Hypertension, Living Kidney Donors, and Transplantation: Where Are We Today?

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Hypertension is a prevalent problem in kidney transplant recipients that is known to be a "traditional" risk factor for atherosclerotic cardiovascular disease leading to premature allograft failure and death. Donor, peritransplant, and recipient factors affect hypertension risk. Blood pressure control after transplantation is inversely associated with glomerular filtration rate (GFR). Calcineurin inhibitors, the most commonly used class of immunosuppressives, cause endothelial dysfunction, increase vascular tone, and sodium retention via the renin-angiotensin-aldosterone system resulting in systemic hypertension. Steroid withdrawal seems to have little impact on blood pressure control. Newer agents like belatacept appear to be associated with less hypertension. Transplant renal artery stenosis is an important, potentially treatable cause of hypertension. Dihydropyridine calcium channel blockers mitigate calcineurin inhibitor nephrotoxicity and may be associated with improved estimated GFR. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are not recommended in the first 3 to 6 months given their effects on reduced estimated GFR, anemia, and hyperkalemia. The use of ß-blockers may be associated with improved patient survival, even for patients without cardiovascular disease. Living donation may increase blood pressure by 5 mm Hg or more. Some transplant centers accept Caucasian living donors with well-controlled hypertension on a single agent if they agree to close follow-up.

Key Words: Hypertension, Human, Kidney, Transplantation, Immunosuppression

Introduction

Kidney transplant recipients are at increased risk of cardiovascular disease, major adverse cardiovascular events, and death compared with the general population.[1,2] Hypertension is a "traditional risk factor" for cardiovascular disease (CVD) that is associated with premature allograft failure after transplantation effecting more than 90% of recipients.[3,4] In January 2014, the Eight Joint National Committee (JNC 8) guidelines for the management of hypertension were published.[5] Here, the management of hypertension in kidney transplant recipients and donors is discussed, with a special focus in the new guidelines, the effects of immunosuppression in blood pressure (BP), transplant renal artery stenosis (TRAS), and the use of hypertensive live kidney donors.

Definition and Diagnosis of Hypertension after Kidney Transplantation

JNC 8 stepped back from prior definitions of hypertension citing lack of evidence to support such rigid categories. However, clear thresholds for the use of pharmacologic agents were defined (Table 1). In adults with CKD and/or diabetes, pharmacologic treatment is recommended when systolic BP (SBP) exceeds 140 mm Hg or diastolic BP (DBP) exceeds 90 mm Hg.[5] There were no specific recommendations for subjects with proteinuria. The authors acknowledged that these recommendations are based on expert opinion citing the absence of high-quality evidence in this patient population. Target BP readings of 140/90 mm Hg represents a change from the JNC 7 guidelines where the goal BP for CKD/DM patients was <130/80 mm Hg. The 2012 Kidney Disease: Improving Global Outcomes guidelines recommend a target BP of 140/90 mm Hg for subjects with CKD and ≤130/80 mm Hg for proteinuric patients or kidney transplant recipients.[6] The European Renal Best Practice Guidelines endorsed the Kidney Disease: Improving Global Outcomes target BP and included definitions of hypertension according to the method used for BP measurement (Table 2).[7,8]

Options for measuring BP include office BP monitoring (OBPM), home or self-BP monitoring (SBPM), and 24-hour ambulatory monitoring (ABPM). OBPM may be elevated by 3 to 4 mm Hg more than the daily average BP.[9] In a study of 49 kidney transplant recipients, ABPM was the most sensitive method, detecting 84% of uncontrolled hypertension, followed by SBPM (71%) and OBPM (47%).[10] Using ABPM, Kayrak and coworkers[11] reported that the prevalence of masked hypertension was 39%. Benefits of ABPM include the ability to detect nocturnal BP changes that predicts CVD and kidney allograft outcomes. The prevalence of nocturnal hypertension after kidney transplantation has been reported to be between 29%[12] and 79%.[13] Nocturnal hypertension 1 year after transplant is associated with the development of a lower GFR by an average of 4.6 mL/min/1.73 m^2 for every 10% increase in nocturnal SBP (P <0.04).[14] Additionally, lack of nocturnal dipping seems to be associated with concentric left ventricular hypertrophy.[15] It has been suggested that "pharmacological dipping" by administering BP medications at night (chronotherapy) may be beneficial in terms of cardiovascular end points although there is no

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clinical trial evidence in transplant recipients to confirm this concept.

Epidemiology

Before the approval of cyclosporine in 1983 by the Food and Drug Administration, nearly half of all transplant recipients were hypertensive.[16] Currently, more than 90% of calcineurin inhibitor (CNI)-treated kidney allograft recipients are hypertensive.[17-19] Conversely, in 1 study, only 5% of kidney transplant recipients were normotensive as defined by AMBP less than 130/80 mm Hg without treatment.[12] This change in the reported incidence of hypertension may reflect changing definitions of hypertension over time; thus, direct comparisons may be misleading.

Hypertension negatively affects graft and patient survival. A retrospective cohort of 1666 kidney transplant recipients found that after adjusting for the effects of rejection and allograft function, each 10 mm Hg increase in SBP was associated with approximately 5% increased risk for graft failure and death.[3] In a post hoc analysis of the folic acid for vascular outcome reduction in transplantation trial, after adjusting for demographics, transplant characteristics, and CVD risk factors, each 20 mm Hg increase in baseline SBP was associated with a 32% increase in CVD risk and a 13% increase in mortality risk. After similar adjustment, at DBP less than 70 mm Hg, each 10 mm Hg decrease in DBP was associated with a 31% increase in CVD risk and mortality. Interestingly, at DBP more than 70 mm Hg, there was no significant relationship with outcomes.[20]

CLINICAL SUMMARY

- Hypertension is common after kidney transplantation.
- Hypertension is a risk factor for premature allograft failure and death.
- Blood pressure control after transplantation is inversely associated with GFR and may be impacted by choice of immunotherapy.

Hypertension may also affect the development of acute rejection. In a study of 1641 kidney transplant recipients, elevated BP levels after transplantation identified patients at high risk of acute rejection independently of graft function (odds ratio 4.24, 95% confidence interval [CI] 3.41 to 5.26 based on a 20 mm Hg change). Higher BP levels were associated with earlier acute rejection, and for every BP level, the use of antihypertensives was associated with decreased risk of acute rejection.[21] These findings have not been reproduced by other studies, and whether hypertension is a cause or manifestation of acute rejection under such circumstances remains unclear.

Pathogenesis and Risk Factors

The pathogenesis of hypertension is both complex and multifactorial (Fig 1). In addition to the traditional risk factors encountered in the general population, unique factors pertain to transplant recipients including pre-existing recipient, donor, and peritransplant factors that include immunotherapy and allograft dysfunction (Table 3). In a prospective, observational study of 85 transplant recipients not on cyclosporine with stable kidney function, recipients without a family history of hypertension engrafted with a kidney procured from a donor with a family history of hypertension were more likely to be hypertensive than those transplanted with kidneys obtained from donors without a family history of hypertension. When the recipient had a family history of hypertension, this effect was not seen.[25] In a follow-up study of the same patients, recipients of kidneys from hypertensive families developed higher DBPs and greater degrees of acute kidney injury during acute rejections than recipients of kidneys from normotensive families.[26]

The role of native kidneys in the pathogenesis of post-transplant hypertension has not been completely elucidated. Native kidneys can induce hypertension through activation of the sympathetic nervous system or increased renin secretion.[27,28] A few small studies have shown improved blood pressure control after bilateral native nephrectomies, regardless if they occur before or after kidney transplantation.[29-31] In contrast, a study of 158 living donor transplant recipients found no BP improvements in those treated with bilateral nephrectomies.[32]

Blood Pressure Goal Early after Transplantation

It has been suggested that BP be "permitted" to remain elevated early after transplantation to optimize kidney perfusion and minimize the risk of delayed graft and need for dialysis. A lax therapeutic BP goal of <160/90 mm Hg may be appropriate immediately after surgery.[33] Evidence-based recommendations surrounding such practice are lacking. Clinical observation supports the concept that BP is often labile within the first week after transplantation. Competing variables often need to be balanced. For example, hypotension because of vasodilatation is extremely common during and after general anesthesia. This can be exacerbated by the use of lymphocyte-depleting antibody induction therapy. This in turn leads to the administration of large volumes of crystalloid (3 or more liters of either lactated ringers or normal saline) that in turn cause intravascular volume expansion, edema, and hypertension as vasodilatation dissipates. The experienced clinician has learned to use short-acting hypertensive agents selectively early after transplant to achieve "reasonable" if not perfect BP control. Agents such as hydralazine that can be ordered with "hold parameters" are most useful in the hospital.

Role of Immunosuppression

Glucocorticoids (GCs) and CNIs, two of the most widely used classes of immunosuppressive agents, have been