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Review Article

Hypertension in Renal Transplant Patient

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ABSTRACT

Newer potent immunosuppressive medications show marked improvements in short-term allograft function but long-term allograft survival continues to be inadequate. Non immunological factors have been increasingly identified as potentially important mediators of reduced long-term renal allograft function known as chronic allograft nephropathy. Hypertension is considered as one of this non immunological risk factor for progressive graft dysfunction. Hypertension is common after transplantation and is present in 50% to 90% of renal transplant recipients. Increasingly severe post-transplantation hypertension is associated with increasing risk of graft loss, and control of hypertension is associated with improved graft survival. Hypertension is a risk factor for both CV disease and kidney graft failure. Here we discussed about post transplant hypertension and its impact on graft function. We also discussed about causes of HT following renal transplant with special emphasis on role of immunosuppressive medication in development of hypertension. At the end we have reviewed management of post transplant HT.

Key words: Antihypertensive drug, Cardiovascular disease, Hypertension, Immunosuppressant drug, Kidney transplant, Renal transplant recipient

INTRODUCTION

Patient with end stage renal disease have gone either renal transplantation or dialysis process for survival of life. Among these two options renal transplantation has emerged as the treatment of choice for many patients with end-stage renal disease[1]. In renal transplant recipient (RTR) the success rates in most centers, measured one year after kidney transplant is exceed up to 95 %[2].

Newer potent immunosuppressive medications show marked improvements in short-term allograft function but long-term allograft survival continues to be inadequate. Allograft failure being one of the most important reasons for (re)initiating long-term dialysis treatment[3] and for allograft failure many non immunological factors have been increasingly identified as potentially important mediators of reduced long-term renal allograft function known as chronic allograft nephropathy[4, 5]. One of such nonimmunological factor is hypertension which have been observed among patients whose allograft failed the most rapidly[6, 7].

In RTR predominant cause of death more than 1 year after transplantation remains cardiovascular disease (CVD), followed by infection and malignant disease[8]. One of the risk factor for both CVD and kidney graft failure after RTR is Hypertension.

In these RTR patients various data shows that increasingly post-transplantation hypertension is associated with increasing risk of graft loss and control of hypertension is associated with improved graft survival[9] and also control of hypertension significantly reduces morbidity and mortality[10, 11]. Close monitoring of blood pressure after transplantation and prescribe appropriate antihypertensive drug/s requires for preservation of kidney function (or slowing of kidney disease progression) and decreasing CVD risk.

Here we reviewed hypertension in RTR and its impact on allograft function and survival. We also reviewed antihypertensive drugs used to treat hypertension with recent guidelines for treatment of hypertension.

Definition of Hypertension & Goals of treatment: Hypertension is defined by the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) as systolic BP (SBP) >140 mm Hg, diastolic BP >90 mm Hg, or the need for antihypertensive therapy[12].

Adult blood pressure thresholds for defining hypertension at various time is mention in Table I. Definition of hypertension, treatment goal in all patients and in highly risk patient described by various regulations is mentioned in table II. Among these regulations only KDOQI describe treatment goal in RTR which is <130/80 mm of Hg[12, 13, 14, 15, 16, 17].

Pathogenesis of post-transplant hypertension: Systemic blood pressure is mainly regulated by the balance between cardiac output and peripheral vascular resistances, which in turn depend on the interplay of a number of factors including salt and water excretion, the balance between vasoconstrictor and vasodilator agents, the activation of sympathetic system, heart rate, stroke volume, blood

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Table 1: Adult blood pressure thresholds for defining hypertension

Method of measurement	Threshold (mm Hg)
Office or Clinic	140/90
24 hr average	125-130/80
Day time	130-135/85
Night time	120/70
Home (day time)	130-135/85

viscosity, arteriolar radius, etc. The kidney plays a central role in regulating blood pressure as it controls the excretion of sodium and water and in the meantime produces a number of vasoconstrictor and vasodilator substances that regulate the tone of the vascular system.

Most transplant candidates are already hypertensive before renal transplantation, but while a well functioning transplanted kidney may allow improvement in blood pressure through a better regulation of homeostatic mechanisms, a number of other factors may trigger or maintain a hypertensive status. In this context, an important role may be played by immunosuppressive drugs. Purine synthesis inhibitors, namely azathioprine and mycophenolate salts, and mTOR inhibitors, sirolimus and everolimus, do not interfere with blood pressure, while there is evidence that both Calciurine inhibitor and glucocorticoids can exert hypertensive effects.

Magnitude of problem: Hypertension is common after transplantation and is present in 50% to 90% of renal transplant recipients[18, 19]. The Collaborative Transplant Study (CTS) registry has documented that only 8% of transplant recipients had a systolic blood pressure below 120 mm Hg at 1 year; 33% had a blood pressure in the pre-hypertension range; 39% had stage 1 hypertension; and 20% had stage 2 hypertension despite antihypertensive therapy. Systolic blood pressure is highest immediately after transplantation and declines during the first year[7].

Etiology of hypertension in renal transplant patient: Many factors have been identifying which are responsible for development of hypertension after renal transplantation.

Preexisting hypertension, tacrolimus and to a greater degree cyclosporine, corticosteroids, quality of donor organ, delayed graft function, chronic allograft nephropathy, high body mass index (BMI) or excess weight gain, acute rejection episodes independent of creatinine clearance, recurrent or de novo glomerulonephritis, and transplant renal artery stenosis have all been implicated in post-transplantation hypertension. In rare cases, excess renin output from the native kidneys has also been suggested to contribute to post-transplantation hypertension[18]. It is also reported that factors related to the presence of the native kidneys also responsible for development of hypertension[20, 21, 22].

Immunosupression and its association in RTR: Hypertension in RTR patient develops mainly due to concomitant treatment given to the patient like immunosuppressant drug therapy which is required to prevent allograft rejection[23]. Some important immunosuppressant drugs and its effect on hypertension are defined as bellow.

Corticosteroids: Steroid which is prescribe to RTR produce hypertension by variety of mechanisms that include mineralocorticoid-induced sodium retention, increased responsiveness to vasoconstrictors like endothelin-I and angiotensin II and decreased vasodilator production like prostaglandins[24]. The estimated incidence of glucocorticoid-associated hypertension is 15%, with the effect highest in those with pre-existing hypertension[25, 26]. If considering to Vincenti F *et al*.[27], there is no significant BP difference is observed between steroid treated, steroid withdrawal and steroid free RTR but in steroid free and steroid withdrawal RTR rejection rate is higher than steroid treated patient.

Calcineurin inhibitors: Prior to the introduction of cyclosporine as a maintenance immunosuppressor in 1983, post transplant hypertension was seen in less than half of all patients; since the introduction of calcineurin inhibitors, systemic hypertension is now found in 70–90% of recipients[28, 29, 30].

This Calcineurin inhibitors cause's reduction in GFR and renal blood flow, increase in sympathetic nervous tone, increase of intra-renal vascular resistance and increased sodium retention, a rise in peripheral vascular resistance and vasoconstriction of the afferent arterioles which produces vessel wall damage and impaired autoregulatory function[31, 32, 33]. These may be the result of imbalance between vasoconstrictive (endothelin and thromboxane) and vasodilator factors (NO and prostacyclin) in Cyclosporine (CsA) and tacrolimus (TAC) treated patients[34, 35]. Now it is known that tacrolimus has less of an effect on BP than cyclosporine[36] when used with prednisone and mycophenolate mofetil. While decrease in glomerular filtration and enhanced sodium reabsorption in the renal tubules was observed universally during both TAC and CsA administration[36, 37].

Hypertension in patients taking cyclosporine in combination with corticosteroids has been described in 50% to 80% of cases[32]. CsA induced hypertension is characterized by nocturnal hypertension[31]. In RTR, decreasing the dose of cyclosporine by 50% at 1 year or longer post–kidney transplant has decreased the risk of hypertension in patients treated with steroids and mycophenolate mofetil without increasing rejection risk[38].

Mycophenolate Mofetil: Mycophenolate Mofetil is not nephrotoxic and does not have any hypertensive effect, does not cause diabetes or hyperlipidaemia[32, 33, 39].

Sirolimus: In Phase III studies using sirolimus in combination with CsA, there was a higher frequency of hypertension than control groups. It is possible that sirolimus potentiates the nephrotoxic effect of cyclosporine, which would explain the increase of blood pressure[40].

Table 2: Definition of hypertension and goals of treatment defined by various agencies

Guideline	Hypertension definition	Treatment goals (mm Hg) All	In Sub-populations
JNC 8 2013	≥140/90	<140/90	<130/80 in diabetics and CKD
WHO ISH 2003	≥140/90	<140/90	<130/80 in diabetes
KDOQI 2004			<130/80 in Renal transplant recipient
NHBPEWG Children 2004	≥95th percentile [a]	<95th percentile [a]	<90th percentile[a] in concurrent conditions [b]
ESH ESC 2007	≥140/90	<140/90	<130/80 in diabetes and high risk patients
USPSTF 2007	≥140/90	<140/90	<130/80 in diabetics and CKD

[a] *For gender, age and height on three occasions.*

[b] *Concurrent conditions are CKD, diabetes and hypertensive target organ damage*

Impact of hypertension on Kidney transplant recipient health: In the general population, there is strong evidence that treatment of hypertension is effective in preventing CVD and in retarding the progression of CKD. If considering hypertension in RTR, blood pressure is a risk factor for CVD and Chronic allograft injury.

The leading cause of death in RTR is CVD, making it likely that treatments that reduce the risk of CVD in the general population will also be cost-effective in RTR.

Observational studies have shown that hypertension is an independent risk factor for CVD after kidney transplantation[41, 42]. There are also studies linking hypertension to poor graft function, although it is difficult to separate cause and effect relationships in these studies[3, 7, 43].

It is also reported that recipients without a family history of hypertension engrafted with a kidney derived from a hypertensive family developed hypertension more frequently than those with a kidney transplant derived from a normotensive family or recipients with familial hypertension (in whom the origin of the kidney did not influence the prevalence of posttransplant hypertension). In the follow-up study of these patients, recipients of kidneys derived from hypertensive families developed higher diastolic BPs and greater degrees of acute kidney injury during acute rejection than the other recipients[44].

According to JNC 8 report, systolic BP (SBP) >130 mm Hg, diastolic BP >80 mm Hg is require to prevent kidney damage. Increase in BP produces negative effects on transplant and patient survival and outcomes. One retrospective cohort study on 1,666 RTR[18] shows that increase in each 10 mm Hg of SBP was associated with a 5% increased risk of transplant failure and death. In another study of nearly 25,000 primary deceased donor kidney recipients, improved long-term transplant outcome was observed in patients with SBP >150 mm Hg at 1 year posttransplant when SBP was controlled to <140 mm Hg at 3 years versus those with sustained increases in SBP[42].

Chronic allograft nephropathy and Recurrent disease are the second and third most common cause of long-term transplant loss after death with function respectively and often is associated with new-onset or worsening hypertension[45, 46].

Management of hypertension: Guidelines from the general population recommend targeting <140/90 mm Hg for all patients, even low-risk Patients. However, these same guidelines recommend blood pressure targeting <130/80 mm Hg for high-risk patients, such as patients with diabetes and CKD[12, 13].

Therapeutic lifestyle modification is first-line therapy for patients with renal transplantation[47]. For optimal management of hypertension after transplant require manipulating immunotherapy when possible. For example, patients using cyclosporine often experience improved BP control after dose reduction or conversion to either tacrolimus or sirolimus[36, 38, 48]. Despite this it's also require to use single or combination of two or more antihypertensive drug to control hypertension.

Choice of antihypertensive agent: A number of small randomized trials have demonstrated the efficacy and safety of lowering blood pressure with most classes of antihypertensive medications.

At present KDIGO guideline on care of kidney transplant recipient, does not recommend any class of antihypertensive agents as preferred for long-term therapy for reducing CVD or improving long-term graft survival and also no antihypertensive agent is contraindicated in RTR[49].

The choice of initial antihypertensive agent may be determined by the presence of one or more common post transplant complications that may be made better or worse by specific antihypertensive agents.

Antihypertensive agents:

ACE Inhibitors (ACEI)/ARBs: The use of ACEI and angiotensin II receptor blockers (ARB) in RTR is more widespread now than in the past[50]. This class of drugs, introduced in 1981 and 1995 respectively, has proved widely effective in treating hypertension. ACE Inhibitors prevent kidneys from retaining sodium and water by deactivating angiotensin-converting enzyme, which converts inactive angiotensin I to the active angiotensin II. While ARBs blocks angiotensin II. This angiotensin II raises blood pressure by triggering sodium and water retention and constricting the arteries. Thus this agents use to treatment of hypertension and slowing the progression of chronic kidney disease has been well defined in the nontransplant population particularly in patients with proteinuria[51, 52, 53, 54]. Both ACE inhibitors and angiotensin II receptor antagonists may inhibit the activation of TGF-β, which is one of several growth factors involved in the pathogenesis of chronic allograft dysfunction. The ability of ACE inhibitors to slow the progression of chronic

Table 3: Advantages and disadvantages of antihypertensive classes drugs in renal transplant recipient

Agent class	Advantages (additional indications that are common in RTRs)	Disadvantages (adverse effects that are common in RTRs)
Diuretics	CHF with systolic dysfunction High CAD risk Recurrent stroke prevention Hyperkalemia Edema	Hypomagnesemia Hyperuricemia Hyponatremia Dyslipidemias Glucose intolerance
Aldosterone antagonists	CHF with systolic dysfunction Post MI	Hyperkalemia
Beta-blockers	CHF with systolic dysfunction Chronic stable angina Post MI High CAD risk Supraventricular tachycardia	Hyperkalemia Dyslipidemias Glucose intolerance
Angiotensin-converting enzyme inhibitor	CHF with systolic dysfunction Post MI High CAD risk Recurrent stroke prevention Reduce proteinuria Polycythemia	Hyperkalemia Anemia
Calcium-channel blockers	Chronic stable angina High CAD risk Supraventricular tachycardia Increased CNI levels (allowing a reduction in dose and cost)	Edema Increased CNI levels Reduced kidney function
Alpha blocker	Control of benign prostatic hypertrophy Rapid onset	Increase cardiovascular risk Rebound hypertension Sedation

allograft dysfunction does remain, however, unproven.

Randomized control trials in RTR have not had sufficient statistical power to determine whether ACE-I or ARB therapy improves patient or graft survival[55]. Hypertensive RTR with ischemic heart disease and/or CHF may benefit from ACE-Is, ARBs and/or beta-blockers[56]. KDIGO suggested that when urine protein excretion ≥1 g/day for ≥18 years old and ≥600 mg/m^2/24 h for <18 years old, consider an ACE-I or an ARB as first-line therapy[49].

The cardioprotective and renoprotective effects of ACEI and ARBs make the use of these agents attractive in the RTR population; however, limited prospective data in the transplant population confirm these benefits. According to Midtvedt *et al.*[57] there is an equal benefit of lisinopril and nifedipine in controlling blood pressure and reducing left ventricular mass index after transplantation for cardioprotection effect. In other study for meta-analysis of the use of ACE/ARB in >1500 RTR who were enrolled in randomized trials, ACE inhibitor and ARB significantly decrease GFR and also decease level of hematocrit, proteinuria and also reported that this drugs does not affect serum potassium level[55] which prove this agents having renoprotective effect. Although caution has been advised in using these agents too early after transplantation, there was no deleterious effect of these drugs on GFR when used in the early post transplantation period[58, 59]. In one report involving 2031 RTR from a single center, improvement in 10-yr actual patient survival (74 *versus* 53%; $P = 0.002$) and graft survival (59 *versus* 41%; $P < 0.001$) was reported in patients who were *versus* were not on ACEI/ARB therapy[60]. While in another report involving 17,209 RTR in the Collaborative Transplant Study, no benefit on ACEI or ARB use could be demonstrated[61].

Out of this ACE inhibitors prescribed to RTR may produce many side effects but most common are reduced sense of taste and a dry cough. ACE-inhibitor or ARB therapy can cause or exacerbate a decrease in GFR[62], and this property may mimic or mask early signs of acute transplant rejection so caution require to the patients that are at the highest risk of developing complications. Also ACE-inhibitor/ARB therapy can exacerbate the frequency and severity of hyperkalemia and sometimes is life-threatening when prescribing with calcineurin-inhibitor (particularly tacrolimus). ACE inhibitors can also cause or exacerbate anemia in transplant recipients, decreasing hematocrit by as much as 5%-10%[63] through a mechanism that may be potentiated by cyclosporine[64]. So it is suggested to avoid using ACE-inhibitor or ARB therapy until 3-6 months have elapsed from transplant to avoid hyperkalemia, acute kidney injury and anemia.

Calcium channel blocker (CCBs): CCBs inhibit voltage-gated calcium channels in cardiac and vascular smooth muscle so reduce contractility and induce vasodilatation. They also increase renal blood flow and GFR. Besides the blood pressure lowering effect of calcium channel blocker, these drugs also efficiently counteract the intrarenal vasoconstriction associated with cyclosporine treatment (and possibly tacrolimus) and also reduce cyclosporine induced hyperuricaemia[65]. Their effect on renal haemodynamics may also reduce long term cyclosporine nephrotoxicity[66]. Thus, vasodilatory CCBs have been an attractive option at least for the early management of hypertension after transplant[65].

Effects of CCBs on long-term kidney function in calcineurin inhibitor treated kidney transplant recipients have been reported with variable efficacy[67, 68]. A meta-analysis of 21 studies published in 1994 concluded that the proposed benefits of CCBs and calcineurin inhibitors (decrease in both delayed transplant function and acute rejection episodes and possibly also better long-term transplant function) were conflicting[67]. Despite this, such drugs typically are thought of as first-line agents for management of hypertension after kidney transplant, especially when target calcineurin-inhibitor levels are highest.

CCBs are mainly falling into 2 major classes: dihydropyridine (eg, amlodipine and nifedipine) and nondihydropyridine (eg, diltiazem and verapamil) and both have different pharmacokinetic profile in RTR.

Nondihydropyridine CCBs like Verapamil and diltiazem are potent inhibitors of cytochrome P450 C3A4 and cause plasma levels of the immunosuppressive drugs to increase sharply soon after initiation like have cyclosporine, tacrolimus, or sirolimus[69]. So these drugs should be used with caution and frequent monitoring. The dihydropyridine CCBs share these properties to a much lesser extent which makes this drugs use easier to in transplant recipients. But this dihydropyridine is associated with the development of edema in transplant patient.

CCBs and ACE inhibitors reduce blood pressure to a similar extent in RTR. But a large, prospective, randomized, comparative study found clear sustained improvement in kidney transplant function in patients treated with nifedipine compared with lisinopril[70]. At 1 year, GFR had significantly increased in those treated with nifedipine (56 vs 46 mL/min at baseline), but was unchanged with lisinopril (44 and 43 mL/min, respectively) and at 2 years, improvement in GFR with nifedipine was maintained (10.3 mL/min; confidence interval, 4.0-16.6); no such benefit was observed with lisinopril.

Another study on long-term evolution of 88 RTR show that use of Cyclosporin -verapamil interaction may permit a reduction of cyclosporine doses and thus decrease the cost of immunosuppression but calcium channel blockers are associated with side effects in a low percentage of patients [71].

These properties of CCBs make use of calcium channel blockers (CCB) is popular as first-line therapy[18], because they are often used to counteract the vasoconstrictive effects of cyclosporine as well as posttransplantation hyperuricemia[72]. This drug is cautionly prescribe as use of dihydropyridine CCBs in RTR can be produce edema and the non- dihydropyridine CCB can delay metabolism and elevate the levels of cyclosporine and tacrolimus[18].

β- Blocker: β- Blocker is a first line therapy for post transplant hypertension in patients with concomitant heart disease[73]. It also reduces morbidity and mortality after myocardial infarction. Many β blockers, increase triglyceride levels and decrease HDL cholesterol levels[74, 75] and also it is associated with developing diabetes[76]. The risk of developing impaired glucose tolerance or diabetes after transplantation is high on a drug regimen consisting of calcineurin inhibitors and corticosteroids[77].

Diuretics: Thiazide or a loop diuretic prescribes to RTR to remove excess sodium and water from body which retain by immunosuppressant drugs like corticosteroids and calcineurin inhibitors. Recent studies suggest that thiazides may be more effective than previously thought in patients with reduced kidney function[78, 79, 80].

Loop diuretics are the drugs of choice, alone or in combination with CCBs, especially in cases with urine output less than 50 ml/h and gross haematuria. A potential problem associated with Loop diuretics is hypokalemia which interference with insulin release and subsequent impairment of glycemic control. The extended use of diuretics and calcineurin inhibitors may require close electrolyte monitoring to avoid gout and cardiac mortality associated with low magnesium levels[81]. On the contrary thiazide diuretics may induce hypercalcaemia and potassium sparing agents hyperkalemia.

α Blockers: Alpha adrenergic antagonists can lower blood pressure by reducing peripheral vascular resistances. Early alpha adrenergic receptor blockers non-selectively block both alpha 1 and alpha 2 receptors and can cause tachycardia and other adverse events. The more recent alpha 1-adrenergic blockers are better tolerated and may decrease levels of triglycerides and cholesterol[82]. However, these agents may cause postural hypotension and may increase the risk of cardiovascular disease in high-risk transplant recipients[50]. Some of the more common adverse reactions associated with these drugs include postural hypotension, edema, somnolence, and sexual dysfunction

CONCLUSION

In RTRs cardiovascular disease is one of the leading causes of death after kidney transplant and this cardiovascular disease is mainly produce due to hypertension. Various regulatory agencies defined treatment target <130/80 for high risk patient like RTR and data shows that increase level of blood pressure is associated with increase the chances of cardiovascular disease and graft loss. So its require to control BP in RTR. None of agencies recommend any class of antihypertensive agents as preferred for long-term therapy for reducing CVD or improving long-term graft survival and also no antihypertensive agent is contraindicated in RTR. The choice of initial antihypertensive agent may be determined by the presence of one or more common post transplant complications that may be made better or worse by specific antihypertensive agents.

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