Hypertension in end-stage kidney disease
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Abstract
Hypertension remains a leading etiology of end-stage kidney disease. The disease has a complex pathophysiology and contributes to a wide array of morbidities and mortality for patients across the globe. Due to the lack of published data on the subject, diagnosing and monitoring hypertension in the dialysis population poses a great challenge, as currently there are no published blood pressure target goals and in-center monitoring is often not reliable. Moreover, the management of this condition involves conservative approaches for both adjusting dialysis prescriptions and limiting dietary fluid and sodium intake. Therapy is often escalated with pharmacologic agents, of which emerging data suggest that it may be useful to use certain drug classes initially. However, professional guidelines do not provide specific drug therapy recommendations at this time.

Key words: Dialysis, End-stage kidney disease, Hypertension, Management, Pathophysiology

Introduction
Hypertension remains prevalent among end-stage kidney disease (ESKD) patients. Not only does it significantly impact the overall well-being of patients but it also remains a challenging portion of patient care for nephrologists. To date, the topic of hypertension in ESKD remains controversial. Thus, the purpose of this review is to highlight and summarize the current data and its clinical implications in the treatment of this complex patient population. Beyond discussing the prevalence and pathophysiology of hypertension among ESKD patients, we will also highlight the data on recent blood pressure (BP) goals and monitoring. Finally, we will explore the current literature as it relates to both non-pharmacologic and pharmacologic treatments for hypertension in ESKD patients.

Prevalence
Although commonly observed, the exact prevalence of hypertension among patients undergoing renal replacement therapy varies widely from center to center around the world; data overall is lacking for exact prevalence values in several countries. Data from the United States show up to 70%–88% of all ESKD patients experience some form of hypertension.[1] One 2011 study showed that only 38% of a patient population on hemodialysis (HD) had BP controlled with pharmacologic therapy.[2] Another 2003 study showed that 86% of a patient population on HD had systolic BPs more than 150 mmHg or diastolic BPs more than 85 mmHg.[3] Studies from the early 1990s initially suggested that patients on peritoneal dialysis (PD) had better BP control when compared to patients on HD. However, more recent studies have shown a high burden of hypertension affecting up to 93% of patients at time of PD initiation and up to 79% of those PD patients already being treated with pharmacotherapies.[4]

Pathophysiology
The pathophysiology of hypertensive changes among patients with ESKD is complex and involves several mechanisms of intrinsic vascular control, volume status, and sodium loading [Figure 1]. One of the primary mechanisms responsible for hypertension in ESKD patients is volume overload beyond...
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The percentage of interdialytic weight gain above one’s clinically defined dry weight. Although clinically difficult to measure exactly due to the inability to reliably measure one’s extracellular volume status, a patient’s dry weight can be defined as clinically the weight at which there are no signs of hypervolemia or hypovolemia. Dry weight is closely related clinically with BP. Among ESKD patients, the impaired ability to properly renally excrete water and sodium results in an increase in extracellular volume, cardiac output, and subsequently systemic BP. The percentage of interdialytic weight gain above one’s dry weight is linked to increased pre-HD systolic BP and greater reduction in systolic BP from pre- to post-HD in younger non-diabetic patients. Greater increases in interdialytic weight gain have also been linked to increased mortality. Sodium load also plays a significant role in hypertension in ESKD patients. It is known that sodium accumulation contributes to greater extracellular fluid volume and hypertension. However, it has also been postulated that sodium triggers endothelial-mediated vasoconstriction further leading to hypertension. In addition, it has been shown that ESKD patients have high BP sensitivity to sodium. This can be especially seen when examining the effect of dialysate sodium concentration on BP. As traditionally seen through the concept of sodium modeling, higher dialysate concentrations of sodium traditionally used to combat intradialytic hypotension often contribute to increased thirst and further interdialytic weight gain. Other factors involved in the pathogenesis of hypertension among ESKD patients include overactivity of plasma renin; inability to properly metabolize catecholamines; premature arterial stiffness due to impaired calcium and phosphate handling; and endothelial dysfunction due to ramped responses to inherent vasodilators such as nitric oxide. Furthermore, although BP typically declines from the start to the end of each dialysis session, intradialytic hypertension occurs in 5–15% of cases. Such a phenomenon involves an increase in systolic BP by more than 10 mmHg from pre- to post-dialysis and has been attributed to sodium exposure and endothelial dysfunction mediated by vasoconstrictors.

BP Goals and Monitoring

Kidney Disease Outcomes Quality Initiative guidelines in 2005 initially recommended a pre-dialysis BP goal of <140/90 mmHg or post-dialysis goal of <130/80 mmHg for ESKD patients. However, observational studies found that pre- and post-dialysis BP values had either no correlation or a U- or J-shaped correlation with mortality. Further, such BP readings have been deemed imprecise. Therefore, updated guidelines and data have stepped away from such recommendations, not giving any concrete targets for BP among ESKD patients. As per 2020 Kidney Disease Improving Global Outcomes (KDIGO) recommendations, extrapolating BP targets from the general population to ESKD patients may be reasonable. Such recommendations include a BP target of ≤130/80 mmHg as per American College of Cardiology guidelines. Non-pharmacologic Management

Sodium intake and volume control remain cornerstone elements of non-pharmacologic BP management for patients requiring renal replacement therapy. As mentioned above, sodium plays a pivotal and complex role in the pathophysiology in ESKD patients. Overall, it is recommended to limit dietary sodium intake to <2 g daily. Doing so helps to limit interdialytic weight gain, thirst, and allows clinicians to more easily achieve patients’ dry weights. As introduced above, achieving dry weight is imperative to BP control. A dry weight reduction of 0.9 kg over an 8-week period resulted in a 6.6/3.3 mmHg interdialytic BP reduction according to the Dry Weight Reduction in Hypertensive HD Patients Trial. Optimizing ultrafiltration during dialysis also helps to achieve adequate BP control. However, such tight control must be balanced by the risks of intradialytic hypotension, arteriovenous fistula clotting, and complications requiring hospitalization. Furthermore, ultrafiltration rates exceeding 12.4 ml/kg/hr have been shown to be associated with increased mortality. Among HD patients, utilizing longer dialysis times have beneficial outcomes for BP control. Several randomized trials have illustrated that longer dialysis sessions of 8 h 3 times a week or more frequent dialysis sessions up to 6 times a week led to lower overall BP and patients required less anti-hypertensive medications. Among PD patients, adapting the PD prescription to a patient’s membrane characteristics is useful for limiting hypertension. Observational studies illustrate that high transporters carry overall higher risks of uncontrolled BP as well as higher overall mortality. This may be secondary to sodium and water reabsorption when high transporters have been prescribed longer dwell times with glucose-containing solutions. It may thus be considered to switch such high-transport patients to automated PD to maximize ultrafiltration. For low transport patients, clinicians should also be aware of shorter dwell times leading to sodium sieving and thus limiting net diffusive sodium removal. The type of dialysate also plays a role in BP control in PD. The beneficial effects of icodextrin on BP control have been illustrated in several randomized studies. A double-blind trial with 50 hypertensive PD patients randomized to icodextrin or 2.27% glucose solutions during the long dwell for 6 months.
resulted in overall fewer anti-hypertensive medications to achieve BP control in the icodextrin group. Moreover, the use of icodextrin avoided the risks of peritoneal membrane damage and adverse metabolic effects caused by hypertonic glucose PD solutions.

**Pharmacologic Management**

BP control using medications should be implemented for patients on dialysis if conservative measures fail [Figure 2]. Highlighting the need for medication use in such cases, a meta-analysis of five randomized control trials showed a 31% reduced risk of cardiovascular mortality when anti-hypertensive medications were used. Among all medication classes, clinicians must often consider a drug’s half-life, dialyzable properties, cardiovascular benefits, and side effects when choosing anti-hypertensive therapy for ESKD patients. The choice of such medications often is individualized as per the patient’s HD needs, extent of pill burden, and intra-/inter-dialytic BP readings.

Various pharmacologic classes have shown beneficial roles in treating hypertension in ESKD patients. The Fosinopril in Dialysis Trial (FOSIDIAL) enrolled 397 HD patients with left ventricular hypertrophy. The results showed significant lowering of pre-dialysis BP with fosinopril, but no significant difference was found between fosinopril and placebo in preventing adverse cardiovascular events. Similarly, the Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study trial showed no significant benefit of olmesartan use in 469 HD patients in relation to all-cause mortality or adverse cardiovascular events.

Overall, renin-angiotensin-aldosterone (RAAS) blockade in HD patients does not appear to confer the same benefits as such therapies do in the general population. In contrast to HD patients, the effects of RAAS blockers in PD patients have been more beneficial. A prospective cohort study of 306 PD patients showed a 62% lower risk of overall cardiovascular mortality when treated with RAAS blocking drugs. A further meta-analysis showed a slower rate of residual kidney function decline in PD patients taking RAAS-blocking medications.

With respect to dihydropyridine calcium channel blockers, amlodipine reduced all-cause mortality and fatal myocardial infarction by 47% in HD patients. Such effect may be enhanced by the drug’s poor dialyzability.

Mineralocorticoid receptor antagonists (MRAs) have shown concrete clinical benefit in HD patients. The Dialysis Outcomes Heart Failure Aldactone Study found a reduced risk of cardiovascular mortality or cardiovascular hospitalization with spironolactone use in 309 oligoanuric HD patients, with drug discontinuation due to hyperkalemia at 1.9%. Similar benefits were observed in a study that showed reduced cardiovascular mortality in 253 patients on HD and PD when MRAs add-on therapy was used.

Beta-blockers have recently emerged as promising treatments for hypertension in ESKD patients. In the Hypertension in HD Patients Treated with Atenolol or Lisinopril (HDPAL) trial, 200 HD patients with hypertension and left ventricular hypertrophy were randomized to receive lisinopril or atenolol over 12 months. Trial results showed no significant difference in ambulatory BP readings. However, the study showed more potent BP lowering in the atenolol group with a 2.3-fold higher risk of adverse cardiovascular events in the lisinopril group. The results were attributed to better intradialytic arrhythmia control among dialysis patients taking beta-blockers. Furthermore, the beta-blocker carvedilol has been associated with reduced incidence of intradialytic hypertension. More recently, a large multicenter Taiwanese study of 101,222 HD patients compared dialyzable beta-blockers (atenolol, metoprolol, and bisoprolol) with non-dialyzable beta-blockers (carvedilol and propranolol) on outcomes of all-cause mortality and major adverse cardiac events over 7 years of treatment. Contrary to prior school of thought, the use of dialyzable beta-blockers was associated with a significantly lower risk of both all-cause mortality and major adverse cardiac events, suggesting that properties other than...
the drug’s dialyzability contributed to their observed clinical benefits.

With regard to other medication classes, observational studies have shown that continuation of loop diuretics in patients with residual renal function can play a role in limited interdialytic weight gain.[31] Other medication classes such as alpha-agonists, alpha-blockers, and vasodilators have been used in ESKD as add-on therapies, individualizing such therapies to patient tolerance and side effects. Overall, recent clinical evidence suggests that beta-blockers followed by calcium channel blockers can be considered as first-line anti-hypertensive therapy for HD patients; the current evidence suggests benefits for RAAS blockade among PD patients. MRA agents have shown benefit in both HD and PD. Despite this, recent KDIGO guidelines do not specify a preferred first-line anti-hypertensive regimen in dialysis patients.[8]

Conclusion

The treatment of hypertension in ESKD patients remains a clinically challenging task for clinicians around the world [Figure 2]. The high prevalence of this disease continues to motivate nephrologists to diagnose and treat it. However, its pathophysiology remains complex, and understanding it can continue to drive our therapeutic options. The current literature does not provide clear guidance for target BP goals; however, BP goals may be able to be extrapolated from the general population to guide therapy. Monitoring BP may be best in the ambulatory setting and encouraging patients to be attentive of their home BP recordings appears best. A variety of non-pharmacologic options have been proposed for hypertension treatment, including an array of dialysis prescription alterations as well as individual restrictions on fluid and sodium intake. If pharmacologic options are required, beta-blockers and calcium channel blockers, among other agents, may be best in HD, although some data do suggest benefit from the use of RAAS blockade in PD patients. Overall, other guidelines still do not suggest preferred first- and second-line anti-hypertensive agents in the ESKD population, and further data are needed to make more concrete recommendations.

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