Hypertension after kidney transplantation

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INTRODUCTION

- Kidney transplantation is considered the optimal choice for renal replacement therapy in ESKD due to improved survival and quality of life compared to dialysis modalities
- Nevertheless, cardiovascular disease remains the leading cause of death in these patients in the early (< 10) post-transplant years.
- Among traditional cardiovascular disease risk factors, hypertension represents the most prominent comorbidity post transplantation and a major cause of allograft dysfunction and adverse patient outcomes.

- The diagnosis and treatment of hypertension in kidney transplantation has been traditionally based on office BP measurements; BP control therefore remains suboptimal due to high rates of resistant and masked hypertension and abnormal diurnal BP patterns.
- Controversies over BP targets and optimal antihypertensive regimen remain unresolved and should be further explored in well-designed RCTs in order to optimize hypertension management in this population.

Prevalence of hypertension and abnormal BP phenotypes

- The prevalence of hypertension is particularly high among KTRs with previously reported rates between 70%-90% and more recently even exceeding 95% of this population.
- The source of variability in estimates of prevalence, control and different phenotypes of hypertension : differences in the definitions and in the type of BP measurement used (in office *vs* out-of-office setting) across various studies.
- Defining the diagnostic threshold for hypertension based on office and ambulatory BP measurements has been a matter of intense debate in CKD patients and more specifically in KTRs, with the two major existing hypertension guidelines producing confusion.

- The cutoff values for hypertension diagnosis proposed by the 2017 ACC/AHA guidelines for office and ABPM measurements were ≥ 130/80 mmHg and ≥ 125/75 mmHg, respectively, while those proposed by the 2018 ESC/ESH guidelines were office BP ≥ 140/90 mmHg and ABPM ≥ 130/80 mmHg.
- In the more recent KDIGO BP guidelines, hypertension was defined as office BP ≥ 130/80 mmHg and ABPM ≥ 125/75 mmHg, in agreement with the 2017 ACC/AHA guidelines.

- Recent guidelines recommend the use of out-of-office BP measurements as a complementary tool for improving the management of hypertension.
- In KTRs the wider use of ABPM has led to the recognition of abnormal diurnal BP patterns and BP phenotypes.
- The rates of non-dipping status have been reported to range between 36%-95% and that of nocturnal hypertension between 69%-77% (according to the nighttime ABPM > 120/70 mmHg cutoff value for both).

- In an Italian cohort of 260 KTRs followed-up for 3.9 years, the agreement between 785 paired office and 24-h ABPM measurements was assessed, revealing significant discordance in 37% of all visits (κ-statistics = 0.25, indicating poor agreement).
- In 12% of all visits, patients were misclassified as hypertensive according to the office BP > 140/90 mmHg criterion while 24-h ABPM was normal according to the < 130/80 mmHg criterion (white-coat hypertension).
- in 25% of all visits patients were classified as normotensive according to the office criterion, while 24-h ABPM was > 130/80 mmHg (masked hypertension).

- In a cross-sectional study from Spain with 868 KTRs, the prevalence of white-coat and masked hypertension was 12% and 20%, respectively, applying similarly the ESC/ESH criteria.
- Absence of SBP dipping pattern was evidenced in 80% of patients.

- In a recently published cross-sectional study with 205 KTRs, the prevalence of hypertension and the diagnostic performance of the two existing office BP thresholds for defining hypertension (adopted by the ESC/ESH and ACC/AHA guidelines mentioned above) was comparatively assessed.
- Prevalence of hypertension was 88.3% and 92.7% according to the ESC/ESH with ACC/AHA definitions for office BP measurements and 94.1% and 98.5% according to the respective ABPM thresholds.

- Moderate to fair agreement between office BP and 24-h ABPM was shown for both thresholds (κ-statistics = 0.52, $P < 0.001$; κ-statistics = 0.32, $P < 0.001$, respectively).
- Prevalence of white coat and masked hypertension was 6.7% and 39.5% using the office BP ≥ 140/90 mmHg and 5.9% and 31.7% using the office BP ≥ 130/80 mmHg threshold.
- Notably, ABPM revealed significantly lower control rates among hypertensive patients compared to office BP measurements using both definitions (69.6% for office *vs* 38.3% for ABPM measurements with the ESC/ESH thresholds; 43.7% *vs* 21.3% respectively with ACC/AHA thresholds).

- The above findings underline the need for more extensive use of 24-h ABPM in KTRs, similarly to what is currently being increasingly recommended for the general population.

Association of hypertension with target organ damage

- In KTRs, abnormal dipping status (non-dipping and reverse-dipping) independently predicts kidney function deterioration, while nighttime BP and night-day ratio are strongly associated with carotid-intimal media thickness.
- Increased urinary albumin and protein excretion have been associated with hypertension in KTRs and are both independent predictors of graft loss.

- Several longitudinal studies have reported an association of hypertension with LVH in KTRs, while significant reduction in LVMI and regression of LVH have been observed in the first 2-3 years following kidney transplantation.
- However, this regression may be compromised by persistence of hypertension, high pulse pressure and high sodium intake.
- Moreover, reversal of uremic cardiomyopathy has been recently questioned according to the results of a recent meta-analysis where no difference in LVMI was detected following kidney transplantation after pooling data from four studies with 236 participants [standardized mean difference = 0.07, 95% CI: 0.41-0.26].

- Masked or sustained hypertension were independent predictors for LVH in a cohort of 221 children and young adults with kidney transplant .
- In a recently published meta-analysis pooling data from 22 studies (2078 participants), 24-h ABPM was found to be a stronger predictor of renal function decline
- Abnormal dipping status also identified a subgroup of KTRs at risk for target organ damage.

Prognostic impact of hypertension for adverse clinical outcomes

- Hypertension in KTRs has been consistently shown to be associated with a higher incidence of kidney function decline, poor graft survival and worse patient survival.
- In the Collaborative Transplant Study, a retrospective cohort that evaluated the impact of hypertension on long-term kidney function in 29751 KTRs, a strong graded relationship between post-transplant BP and subsequent graft failure, even when patient death was censored, was reported for the first time.
- In a subsequent sub-analysis of the Collaborative Transplant Study with data from 24404 patients, the same authors showed that SBP values consistently lower than 140 mmHg during the first 3 years post transplantation were associated with the best 10-year graft and patient outcomes

- In another retrospective cohort of 1666 patients, each rise in SBP by 10 mmHg was associated with a 12% higher risk for graft failure [RR= 1.12, 95%CI: 1.08-1.15], a 17% higher risk for death censored graft failure (RR = 1.17, 95%CI: 1.12-1.22) and an 18% higher risk for death (RR = 1.18, 95%CI: 1.12-1.23), even after adjusting for acute rejection and decreased kidney failure that were previously reported to trigger BP increases and therefore further supported the independent beneficial effect of BP control.
- Microalbuminuria and macroalbuminuria, both markers of target organ damage associated with hypertension, have been similarly shown to be independent predictors of death compared to normoalbuminuria OR = 5.55, 95%CI: 2.43-12.66; OR = 4.12, 95%CI: 1.65-10.29, respectively.

- In a French retrospective cohort of 17526 KTRs and 3288857 non-transplanted non-dialysis participants with a 5-year follow-up, an increased incidence of myocardial infarction in the former compared to the latter (5.8% *vs* 2.8%) was shown [HR = 1.45, 95%CI: 1.35-1.55].
- KTRs experiencing an MI were more likely to be hypertensive than their non-KTR counterparts (76.0% *vs* 48.1%, $P < 0.0001$).
- Hypertension is an independent predictor of death from IHD and major ischemic heart events, with a reported increase by 20% in the risk for death from IHD per 10 mmHg SBP increments, during a follow-up of 5 years.

PATHOPHYSIOLOGY OF HYPERTENSION IN KTRS

1-Traditional risk factors

- Factors considered to be associated with an increased risk of hypertension in the general population, including age, male sex, smoking status, obesity, insulin resistance and syndrome of obstructive sleep apneas, are also present in patients undergoing kidney transplantation and may be aggravated, further contributing to new-onset or worsening hypertension.

2-Factors associated with impaired kidney function

- Impaired homeostatic mechanisms handling sodium and water excretion leading to hypervolemia and increased BP
- Renal sodium retention may be worsened by the use of immunosuppressive regimens, mainly corticosteroids and CNIs as well as during episodes of acute rejection(ischemic allograft damage)
- Dysregulation of the RAS system and sympathetic nerve overactivity, driven in the early post transplantation period by the native kidneys(increased peripheral vascular resistance)
- Increased arterial stiffness, endothelial dysfunction and imbalance between vasoconstrictive and vasodilating agents are also pertinent to CKD and further contribute to increased BP.

3-Factors associated with kidney transplantation

- **1-Immunosuppressive regimens**
- While mycophenolate mofetil and mammalian target of rapamycin inhibitors are considered low risk agents, corticosteroids and CNIs potentially trigger hypertension and other major comorbidities in KTRs.
- According to the results of a meta-analysis (34 studies, 5637 patients), complete steroid avoidance or withdrawal reduces the risk of incident hypertension and diabetes with no significant effect on graft or patient survival.

- The main cause of corticosteroid-induced hypertension is associated with partial activation of mineralocorticoid receptors by cortisol causing urinary sodium and water retention and therefore volume expansion.
- This mechanism has been however called into question, and a similarly important role of glucocorticoid receptors in vascular smooth cells has been proposed, leading to an increase in peripheral vascular resistance through attenuation of vascular response to vasodilators (nitric oxide) and upregulation of the angiotensin II receptor.

- The mechanisms of CNI-induced hypertension are multifactorial and involve impaired sodium and water excretion, upregulation of vasoconstrictive agents (thromboxane, endothelin-1), downregulation of vasodilating prostaglandins and alterations in regulation of intracellular calcium ions, leading to vasoconstriction of afferent arteriole, a decrease in GFR and an increase in peripheral vascular resistance.
- Tacrolimus has been associated with a lower incidence of hypertension but a higher risk for new-onset diabetes compared to cyclosporine.

- In an open-label RCT, 1645 KTRs were randomly allocated to receive standard-dose cyclosporine (target trough level 150-300 ng/mL for the first 3 mo; 100-200 ng/mL thereafter), low-dose cyclosporine (target trough level 50-100 ng/mL throughout the study), low-dose tacrolimus (target trough level 3-7 ng/mL throughout the study) or low-dose sirolimus (target trough level 4-8 ng/mL throughout the study) for 12 mo.
- Patients in all treatment groups received mycophenolate mofetil and corticosteroids; those randomized to low-dose regimens followed a 2-mo induction treatment with daclizumab.

- At study-end, patients in the low-dose tacrolimus group had the highest estimated GFR (65.4 mL/min) and highest rates of allograft survival (94.2%), followed by low-dose cyclosporine (93.1%), standard-dose cyclosporine (89.3%) and low-dose sirolimus (89.3%) ($P = 0.02$), therefore providing further evidence in favor of low-dose tacrolimus regimens.
- Accordingly, it is usually recommended to use minimal dosages of steroids (for example, 5 mg per day dose of prednisone) to achieve long-term immunosuppression in organ transplant patients without increasing the risk for hypertension.

- Belatacept is another biologic immunosuppressive agent approved by the US FDA since 2011 on the basis of evidence of non-inferiority in preventing acute rejection in KTRs provided from three RCTs comparing belatacept to cyclosporine.
- According to a meta-analysis (5 studies, 1535 participants), use of belatacept has been associated with lower BP levels and reduced incidence of chronic kidney scarring compared to CNIs.

- **2-Donor/recipient factors**
- Donor's age represents a major risk factor for development of post-transplant hypertension, along with considerable discrepancies in somatometric characteristics between donors and graft recipients (female to male transplantation, pediatric to adult transplantation, low donor/recipient body weight ratio), leading to a phenomenon of "underdosing" due to reduced donor nephron mass compared to recipient needs.
- These differences result in hyperfiltration, glomerular hypertrophy and increased intraglomerular pressure.

- Pre-existing donor hypertension : increased risk of post transplantation hypertension and allograft dysfunction
- Recipients from donors with a family history of hypertension :10-fold higher risk of requiring antihypertensive treatment
- Recipients of transplants from expanded criteria donors : higher risk for hypertension post transplantation.
- presence of genetic variants that affect the expression of cytochrome P450 3A5, apolipoprotein L1, P-glycoprotein and multidrug resistance protein 2

- With regards to recipient factors, the presence of native kidneys may further contribute to BP increments probably due to renin secretion.
- longstanding hypertension: atheromatosis of middle-sized conduit arteries and most importantly with reduced compliance and arterial stiffness of the aorta and the large arteries
- This vascular remodeling may not be fully reversible after kidney transplantation.

- **3-Transplant renal artery stenosis:** Prevalence of TRAS reportedly between 1%-23%, with a significant increase noted in diagnosed cases with the use of non-invasive imaging techniques.
- Refractory hypertension and worsening kidney function are the main clinical manifestations of TRAS, which usually develops 3-24 mo post transplantation and is associated with an increased risk of graft loss.

- With regards to the anatomic site, the stenosis can be: (1) Anastomotic (vascular damage at the time of surgery); (2) Proximal (recipient's atherosclerosis); and (3) Distal (with a non-fully elucidated pathogenesis related to mechanical and immunological factors).
- Since the recipient's iliac artery and not the abdominal aorta is the most common site of donor renal artery anastomosis, this connection between smaller arteries is prone to narrowing and subsequent development of TRAS pathophysiology, involving impediment of blood flow, renal hypoperfusion and activation of the renin-angiotensin- aldosterone system.

- Immunological factors leading to TRAS include immune-mediated vascular endothelial injury and development of *de novo* class II donor-specific antibodies.
- The association between TRAS and cytomegalovirus infection, as well as ischemia/reperfusion injury, has also been reported.
- In the absence of an RCT comparing endovascular angioplasty with or without stenting *vs* surgical vascularization in KTRs, angioplasty is the preferred treatment of TRAS with reported rates of clinical success (improvements in BP or kidney function) between 65.5%-94.0% and of technical success > 90%.

- **4-Acute and chronic kidney dysfunction:**
- Acute rejection may trigger new-onset hypertension, probably *via* activation of the renin-angiotensin system according to the patient's volume status.
- In this case, treatment of rejection is accompanied by improvement in BP levels, whereas hypertension that is not associated to acute rejection would be further deteriorated with modifications in doses of immunosuppression.

- Recurrence of the primary glomerular disease, tubular atrophy, interstitial fibrosis, chronic antibody mediated organ rejection, development of non-HLA agonistic anti-angiotensin-II type 1 receptor antibodies and thrombotic microangiopathy are the major contributors to chronic allograft injury leading to sudden rises of BP.
- Patients with positive angiotensin-II type 1 receptor antibodies represent a subset of those with antibody-mediated rejection in whom kidney dysfunction is associated with malignant hypertension and acute vascular lesions on biopsy.

HYPERTENSION TREATMENT IN KTRS

Targets of BP therapy

- Historically, no universal agreement regards to BP targets in CKD and more particularly in kidney transplantation (different BP thresholds used for diagnosis of hypertension)
- In the absence of specific focus on KTRs, the BP targets of CKD population were expected to be endorsed; according to the 2018 ESC/ESH guidelines : lowering BP to < 140/90 mmHg and towards 130/80 mmHg.
- However in the latest 2017 ACC/AHA and 2021 KDIGO guidelines: targeting BP less than 130/80 mmHg have been provided for KTRs.

Non-pharmacological measures

In the absence of evidence focused on KTRs:

- lifestyle modifications
- Low sodium intake (< 2 g/d)
- moderate-intensity physical activity (≥ 150 min/wk)
- adoption of a balanced diet
- maintenance of BMI and waist circumference within normal range (18.5 and 24.9 kg/m2 and < 102 cm, respectively)
- reduction in alcohol consumption and smoking cessation

Pharmacological measures

- In KTRs, the use of a dihydropyridine CCB is commonly advocated notably in the early post transplantation period (improving graft function and minimizing the vasoconstrictive effects of CNIs)
- CCBs have been uniformly associated with improved patient and graft outcomes in several studies.
- In contrast, the use of ACEis/ARBs in KTRs was considered a source of controversy for many years.

- RCT with 154 hypertensive KTRs : nifedipine 30 mg or lisinopril 10 mg 3 wk post transplantation, no differences were noted in BP control.
- Nevertheless, a significant increase was observed in measured GFR for nifedipine compared to lisinopril (mean between-group difference 9.6 mL/min, 95%CI: 5.5-13.7 mL/min) at 1 year, an improvement that was maintained at 2 years.

- The results of a 2009 Cochrane systematic review claimed that patients receiving ACEis were exposed to a higher risk of hyperkalemia and anemia and that in direct comparison with CCBs their use was associated with worse kidney function (mean between-group difference for estimated GFR -11.48 mL/min, 95%CI: -15.75 to -7.21).
- In a more recent meta-analysis conducted by Pisano *et al* pooling data from 71 RCTs and providing evidence on both ACEis and ARBs, a significant reduction in the risk for graft loss was observed by 42% with CCBs (16 studies, 1327 participants) and by 38% with ACEi/ARBs (9 studies, 1246 participants).

- In the 2021 KDIGO guidelines, use of a dihydropyridine CCB or an ARB has received a grade 1C recommendation for first-line treatment in KTRs, with potential benefits on graft survival (RR for graft loss compared to placebo: Dihydropyridine CCBs 0.62, 95%CI: 0.43-0.90; ARBs: 0.35, 95%CI: 0.15-0.84) outweighing side effects related to each class of agents.
- No significant effect on mortality or cardiovascular events was detected with either of these classes.

CONCLUSION

- More recent studies using ABPM suggesting a higher prevalence of uncontrolled, masked and nocturnal hypertension in KTRs
- Recent analyses provide evidence that 24-h ABPM outperforms office BP measurements with regards to markers of target organ damage, including LVMI, carotid-intimal media thickness and flow-mediated dilation, and represents an independent predictor of kidney function decline and graft loss.

- Recent guidelines recommend the use of dihydropyridine CCBs, as they exhibit a favorable profile due to their vasodilatory effects counteracting vasoconstriction induced by CNIs and their favorable effects on outcomes, or ARBs due to their favorable effects on graft survival, despite previously reported undesirable effects on risk of hyperkalemia and anemia.

Thanks for your attention