Review

HYPERTENSION AFTER KIDNEY TRANSPLANTATION

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Abstract

Cerebrovascular and cardiovascular events are among the most common causes of death in patients with a functioning graft. Hypertension has been well-known as major "traditional" risk factor for atherosclerotic cardiovascular disease being also frequent in kidney transplant recipients. A number of factors may contribute to developing or aggravating hypertension after transplantation. Among them, a central role is played by calcineurin inhibitors, corticosteroids and allograft dysfunction. Apart from the increased risk of myocardial infarction and sudden cardiac death, post-transplant hypertension also has implications on the graft outcome and survival. Considering kidney transplantation as the best treatment option for renal replacement therapy with an improved quality of life and survival compared to other treatments, the management of hypertension becomes crucial issue after kidney transplantation. In addition to pharmacologic and lifestyle interventions, risk reduction may also require tailoring a patient's immunosuppressive regimen to achieve optimal balance between efficacy and adverse events.

Keywords: kidney transplantation, post-transplant hypertension, cerebrovascular disease, allograft dysfunction, corticosteroids, calcineurin inhibitors

Introduction

Despite marked improvement in short-term graft survival with administration of newer immunosuppressive drugs, long-term morbidity and mortality after kidney transplantation (KTx) is still high and often associated with cardiovascular disease (CVD). Hypertension (HTN) is perhaps the co-morbidity that causes the greatest concern, as one of the major contributing factor to development of CVD, the primary cause of death with a functioning graft in KTx recipients [1-3].

In this review we address some important aspects of the etiology, pathogenesis and treatment of HTN after KTx.

Definition, incidence and pathogenesis

Although without universal consensus in KTx recipients, HTN has been defined as systolic blood pressure (SBP) $\geq$ 140 mmHg and/or diastolic blood pressure (DBP) $\geq$ 90 mmHg or otherwise, if a patient is at need of antihypertensive drugs [4,5]. However, some clinical centers use the blood pressure (BP) criteria of the World Health Organization/International Society of Hypertension as BP $>$ 130/85 mmHg [6].

In the pre-cyclosporine era the incidence of HTN was estimated as high as 40-50% of KTx recipients, while the introduction of cyclosporine (CyA) has increased its incidence to 70-90% of all transplanted patients [7,8]. Indeed, in the very first reports the prevalence of HTN was 63% and 67% in CyA compared to 42% and 46% in the azathioprine-treated group, respectively [9,10]. Furthermore, the incidence of HTN decreased significantly when CyA was replaced by azathioprine [10]. Many factors contribute to the development of post-transplant HTN in KTx recipients where the greater incidence of cardiovascular disease (CVD) could not be entirely explained by traditional risk factors for HTN, i.e. older age, male, obesity, physical inactivity, pre-transplant-HTN, cigarette smoking, DM, hyperlipidemia, etc. The use of immunosuppressive agents after KTx and graft dysfunction *per se* may accelerate the risk of CVD by causing post-transplant HTN, hyperlipidemia and/or diabetes mellitus [5].

However, regardless of the cause, kidney disease is associated with salt and water retention, with an increase in the extracellular volume and cardiac output, inappropriate activation of the RAS, increased sympathetic activity and peripheral vascular resistance, and thereby confirming the fact that most transplant candidates are already hypertensive before kidney transplantation is performed [11].

In this context, while a well-functioning transplanted kidney may allow improvement in the blood pressure (BP) control through a better regulation of homeostatic mechanisms, a number of other factors may trigger or maintain HTN in renal transplant recipients (Table 1).

Table 1. Multifactorial Etiology of Post-Transplant Hypertension**Immunosuppressive therapy**

Corticosteroids

Cyclosporine and tacrolimus

Dysfunction of the graft

Acute and chronic rejection

Chronic allograft nephropathy

Nephrotoxicity due to anticalcineurin drugs

Obstructive uropathy

De novo glomerulonephritis

Recurrent disease

Pre-transplant hypertension**Donor hypertension****Transplant renal artery stenosis****Native kidneys****Others:** Obesity, age, alcohol, familiar history, delayed graft function, prolonged ischemia times, female older donor**The hypertensive role of immunosuppressive drugs**

Purine synthesis inhibitors (azathioprine and mycophenolate salts), and mTOR inhibitors, (sirolimus and everolimus), do not interfere with BP, while there is an evidence that both calcineurin inhibitors (CNI) and corticosteroids (Cs) can exert hypertensive effects [12-14]. Corticosteroids (Cs) have been a known precipitant of HTN in the general population, while the hypertensive role of Cs studied after kidney transplantation showed that Cs are independently associated with post-transplant HTN [15,16]. The hypertensive effect of Cs is mainly related to the sodium and water retention caused by the partial activation of mineralocorticoid receptors, increased density of glucocorticoid receptors, activation of vascular smooth muscles, increased renal vascular resistance, increased sensitivity to endothelin-1 and angiotensin II, renin secretion and decreased production of vasodilator prostaglandins. Several studies have shown that steroid reduction to less than 10 mg/day, alternate day dosing or total steroid withdrawal resulted in decreased incidence of HTN [15-17]. Yet, some issues concerning the steroid withdrawal or conversion from every day to alternate day and the reduction of arterial BP remain debatable [18]. On the other hand, it is well-known that CNIs (cyclosporine and tacrolimus) may cause acute and chronic nephrotoxicity and HTN. The hypertensive role of the CNIs may be explained by an increase in the systemic vascular resistance causing renal vasoconstriction through several mechanisms, including activation of vasoconstrictor factors, such as renin-angiotensin-aldosterone system (RAAS), endothelin, and thromboxane A₂, while reducing the production of vasodilator compounds such as nitric oxide and prostacyclin [12-14,19]. In addition, it has been shown that CNI may increase the level of plasminogen

activator inhibitor (PAI) causing over-expression or inadequate contra-regulation of transforming growth factor-beta1 (TGF-beta1), and can enhance the expression of platelet-derived growth factor, fibroblast growth factor, and endothelin, thereby leading to cellular proliferation, HTN and chronic allograft dysfunction (CAD) [20,21]. Although cyclosporine (CyA) and tacrolimus (TAC) induce post-transplant HTN via similar mechanisms, it seems that HTN is less common and severe in patients on TAC than in those receiving CyA. Namely, it has been reported that around 20-100% of patients on CyA for more than a year have required an antihypertensive drug. In contrast, the probability for developing post-transplant HTN in patients on TAC has been reported to be at least 15% lower than those on CyA [22]. In this regard, a three-year follow-up results from the US randomized trial indicated that significantly lower number of kidney recipients on TAC were receiving antihypertensive therapy when compared with those on CyA [23]. In addition, in cases of severe HTN in CyA-treated patients, switching to TAC or sirolimus resulted in a significant reduction in BP [12,24, 25]. Thus, it is reasonably considered that HTN may be easily controlled by either minimizing the doses of CyA [26], or use the CNI-sparing regimens in KTx recipients [27].

Other etiology of HTN

Allograft dysfunction is frequent after renal transplantation and is strongly associated with the occurrence of post-transplant HTN. Causes for allograft dysfunction include: acute rejection, chronic allograft nephropathy (CAN), CNI nephrotoxicity, obstructive uropathy, *de novo* or recurrent glomerulonephritis, etc. In all of them several mechanisms may be already involved in the pathogenesis of HTN such as: salt and water retention with an increase in extracellular volume and cardiac output, inappropriate activation of the RAS with increased peripheral vascular resistance and an increase of sympathetic activity [12,15, 26,28]. During acute rejection episodes, HTN occurred as a result of impaired renal excretory function combined with volume expansion and glomerular ischemia, while in chronic allograft rejection HTN it is accompanied by ischemia, fibrosis and secondary stimulated renin production [12]. In addition, HTN is a well-recognized risk factor for atherosclerotic CVD and leading cause of long-term mortality in KTx patients and would require therapy because of its known benefit on the cardiac and cerebral vascular systems.

The presence of pre-transplant HTN is considered to be one of the risk factors that contribute to the development and severity of post-transplant HTN. Pre-transplant HTN has been independently associated with the development of progressive CAD along with the other risk factors such as HLA mismatching and acute rejection episodes [29]. The presence of native kidneys may be considered as another cause of post-transplant HTN, reported by a higher prevalence of HTN in transplant recipients with

native kidneys compared to those who received bilateral nephrectomy [30].

It has been reported that patients who received the kidney from a subject of a hypertensive family have a higher probability of developing HTN after transplantation compared to patients who received a kidney from a member of a normotensive family [31], and a greater hypertensive response during acute rejection [32]. Additionally, it has been reported that the risk of post-transplant HTN increases by 28% for each 10-year-increase in donor age and is more than doubled if the donor has generalized atherosclerosis [33,34].

Post-transplant HTN due to renal artery stenosis usually occurs between 3-24 months post-transplantation, and accounts for 1-7% of KTx recipients [35] in association with harvesting and operative complications, atherosclerotic disease, cytomegalovirus infection and delayed graft function [36]. Early diagnosis and adequate therapeutical approach of TRAS are crucial issues. Clinically, TRAS may be suspected in the presence of severe HTN (as a result of over activity of RAAS), in the presence of a bruit at auscultation, and/or in cases of a rapid deterioration in renal function after administration of RAS inhibitors [37], or in presence of lymphocele adjacent to the graft renal artery [38]. Here, it is important that TRAS related to any other cause of HTN is differentiated by duplex doppler of the allograft artery as a routine screening method [39]. Thereby, arteriography, magnetic resonance angiography, or computed tomography angiography, may confirm the diagnosis, but cannot predict the treatment success of surgery or percutaneous transluminal angioplasty. However, a captopril renogram test is also a high sensitivity precise diagnostic method that may help in identifying functionally significant stenosis, as well as the need of a surgical treatment [40].

Consequences of post-transplant hypertension

Cardiovascular complications

Arterial HTN is a strong risk factor of CVD. Several mechanisms are included in the pathogenesis of atherosclerosis due to HTN: elevated angiotensin II can contribute to atherogenesis by stimulating the growth of smooth muscle cells and lipooxygenase activity which in turn can increase inflammation and oxidation of low density lipoproteins, as well as the pro-inflammatory actions of HTN on endothelium with increased formation of hydrogen peroxide and free radicals in plasma [41]. A major consequence of HTN is the left ventricular hypertrophy (LVH), which is an important risk factor for a variety of cardiovascular consequences, such as an ischaemic heart disease (IHD-angina pectoris, myocardial infarction), congestive heart failure, arrhythmias, coronary heart disease and stroke, as well as a sudden cardiac death [42]. It was confirmed in a 15-year follow-up study with a progressive increase in the rate of vascular diseases in hypertensive

KTx recipients (23% cases with a new-onset of IHD, 15% with a major cerebrovascular event and 15% with peripheral vascular disease) [43].

Hypertension and long-term graft and patient outcome and survival

HTN jeopardizes renal allograft function and has been shown to be harmful for the long-term graft outcome and survival [44]. In the collaborative study of Opelz *et al.* on almost 30.000 KTx recipients were evaluated and a statistically significant association between elevated SBP at one year and allograft failure. Thus, HTN has been confirmed as an independent risk factor for graft failure, even in cases when serum creatinine levels were normal and when patients had never been treated for acute rejection [45]. Each 10 mmHg increase in either SBP or DBP was observed to have an independent negative effect on the graft survival. The same inverse correlation between severity of post-transplant HTN and graft survival was also reported by Kasiske *et al.* showing that each 10 mm Hg rise in SBP independently increased the relative risk of graft failure and patient death by 12% and 18%, respectively [44].

Management of post-transplant HTN

The management of post-transplant HTN is extremely important since it is implicated as a major risk factor for long-term graft outcome and cardiovascular morbidity and mortality in KTx recipients. Two recent meta-analyses of hundreds of randomized trials in non-transplant patients provided evidence that reducing BP may decrease the risk of CVD [46,47]. Reasonably, a good control of BP may also protect renal graft function in KTx recipients even after 3 years of post-transplant HTN [18] and lead to a longer graft survival in KTx recipients compared to the non-controlled BP patients [48].

Although, there is no general consensus about optimal BP after kidney transplantation, the National Kidney Foundation Task Force on cardiovascular disease and The European Best Practice Guidelines for KTx have recommended BP<130/85mm Hg for renal transplant recipients without proteinuria and<125/75 mm Hg for patients with proteinuria [5,49]. The last KDIGO guidelines recommend measuring BP at each clinic visit and suggest maintaining BP at <130 mmHg systolic and <80 mmHg diastolic if >18 years of age [50]. However, in spite of the treatment it is reported that about 50% of transplant recipients have a systolic BP >140 mmHg [5,51]. Thus, the goals of management of post-transplant HTN should be to improve better graft outcome and kidney recipient survival minimizing the cardiovascular risk though lifestyle modification and pharmacological treatment.

Lifestyle

Lifestyle modification is the first measure for treating HTN in renal transplant recipients. The recommendations of the Canadian Hypertension Education Program that can be used in kidney transplant recipients as well [52] include: avoidance of the increase in body weight (BMI 18.5–24.9 kg/m² and waist circumference <102 cm for men and <88 cm for women), dietary sodium restriction (1500 mg per day in adults 50 years of age or younger and to 1300 mg per day in adults 51–70 years of age), regular exercise (30 min to 60 min of moderate aerobic exercise 4–7 days per week), avoidance of smoking and alcohol consumption, diet with emphasis on fruits, vegetables and low-fat dairy products, soluble fiber, whole grains and protein from plant sources.

Finally, it is also very important to control other concomitant CV risk factors usually present in kidney transplant recipients such as: diabetes (use of insulin sensitizers), hyperlipidemia (statins, fibrates), hyperhomocysteinemia (folic acid, vitamin B6 and B12) and platelet aggregation (aspirin) [53].

Pharmacological treatment

The KDIGO guidelines recommend that transplant recipients should be treated with any class of antihypertensive agents [50]. At present, however, there are no prospective trials demonstrating that lowering the BP protects the allograft or that any class of drugs has superior efficacy [54]. Although all antihypertensive drugs are useful in kidney transplant patients, the choice of the drugs depend on their efficacy and tolerance, their possible impact on the graft function and on the pharmacological interference with immunosuppressive drugs. Thereby, the choice has to be individualized by the presence of other risk factors at each single patient.

Nowadays, it is reported that a combination of two first-line agents should be considered for initial treatment of HTN in renal recipients if SBP is 20 mmHg above target or if DBP is 10 mmHg above target [52]. The most commonly used antihypertensive drugs in kidney recipients are calcium channel blockers (CCB) and angiotensin converting enzyme inhibitors (ACEI) [5,54]. CCB may reduce the mean BP modulating the calcium flux that may diminish the vascular smooth muscle reactivity to vasoconstrictor stimuli reversing the increase in the renal vascular resistance induced by CNI, particularly at the pre-glomerular level acting on the vascular smooth cells [55,56]. In a recent meta-analysis of randomized controlled trials comparing the effect of CCB with placebo or no treatment, CCB reduced graft loss (risk ratio 0.75) and improved GFR for 4.5 ml/min [57]. Other studies showed that CCB could reverse ventricular hypertrophy in KTx recipients [3,58], suggesting also that CCB may be preferred as a first-line choice in the hy-

pertensive KTx recipients. However, it is still a matter of controversy whether the use of dihydropyridinic CCB may cause an increased risk of CVD events in high risk patients [59] as well as in renal transplant recipients [60]. Furthermore, it has been reported that non-dihydropyridinic CCB (verapamil and diltiazem), and the dihydropyridinic nicardipine can increase the blood levels of CyA [61]. Nevertheless, CCB are widely used to normalize BP and appear to improve renal function soon after transplantation being also effective in decreasing of proteinuria in KTx recipients [54,62].

The administration of ACEI and angiotensin-II-receptor blockers (ARB) in the presence of stable allograft function is an attractive option, since these drugs have been shown to have renoprotective and antiproteinuric affect [54,62, 63]. However, in a recent systematic review of randomized trials to determine the effect of ACEI and/or ARB use after kidney transplantation, the ACEI and/or ARB use was associated with a significant decrease in GFR (5.8 ml/min), a lower hematocrit (3.5%) and reduction in proteinuria (0.47 g/day) [64].

On the other hand, several studies have reported that use of ACEI and ARB may cause hyperkalemia as well as may induce anemia [65,66]. Therefore, an early use of RAS inhibitors is not recommended in patients with graft dysfunction, whereas it appears to be safe in transplant patients with a good early function [66]. The use of ARB and ACEI may also prevent heart failure in patients with left ventricular dysfunction, and may favor the regression of LVH having also a role in prevention of atherosclerosis [67,68]. Interestingly, this combination of drugs was also shown to have a better patient and graft survival at 10 years in comparison with patient who did not receive these agents [69].

Beta-blockers may be cardioprotective and should be considered as a first-line therapy for post-transplant HTN in patients with concomitant coronary artery disease, stable heart failure and arrhythmias. However, these agents may contribute to adverse effects on lipids and glucose metabolism [70]. It was also found that treatment with beta blockers as a side effect increased the risk of developing diabetes by 28% [71]. Finally, the centrally acting drugs, alpha adrenergic antagonists, can lower BP by reduction of the sympathetic tone and decreasing cardiac output and peripheral vascular resistance [72]. These agents may be used in various combinations with other antihypertensive drugs.

Conclusions

Post-transplant HTA is highly prevalent after KTx and may contribute to CV morbidity and mortality influencing the graft and patients' outcome and survival. Pharmacological treatment of post-transplant HTN is often based on a combination of two or more antihypertensive drugs. Generally, there is no preferred antihypertensive agent but it is important that the chosen drug (or com-

bination of drugs) is effective and does not cause adverse events. In the early post-transplant period, dihydropyridinic CCB should be preferred, not only because they are among the more effective drugs in reducing BP but also because they can induce renal arteriolar vasodilation contrasting the vasoconstrictive effects of CNIs. Instead, in patients with heart failure and in diabetics at risk of CVD, RAS inhibitors and beta-blockers may be preferred over CCB, unless HTN becomes difficult to control with these agents. As pointed out by KDIGO guidelines, in proteinuric patients, combination of CCB, ACEI or ARB, associated with loop diuretics, remain the first-line agents. However, in many cases, the addition of other drugs (beta-blockers, centrally acting drugs, and/or alpha-adrenergic antagonists) may be required. Modifying lifestyle and immunosuppression are other preferable choices that may improve outcomes as well. Maintenance therapy with a low dose of Cs or TAC may avoid some immunologic risk while certainly improve HTN control [73]. Conversion from CyA to TAC/ Sirolimus, or CNI withdrawal may lead to decreased BP, improving long-term graft and patient survival. However, there is still much room for continued studies of novel strategies aimed to improve long-term outcomes after kidney transplantation.

Conflict of interests: *none declared*

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