either ramipril, metoprolol, or amlodipine once daily and other antihypertensive agents to achieve 1 of 2 mean arterial pressure goals of less than 92 mm Hg or 102 to 107 mm Hg. The ACE inhibitor ramipril was found to be more effective in reducing risk for rapidly decreasing GFR, ESRD, and death as compared with either amlodipine or metoprolol XL. In addition, ramipril treatment was associated with reduced proteinuria as compared with amlodipine. However, the AASK study did not find that a lower systolic blood pressure decreased the risk for ESRD among those with hypertensive nephrosclerosis. Meta-analyses of more than 1,800 nondiabetic proteinuric hypertensive patients support this blood pressure goal.[28-30] Systolic BP in the range of 120 to 130 is associated with lower risk for ESRD in patients with more than 1 g/d of urine protein excretion, whereas for those with lesser degrees of proteinuria decreasing the systolic blood pressure to less than 140 mm Hg was not. Recent post-hoc analyses of the Modification of Diet in Renal Disease study indicate that lower blood pressure may provide long-term kidney protection in patients with nondiabetic kidney disease. Specifically a mean arterial pressure <92 mmHg (e.g. 120/80 mmHg) as compared to 102-107 mmHg (e.g. 140/90 mmHg) is associated with reduced risk for ESRD.[31] Taken together these data support the National Kidney Foundation recommendations as shown in Table 1. ACE inhibitor–based regimens are recommended as first-line therapy for all groups except those with a very low level of proteinuria. Most patients with hypertensive CKD, including those with diabetic nephropathy and hypertensive nephrosclerosis, have stage 2 hypertension; therefore, to achieve and maintain BP goal both nonpharmacologic and multidrug therapy usually is necessary.

Nonpharmacologic Approaches

All patients should be educated about lifestyle modification to include smoking cessation, regular aerobic exercise, moderate alcohol consumption, and weight loss for overweight (weight, >24 and >27 kg/m^2 for women and men, respectively) individuals. Smoking cessation may slow progression of kidney disease and reduction in alcohol consumption and exercise and weight loss also can decrease blood pressure markedly. Finally, for those on high sodium intake, decreasing the dietary sodium may have a profound effect on systolic blood pressure, including in African Americans. Diets rich in fruits and vegetables (high fiber) and low-fat dairy products and low in saturated fat and low (Dietary Approaches to Stop Hypertension diet) are effective in decreasing blood pressure.[32]

Pharmacologic Approaches

Consistent with the Joint National Committee 7 recommendations, all patients with a systolic blood pressure of 160 mm Hg or higher should begin with 2-drug therapy in addition to nonpharmacologic intervention. The use of a once-daily ACE inhibitor combined with a diuretic is recommended by the National Kidney Foundation. For those with an estimated GFR of less than 50 mL/min, a loop diuretic administered 2 or 3 times daily is preferable to a thiazide because of the reduced diuretic effect of thiazides and thiazide-like diuretics at lower GFRs. If the BP goal is not achieved on this regimen then the addition of a once-daily calcium channel blocker (or β-blocker) is reasonable. If 3 agents do not control BP then the addition of a once-daily β-blocker or calcium channel blocker is the next step. Available data do not clearly indicate a preference for a specific class of calcium channel blocker as an add-on agent. In large-scale clinical trials in nephropathy, the addition of dihydropyridine calcium channel blockers or nondihydropyridine calcium channel blockers have been used. In these studies, no apparent difference in efficacy of the BP decrease or outcomes have been shown.[33,34] The subsequent addition of a long-acting α-blocker or centrally acting a-2 sympathomimetic such as clonidine or guanfacine may be used. It is important to mention that adding on a mineralocorticoid antagonist such as spironolactone or eplerenone may be an effective way of controlling blood pres-

sure, particularly in CKD patients with low-normal or low serum potassium concentration. There are no well-controlled trials of combinations of these agents with other antihypertensive agents in patients with CKD. In 1 study, combining an ACE inhibitor with eplerenone in hypertensive patients with proteinuria was an effective way of decreasing blood pressure, however, the safety of this combination requires further study.[35] Finally, for selected individuals the addition of a vasodilator such as hydralazine or minoxidil may be needed.

Monitoring BP Response

BP measurement should be performed frequently, and preferably by the patient with a home BP monitor. Home BP readings should be recorded by date and time and reviewed by the treating physician. The patient's home BP device should be tested and compared with office BP equipment to ensure that the office readings reflect home readings for accuracy. After initiation of antihypertensive therapy in those with CKD, the BP should be measured at least every 2 weeks until the target is reached and then monthly for 3 months to ensure stability and allow for titration of medications as needed. After establishment of the BP goal, quarterly visits for BP measurements should be performed to ensure maintenance of goal BP and to reassess renal function. Renal function monitoring should include measurement of serum creatinine level to estimate the GFR and measurement of the urine protein/creatinine ratio. If BP control cannot be achieved with combining lifestyle modifications and multidrug approaches as outlined earlier then evaluation of other secondary causes of hypertension including primary aldosteronism and renovascular hypertension should be performed. However, compliance and adherence to diet, lifestyle modifications, and medication (including ability to pay for antihypertensive agents) should be investigated before further diagnostic studies are performed.

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