

Posttransplant Hypertension: Multipathogenic Disease Process

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Abstract

Arterial hypertension is prevalent among kidney transplant recipients. The multifactorial pathogenesis involves the interaction of the donor and the recipient's genetic backgrounds with several environmental parameters that may precede or follow the transplant procedure (eg, the nature of the renal disease, the duration of the chronic kidney disease phase and maintenance dialytic therapy, the commonly associated cardiovascular disease with atherosclerosis and arteriosclerosis, the renal mass at implantation, the immunosuppressive regimen used, life of the graft, and de novo medical and surgical complications that may occur after a transplant). Among calcineurin inhibitors, tacrolimus seems to have a better cardiovascular profile. Steroid-free protocols and calcineurin inhibitor-free regimens seem to be associated with better blood pressure control. Posttransplant hypertension is a major amplifier of the chronic kidney disease-cardiovascular disease continuum. Despite the adverse effects of hypertension on graft and patient survival, blood pressure control remains poor because of the high cardiovascular risk profile of the donor-recipient pair. Although the optimal blood pressure level remains unknown, it is recommended to maintain the blood pressure at < 130/80 mm Hg and < 125/75 mm Hg in the absence or presence of proteinuria.

Key words: *Cardiovascular disease, Immunosuppression, Kidney transplant, Atherosclerosis, Genetic*

Introduction

Arterial hypertension is prevalent among kidney transplant recipients. Its prevalence varies according to transplant center, demographics of transplant recipient and kidney donor populations, definition of hypertension, time of diagnosis after the transplant, and when the transplant was performed.¹⁻³ Arterial hypertension has increased from 40% to 85% since the introduction of calcineurin inhibitors.¹⁻³ Data from the Spanish registry show that irrespective of the transplant era, a progressive and significant increase in the prevalence of systolic and diastolic hypertension during follow-up (which stabilizes after the fourth year after transplant) occurs.⁴ The severity of increased systolic blood pressure is most pronounced immediately after the transplant and declines progressively during the first year.²

Interestingly, the prevalence of posttransplant hypertension remains high despite a more-aggressive therapeutic approach by transplant physicians, reflected by administering more antihypertensive medications.¹⁻³ Recent observational data from the Collaborative Transplant Study registry shows that the fraction of kidney transplant recipients with a systolic blood pressure < 140 mm Hg rose significantly from 1998 onward because of the increase in the number in the antihypertensive drugs administered.⁴ These findings were in agreement with similar observations reported during the same time.¹ Yet, despite this increased vigilance in the transplant community⁴ and the well-established negative effect of posttransplant hypertension on graft and patient outcomes⁵⁻⁸; adequate blood pressure control remains poor in most kidney transplant recipients, leading to 20% to 40% graft loss

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from chronic allograft dysfunction or death from cardiovascular disease.⁸⁻¹¹

This review highlights the role of posttransplant hypertension as an amplifier of the chronic kidney disease and cardiovascular disease continuum, its causes that involve pretransplant, peritransplant, and posttransplant parameters, and its adverse effects on graft and patient survivals.

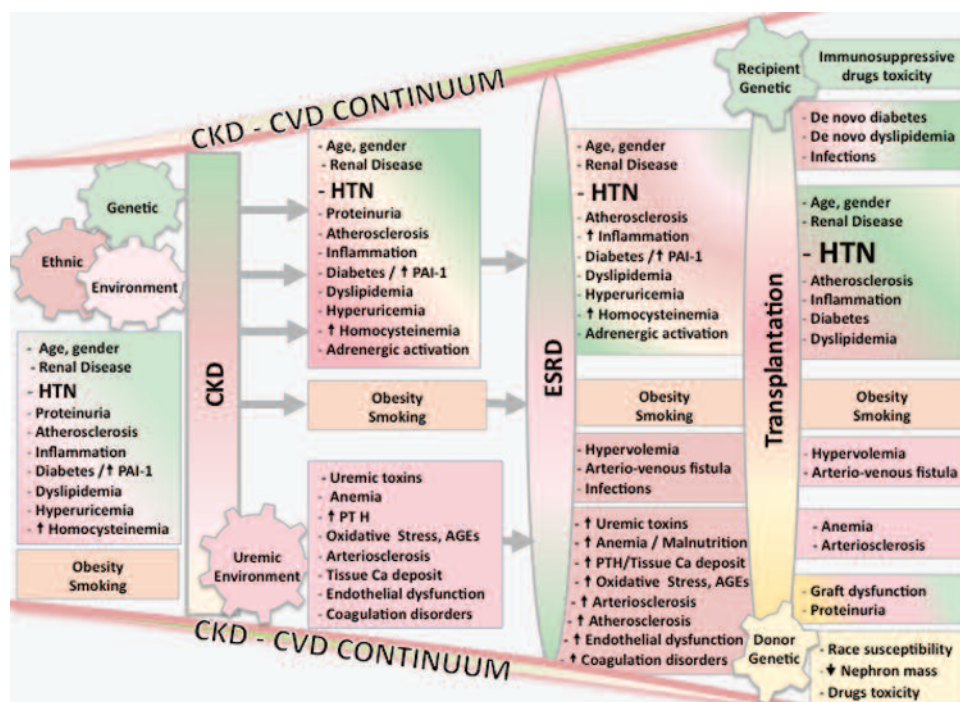
Posttransplant hypertension: Amplifier of the chronic kidney disease-cardiovascular disease continuum

It would be erroneous to consider posttransplant hypertension an isolated phenomenon. It should be regarded as an integral part, and a major amplifier of, the chronic kidney disease and cardiovascular disease continuum—a process that begins with or often precedes the clinical and biological diagnosis of the renal damage (Figure 1).^{12,13} The strong link between chronic kidney disease and cardiovascular disease has been documented in both the general and chronic kidney disease populations.¹³⁻¹⁶ The prevalence of

cardiovascular morbidity and mortality is greater in the patients with renal failure, especially those with end-stage renal disease, and the cardiovascular events often lead to death with chronic kidney disease more so than with individuals without chronic kidney disease.^{17,18} The chronic kidney disease and cardiovascular disease continuum involves 3 phases: the first phase, with its different stages; progressing toward end-stage renal disease, which is the second phase, which requires chronic renal replacement therapies that may lead in some, but not all, patients to kidney transplant; and the third phase, after which the renal allograft is lost to chronic allograft dysfunction and a return of the patient to dialysis, or death of the recipient predominantly from cardiovascular disease.⁹⁻¹¹

The chronic kidney disease and cardiovascular disease continuum amplifies with time according to the duration of each of the phases that may last from months to years.¹⁵⁻¹⁷ It results from the interaction of several genetic, ethnic, environmental, and demographic factors that contribute to the

Figure 1. Chronic Kidney Disease-Cardiovascular Disease Continuum



Abbreviations: AGEs, advance glycosylated end products; Ca, calcium; CKD, chronic kidney disease; ESRD, end-stage renal disease; HTN, hypertension; PAI, plasminogen activator inhibitor; PTH, parathyroid hormone

Chronic kidney disease-cardiovascular disease continuum is a process that usually starts or can even precede the diagnosis of the chronic kidney disease. It will amplify with the time duration of each of the stages that may last from months to years. It is the results of the interaction of several genetic, ethnic and environmental factors that usually contribute to the development and or progression of the renal and cardiovascular diseases. Hypertension is considered to be an integral part of this complex continuum at each of its stages and represents a major amplifier of the disease process with its prevalence increasing with the progression of the continuum.

development or progression of renal and cardiovascular diseases.^{12,17-34} Many of these factors are traditional, and commonly and concomitantly present in chronic kidney disease and cardiovascular disease patients including age, male sex, diabetes mellitus, dyslipidemia, hyperuricemia, hyperhomocysteinemia and sympathetic nervous stimulation, in addition to 2 widespread and devastating factors: obesity and smoking. Other factors are related to the underlying kidney disease itself and the commonly associated hypertension and proteinuria, the resulting atherosclerosis and inflammatory state. The progression of the renal disease leads to the gradual appearance of additional environmental factors specific to uremia, such as the uremic toxic environment, and resultant anemia, hyperparathyroidism, oxidative stress, lipoproteins glycation, endothelial dysfunction, coagulation disorders, increased in tissue calcium deposit, and resultant accelerated arteriosclerosis. Most of these factors continue to progress during the end-stage renal disease phase, during which new additional ones enter into play such as the increase incidence of infections, creation of an arteriovenous fistula, worsening hypervolemia, and both vascular and tissue calcifications, leading to an exaggeration in aortic stiffness, left ventricular hypertrophy, and diastolic dysfunction.^{15-17,35}

Shortening the process through preemptive kidney transplant leads to early reversal of many of the continuum's components. This could explain the superior short-term and long-term kidney allograft and patient survival associated with preemptive transplant from a living donor compared with transplant after being on dialysis.^{36,37} By the time end-stage renal disease patients ultimately reach the transplant phase, they have renal, cardiovascular atherosclerotic, and arteriosclerotic comorbid risk factors responsible for higher cardiovascular mortality than the general population does, when matched for age, race, and sex.³⁸ While some of these factors (such as aortic stiffness) could be gradually and either partially or completely reversed by the process of a successful transplant^{35,39} (leading to a significant reduction in the annual adjusted cardiovascular rates in kidney transplant recipients as compared to end-stage renal disease wait-listed patients)⁴⁰; other pre-existing factors such as diabetes mellitus, dyslipidemia, atherosclerosis, congestive heart failure, and obesity may worsen after transplant along new

ones that could occur as the result of diabetogenic, dyslipidemic, atherogenic, thrombogenic, infectious, and nephrotoxic potential of most immunosuppressive drugs,^{1,35,39,41-44} in addition to anemia and chronic graft dysfunction, which are linked to several immunologic and nonimmunologic components.⁴⁵

Most drug-related adverse effects are mediated by the interaction of 2 distinct genetic profiles of the recipient and the donor with the environment.⁴⁶⁻⁵⁵ These gene-gene and gene-environment interactions lead to systemic and nephrotoxic adverse events that predominantly depend upon the recipient and the donor.⁴⁷

Evidence is emerging regarding the role of donor age and hence, nephron mass, in the pathogenesis of aortic stiffness in nephrectomized donors⁵⁶ and kidney transplant recipients.⁵⁶⁻⁵⁸ Data from animal models show that reduced renal mass is the major factor in the development and maintenance of arterial hypertension and proteinuria, which lead to glomerular injury in 5/6 nephrectomized rats. Supplementing renal mass reverses these changes. These observations provide support for the notion that renal mass is a significant, independent determinant of arterial pressure.⁵⁹

Atherosclerosis is a major component of the chronic kidney disease and cardiovascular disease continuum and may occur early in life. Young adults with end-stage renal disease since childhood exhibit an increase and decrease in carotid artery stiffness and distensibility, respectively, when compared with matched healthy individuals. These arterial wall abnormalities, indicators of arterial dysfunction, are comparable to those measured in the transplant patients with the same risk factors.⁶⁰

Mistnefes and coworkers confirmed these findings in a recent study.⁶¹ In their study, these markers of atherosclerosis were associated with higher mean systolic blood pressures taken within 1 year before the study, higher daytime systolic blood pressure load (via ambulatory blood pressure monitoring), number of kidney transplants, and deceased-donor transplants.⁶¹ These observations show that pediatric kidney transplant recipients might be at an increased risk for accelerated atherosclerosis and premature cardiovascular disease that strongly correlate with systolic blood pressure, deceased-donor donation, and the duration of renal replacement therapy.

Although renal transplant improves arterial function,³⁹ pulse wave velocity (a marker of aortic stiffness) remains significantly elevated during the

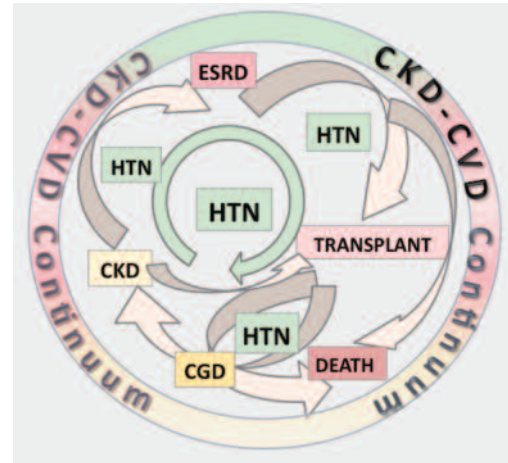
long term in kidney transplant recipients when compared with healthy volunteers.⁵⁶ Interestingly, an increase in pulse wave velocity also was observed in corresponding live donors but was considerably greater in recipients independent of age, sex, and blood pressure. Moreover, among healthy volunteer groups, pulse wave velocity was significantly higher in the recipient-related than in the non-recipient-related volunteers, indicating a possible genetic predisposition for developing atherosclerosis and consequently, renal disease. In all healthy volunteers, pulse wave velocity was exclusively related to age, sex, and blood pressure. In donors and recipients, it was associated with a cluster of cardiovascular risk factors including smoking habits, plasma glucose, and renal factors reflecting nephron mass (eg, time since nephrectomy, age in donors, and rejection in recipients). More recently, pulse wave velocity, in addition to proteinuria and systolic blood pressure, has been reported to be an independent predictor of the rate of decline in renal function in chronic kidney disease patients,¹⁵ and in pediatric⁶² and adult kidney transplant recipients.^{56,58}

While recognizing the likely dual causality between aortic stiffness and renal failure, these observations provide further evidence that atherosclerosis and the resulting arterial stiffness play a pathogenic role in renal function decline. Taken together, these results suggest that the arterial status of the recipient is the result of possible links between the combined donor-recipient genetic backgrounds and their interaction with several environmental and demographic cardio-renal risk factors, the renal mass from the donor at implantation, and the vascular, and immunologic and nonimmunologic renal changes that occur in the recipient posttransplant.

This explains why arterial hypertension is prevalent in each phase of the chronic kidney disease and cardiovascular disease continuum; as the result of the cumulative and progressive nature of the continuum, its prevalence increases with progression of the process, being highest during the posttransplant phase.¹⁻³ It represents a strong predictor of renal and patient cardiovascular outcomes^{1,3,5,6,8,11-13,15,17,35,56,58,60-63} (Figure 2). Therefore, posttransplant hypertension represents a multipathogenic process that amplifies a vicious cycle where allograft and cardiovascular outcomes in kidney transplant recipients are determined by the interaction of 2 distinct donor and recipient genetic

make-ups, and the inherited cardiovascular and renal risk factors from earlier phases and new recipient and donor-related environmental and demographic variables that may occur during implantation and posttransplant (Figure 1).

Figure 2. Posttransplant Hypertension



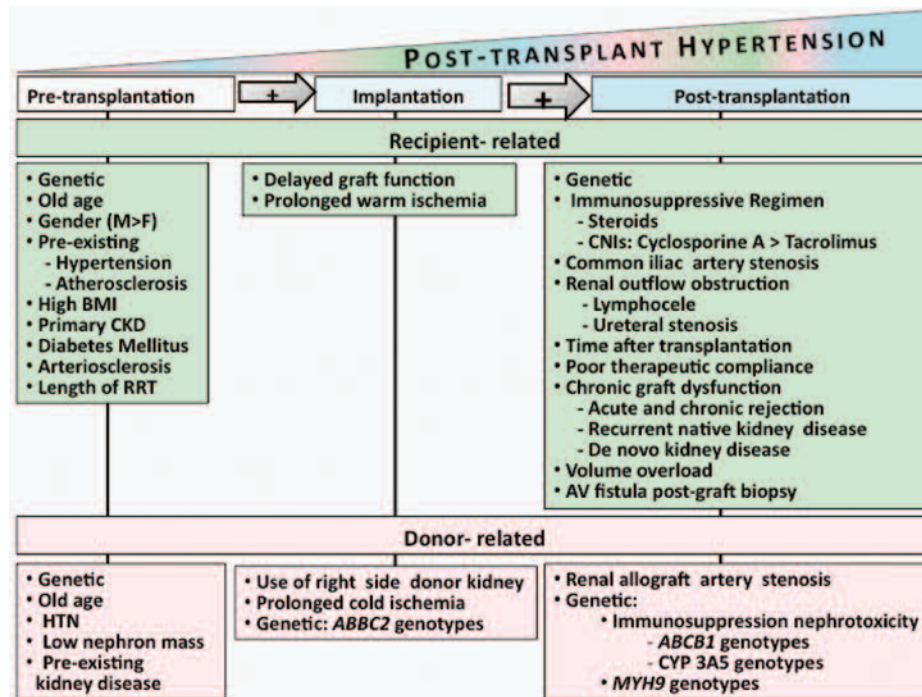
Abbreviations: CGD, chronic graft dysfunction; CKD, chronic kidney disease; CVD, cardiovascular disease; ESRD, end-stage renal disease; HTN, hypertension

Posttransplant hypertension represents a multipathogenic disease process that amplifies a vicious cyclic, progressive and cumulative chronic kidney disease and cardiovascular disease continuum. It constitutes a strong predictor of both renal and patient's cardiovascular outcomes.

Posttransplant hypertension pathogenesis

Arterial hypertension in the kidney transplant population represents a greater risk for cardiovascular outcome and renal survival than it does in the general population, and it plays a major role in the cause of chronic graft dysfunction, and morbidity and deaths from cardiovascular disease.^{5,63} The various causes for posttransplant hypertension are well-documented in the literature.^{1,3,8,64} Given the complexity of the kidney transplant milieu related to the interaction between recipient and donor parameters, and the progressive, cumulative nature of the chronic kidney disease-cardiovascular disease continuum—a proper stratification of the different causes of posttransplant hypertension should take into account the different phases of the continuum and the various donor-related and recipient-related factors of each phase (Figure 3). The causes of arterial hypertension in a kidney transplant recipient are diverse, and posttransplant hypertension should be considered a multifactorial disease state rather than a simple phenomenon. This could

Figure 3. Multifactorial Pathogenesis of Posttransplant Hypertension



Abbreviations: BMI, body mass index; CNIs, calcineurin inhibitors; CYP, cytochrome P450; HTN, hypertension; RRT, renal replacement therapy

Multifactorial pathogenesis of posttransplant hypertension involves the interaction of both donor and recipient genetic backgrounds with several environmental parameters that may precede or follow the transplant procedure such as the nature of the renal disease, the duration of the chronic kidney disease phase and the maintenance dialytic therapy, the commonly associated cardiovascular disease with inflammation, atherosclerosis and arteriosclerosis, the renal mass at implantation, the immunosuppressive regimen used, the lifetime of the graft and the de novo medical and surgical complications that may occur after transplant.

explain the more-pronounced effects of hypertension on renal and cardiovascular outcomes in transplant patients,^{4,38,63} as compared with non-renal-hypertensive individuals.^{65,66}

Uncontrolled blood pressure in renal transplant plays a major role in the pathogenesis of chronic graft dysfunction, accelerated graft loss, and the morbidity and mortality associated with cardiovascular disease.^{2,4,5,8-11,63,67,68} While several epidemiologic studies^{65,66,69} have shown that systolic hypertension in the general population is an independent risk factor for developing chronic kidney disease, fewer than 1% of these cohorts progressed to end-stage renal disease during a minimum follow-up of 15 years and mainly in those individuals with systolic blood pressure >180 mm Hg.⁶⁹ In contrast, Registry data from kidney transplant recipients show a strong and graded inverse association between systolic blood pressure levels and graft outcomes.^{5,8} In fact, 24% and > 50% of the grafts were lost after 4 and 8 years follow-up in kidney transplant recipients who had a systolic blood pressure ≥ 180 mm Hg at 1-year posttransplant. These results were still maintained after censoring for acute

rejection and patient death, and whether the patients were on antihypertensive therapy.⁵

Recipient factors

Several recipient-related factors have been identified in transplant patients as predisposing risk factors for posttransplant hypertension. Many of these antedate the transplant process including the ethnic and genetic make-up, age, body mass index, and male sex of the recipient; the nature of the underlying kidney disease itself (mainly diabetic nephropathy and nephrosclerosis), the pre-existing chronic kidney disease-arteriosclerosis that progresses and worsens with length of the chronic kidney disease and cardiovascular disease continuum and that of the renal replacement therapy; the frequently associated atherosclerosis that may be beginning early in life, and accelerating with advancing age and with the progression of the renal disease itself; and finally, the commonly associated inherited hypertension that, when uncontrolled, could contribute to aggravated atherosclerosis and a deterioration in renal function.^{1,2,3,9,16-18,20,23,52,55,60,61,64,70}

At the time of implantation, additional variables have been shown to be independent correlates of systolic blood pressure: delayed graft function and long warm ischemia time,^{1-3,71} both of which can lead to vascular damage and fibrosis, and a further reduction in nephron mass. Specific recipient genotype (CYP 3A5 nonexpressers) seems to be a strong predisposing factor for delayed graft function and for new-onset diabetes mellitus after transplant in tacrolimus-treated patients.⁷²

After kidney transplant, several new parameters emerge as strong correlates of posttransplant hypertension. They are specific to the kidney transplant recipients and the transplant process involving the genetic makeup of the recipient, the technical procedure with its short-term and long-term complications, the immunosuppressive regimen used and potential new systemic adverse events that may occur after transplant, the time after transplant, and the commonly encountered proteinuric chronic graft dysfunction of multiple immunologic and nonimmunologic origins (ie, acute and chronic rejection, recurrent native and de novo kidney diseases).^{1,2,3,9,31,42-45,64,71-88} Surgical complications (eg, lymphocele and ureteral stenosis causing urinary outflow obstruction) are well-established causes of early onset or aggravating pre-existing hypertension.³ Transplant renal artery stenosis occurring soon after transplant may be related to trauma, clamping, or suturing of the graft artery or the recipient vessels. Kinking of the graft artery from a right donor kidney (which has a longer artery than the vein) may lead to early posttransplant hypertension.

Renal artery stenosis coming late after transplant may be caused by atherosclerotic changes of the renal artery of the graft or the proximal iliac artery of the recipient.^{3,77,78} Postgraft biopsy arteriovenous fistula caused by an abnormal communication between the artery and the vein may result in local ischemia and renin-mediated hypertension.⁸⁸ Modern immunosuppression (including calcineurin inhibitor-based regimen in combination with steroids) has drastically transformed posttransplant hypertension by increasing its prevalence from 40% to > 80%.^{1,2,3} Although the exact mechanism of the calcineurin inhibitor-induced hypertension has not been well clarified, patients treated with cyclosporine are more likely to develop hypertension than are those on tacrolimus. Registry data, and observations from

clinical trials, reveal that tacrolimus-based regimens are associated with lower rates of posttransplant hypertension and a significant reduction in antihypertensive medication requirements.^{1,42,44,78} Furthermore, the conversion of stable transplant patients from cyclosporine to tacrolimus is associated with significant improvement in systolic and diastolic blood pressures.⁴³

The thrombogenic, atherogenic, hyperlipidemic, diabetogenic, and hypertensive effects of corticosteroids are well recognized, and steroid-sparing protocols improve blood pressure control and reduce cardiovascular risk factors—particularly when used with a low-dose calcineurin inhibitor or combined with sirolimus, or sirolimus and mycophenolic mofetil.^{79,80} Poor therapeutic compliance with antihypertensive medications and immunosuppressive drugs is a well-established cause, not only of uncontrolled hypertension in kidney transplant recipients, but also of acute rejection, graft dysfunction, graft loss, and even death of the patient.^{81,82}

With the advancing age of the kidney allograft after implantation, the risk of chronic graft dysfunction increases, translating to a progressive drop in creatinine clearance by nearly an average of 1.5 to 2 mL/min/y.^{74,75} Several immunologic and nonimmunologic factors for recipient and donor origins have been identified.^{45,76} Acute and chronic rejection, and recurrent native and de novo kidney disease, in addition to other posttransplant stress factors (mainly calcineurin inhibitor nephrotoxicity and many of the inherited factors before transplant), are well-established recipient-dependent pathogenic factors for chronic graft dysfunction.

Specific recipient *ABCB1* haplotypes have been shown to modify the risk of acute rejection,⁸⁵ and combined donor-recipient homozygosity for the *C3435T* variant in *ABCB1*, have been significantly associated with increased susceptibility to chronic allograft damage, independent of graft quality at implantation.⁸⁶ Moreover, kidney transplant recipients who are *CYP 3A5*1* expressers are more prone to develop tacrolimus-associated nephrotoxicity, especially in those who continue corticosteroid therapy.⁸⁷ Patients with hereditary nephritis may develop recurrent or de novo kidney disease after transplant.²⁵ Hypertension and proteinuria are commonly associated features with chronic graft dysfunction, and when present, they may result into further deterioration in graft function.

Low estimated glomerular filtration rate and albuminuria have been shown in a recent meta-analysis of large cohorts of chronic kidney disease or increased risk for chronic kidney disease populations to be independently associated with progressive chronic kidney disease, end-stage renal disease, and all cause and cardiovascular mortality.^{31,83,84} Volume overload is a frequent complication of advanced renal failure, representing one of the most common reasons behind the higher proportion of chronic kidney disease patients with uncontrolled hypertension compared with those hypertensive individuals in the general population.

Donor factors

On these recipient-related factors are superimposed additional variables that are related to the kidney donor.^{1-3,9,51-56,59,64,71,73,76,86,88-93} As in the recipient, old age, pre-existing hypertension, diabetes mellitus, subclinical kidney disease, and nephron under dosing (innate, female to male donor, old age, and donor-recipient body mass index mismatch) represent potential causes for development or aggravation of hypertension posttransplant.^{1-3,9,59,64,71,73,91-92}

New evidence is emerging regarding the potential role of the donor genetic makeup in the pathogenesis of posttransplant hypertension. Kidney recipient-related healthy volunteers who can be potential donors, exhibit significantly higher pulse wave velocity (an indicator of atherosclerosis) than do nonrelated donors.⁵⁶ Family members of consanguineous dialysis patients are at increased risk of developing renal disease.⁹³ A particular kidney donor, *ABCC2* genotype, is associated with delayed graft function in certain kidney transplant recipients.⁵¹ Similarly, kidney grafts obtained from donors carrying certain polymorphisms of the *ABCB1* and *CYP 3A5* genes are highly prone to develop cyclosporine nephrotoxicity,^{52,53} a major component of the nonimmunologic cause of chronic graft dysfunction.^{45,76}

Interestingly, these same *ABCB1* polymorphisms affecting *P-gp* expression in the donor are associated with chronic histologic damage,⁸⁶ and adversely influence long-term graft outcomes by decreasing renal function and graft loss in calcineurin inhibitor-treated kidney transplant recipients.⁵⁵ Transplanting kidney allografts from donors with multiple *MYH9* risk alleles into recipients with similar genetic and ethnic background may lead to early fulminant nephrotic

syndrome, hypertension, and subacute loss of kidney function soon after transplant.⁹⁰

In conclusion, arterial hypertension in kidney transplant recipients is a major amplifier of the chronic kidney disease and cardiovascular disease continuum. It does not represent a single phenomenon, but rather, is multifactorial, reflecting a multipathogenic disease state with serious repercussion affecting graft and patients survival. It is a major cause of graft loss from chronic graft dysfunction and from patient cardiovascular mortality. Despite appropriate therapeutic vigilance, blood pressure control remains poor because of the high cardiovascular risk profile of the donor-recipient pair. Although optimal blood pressure level remains unknown, it is recommended that blood pressure be maintained in kidney transplant recipients < 130/80 mm Hg,⁹⁴ and maybe \leq 125/75 mm Hg in the presence of proteinuria (as has been recently reported in diabetic^{95,96} and nondiabetic chronic kidney disease patients^{97,98}).

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