

Hypertension after Kidney Transplantation: Clinical Significance and Therapeutical Aspects

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Abstract

Citation: Severova-Andreevska G, Danilovska I, Sikole A, Popov Z, Ivanovski N. Hypertension after Kidney Transplantation: Clinical Significance and Therapeutical Aspects. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2019.264>

Keywords: Kidney transplant recipients; Arterial hypertension; Antihypertensive drugs; Review article

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Received: 02-Feb-2019; **Revised:** 02-Apr-2019; **Accepted:** 03-Apr-2019; **Online first:** 14-Apr-2019

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Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

Most of the kidney transplanted patients develop arterial hypertension after renal transplantation. Together with very well-known and usual risk factors, post-transplant hypertension contributes to the whole cardiovascular morbidity and mortality in the kidney transplant population. The reasons of post-transplant hypertension are factors related to donors and recipients, immunosuppressive therapy like Calcineurin Inhibitors (CNI) and surgery procedures (stenosis and kinking of the renal artery and ureteral obstruction). According to Eighth National Committee (JNC 8) recommendations, blood pressure > 140/90 mmHg is considered as hypertension. The usual antihypertensive drugs used for the control of hypertension are Calcium channel blockers (CCB), Angiotensin-converting enzyme (ACE) inhibitors, Angiotensin –II receptor blockers (ARB), B- blockers and diuretics. Follow the KDIGO guidelines the target blood pressure < 140/90 mmHg for patients without proteinuria and < 125/75 mmHg in patients with proteinuria is recommended. Better control of post-transplant hypertension improves the long-term graft and patient's survival.

Introduction

Post-transplant cardiovascular disease

Kidney transplantation is the optimal treatment of patients with ESRD who would otherwise require dialysis. Despite the fact that kidney transplantation reduces the risk of both, cardiovascular morbidity and mortality remain a leading cause of death with functioning graft among kidney transplant recipients (KTR) [1], [2], [3], [4]. Among the traditional and non-traditional risk factors, post-transplant hypertension (PTxH) remains one of the major contributors to the post-transplant cardiovascular morbidity (PTCVM) and mortality and the most common causes of chronic graft dysfunction and kidney transplant failure [5], [6], [7], [8]. Cardiovascular pathology is responsible for approximately 40% of deaths among KTR [9]. The

annual risk of fatal and non-fatal cardiovascular events in KTR is 3-5% which is 50-fold higher than in the general population. Both, classical and non-classical cardiovascular factors equally contribute to the increased incidence of PTCVM [10], [11], [12].

Hypertension and Post-Transplant Hypertension

According to 8-the report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 8) the new blood pressure classification was introduced bearing in mind the target organ damage and the presence of other factors of comorbidity like Chronic Kidney Disease (CKD), Diabetes, BMI, Hyperlipidemia etc. Thus, Hypertension is defined if office BP is $\geq 140/90$ and ambulatory BP $\geq 130/90$ in normal persons under the age of 60. The prevalence of PTxH among kidney

recipients is between 55-90% [13], [14]. Significant contributions to the clinical outcome of hypertensive KTR are age, BMI, time after the surgery, gender, presence of chronic allograft nephropathy, cellular and antibody-mediated rejection episodes, use of immunosuppressant, etc.

Regarding hypertension in CKD and transplant patients, KDIGO recommendations are more strict: The BP should be kept below or equal of 130/85 and 125/75 if the patients are proteinuric [15], [16]. The introduction and acceptance of ambulatory blood pressure (ABP) control in the follow up of hypertension in general population as well as in KTR enables more detailed classification of hypertension and therefore a new patient stratification. In KTR both, office and ambulatory BP control should be performed in every day clinical practice. Out of the hypertension classification according to the JNC 8, recently different types of hypertension were clinically introduced as: Masked Hypertension (MH), White Coat Hypertension (WCH), Sustained Hypertension (SH), Isolated Nocturnal Hypertension (INH), Isolated Diurnal Hypertension (IDH), Awake and Asleep hypertension, all with confirmed clinical significance [17], [18], [19], [20]. The most investigated types of hypertension among kidney transplant recipients and CKD patients are WCH and MH. WCH is defined as well-controlled home hypertension but poorly controlled clinic hypertension. MH is the reverse phenomenon, poorly controlled BP at home but normal in the clinic.

The prevalence of MH among KTR is between 23 and 58% with a confirmed harmful effect on graft and patients survival. WCH with a percentage of 4-20% is less important, but still require awareness [20], [21], [22]. The appearance of resistant hypertension (7% of PTxH) is also a confirmed entity which should be treated successfully with carefully chosen antihypertensive drugs [23], [24], [25]. All types of hypertension defined by ABP monitoring are largely investigated in renal transplant recipients and are parts of the efforts to control PTxH on a recommended level according to KDIGO criteria. Table 1 presents a different classification of Hypertension which is also used in KTR.

TABLE 1: Definition, types and classification of hypertension

Types	Values
CBP – clinical blood pressure	Average BP \geq 140/90
ABP – Ambulatory blood pressure	Average BP \geq 130/90
Awake ABP	BP \geq 135/85
Sleep ABP	BP \geq 120/70
Normotension	CBP and ABP within the normal range
Masked Hypertension	CBP – within normotensive range ABP – within hypertensive range
White coat Hypertension	CBP – within hypertensive range ABP – within normotensive range
Sustained Hypertension	CBP – within hypertensive range ABP – within normotensive range
Nighttime Hypertension (Nocturnal)	Awake ABP – within normotensive range Sleep ABP – within hypertensive
Daytime Hypertension (Diurnal)	Awake ABP – within hypertensive range Sleep ABP – within normotensive range
All-day Hypertension	Awake ABP – within hypertensive range Sleep ABP – within hypertensive range

CBP – office control of BP; AMB – 24 h – ambulatory BP control.

Pathogenesis of post-transplant hypertension

The pathogenesis of hypertension during the post-transplant period is multifactorial which include traditional and non-traditional risk factors. Some of them are related to transplant surgery, underlying kidney disease, use of immunosuppression, chronic or acute graft rejections. The majority of these factors are reversible, and some are preventable. They are presented in Table 2.

TABLE 2: Causes of Post-Transplant Hypertension

Factors	Examples
Immunosuppression	Cyclosporine Tacrolimus Glucocorticoid
Graft disease	Delayed graft function Chronic allograft nephropathy De novo and recurrent glomerular disease Acute rejection
Recipient factors	Underlying kidney disease Essential hypertension Native kidney presence Excessive weight gain Secondary Hyperparathyroidism
Donor factors	Preexisting donor hypertension Advanced donor age Subarachnoidal haemorrhage Use of right kidney Female gender
Surgery	Transplant renal artery stenosis Use of right kidney Cold and warm ischemia time Renal artery and vein anastomosis time

Regarding the mechanism of PTxH it seems that both, volume load and vasoconstriction are present. In the case of renal artery stenosis and CNI dependent hypertension, the vasoconstriction dominates due to the increase of renin-angiotensin system, up-regulation of endothelin-1 and reduction of the bioavailability of nitric oxide. Both cyclosporine and tacrolimus may cause a salt-sensitive form of hypertension with the consecutive fluid overload [26], [27], [28].

Among donor dependent risk factors are already well-confirmed age, history of hypertension, underlying disease (diabetes) vascular disease and genetic predisposition. The use of steroids facilitates sodium and volume retention and contributes to insulin resistance and diabetes.

The positive experience of renal denervation of native kidneys in renal transplant recipients, even in several cases, emphasizes the possible role of sympathetic overactivity [29], [30]. The appearance of renal transplant artery stenosis put for sure RA system in the game which could be solved with the appropriate therapeutic procedure. In the cases of recurrent or de-novo glomerulonephritis, classical mechanisms of renal hypertension are involved [31].

Long term consequences

Increased cardiovascular morbidity and mortality

Like in general population many studies confirmed a PTxH as a strong risk factor for ischemic heart disease, congestive heart failure, coronary artery disease, increased arterial stiffness and stroke. The most clinically significant consequence of hypertension is left ventricular hypertrophy, left atrial enlargement and diastolic dysfunction which are responsible for a variety of cardiovascular events after kidney transplantation. Some authors find a strong correlation between left ventricular hypertrophy and post-transplant isolated nocturnal hypertension while 24-hour ABP hypertension and altered Night-Day BP profile are independently associated with Carotid Intima/Media thickness [32], [33].

Chronic Graft Dysfunction

Together with rejection, PTxH is one of the major factors which is responsible for reduced long-term graft and patients survival. A single centre study on long-term kidney transplant survival rate, KTR with diastolic BP of 89-99 mm Hg had statistically decreased GFR compared to recipients with lower blood pressure. Also, recipients with lower blood pressure in the first year have better graft survival. The study of Mange et al. demonstrated the increased risk of graft failure for every 10 mm Hg in SBP and 10 mm Hg in diastolic BP [34]. Higher blood pressure correlates with greater rates of progression of decreased renal function.

Chronic allograft nephropathy, renamed by Banff classification with interstitial fibrosis and tubular atrophy (IF-TA), is associated with gradual deterioration in graft function, relevant proteinuria and new or worsening hypertension in the absence of any other worsening factors. Non-HLA antibody-mediated rejection, with an antibody targeting angiotensin II type receptors, develops hypertension secondary to vascular rejection. According to the Collaborative Transplant Study PTxH is an independent risk factor for chronic allograft nephropathy and graft failure [35]. Increasing systolic BP was associated with decreased graft survival at any level of diastolic pressure.

Regarding the association with host alloimmune response and acute and chronic rejection, post-transplant hypertension has been confirmed among the rejection of free kidney transplant recipients. However, it could be not excluded that PTH has a deleterious effect of graft small vessels with an increasing of immunogenicity of impaired graft tissue. In addition, some experimental studies confirmed that hypertension increases expression of growth factors and MHC II in chronic allograft nephropathy. PTxH is strongly associated with chronic allograft nephropathy

and vice-versa and presents a significant non-immunological risk factor for late graft failure. Altered day-night BP profile, reverse dipper pattern are also associated with early inflammation and constitutes an independent predictor of graft failure [36], [37], [38], [39], [40].

Treatment

Lifestyle

The usual recommendations of the Hypertension Associations worldwide may also be applied to kidney transplant recipients. Slightly reduction of salt intake, 30-60 min of moderate daily physical or aerobic activity, maintenance of body mass index between 18-25 kg/m² and keeping the waist circumference under 102 for men and <88 for women. Light dietetic measures could also be recommended as a low-fat diet, moderate alcohol consumption and more vegetables and fruit in everyday nutrition [27].

Treatment target and pharmacological management

Bearing in mind all the consequences of non-controlled BP in KTR, achievement of target BP level is strongly recommended. The pharmacological treatment should start when office BP is more than 140/90 or ABP more than 130/80 as well as in any case of isolated nocturnal, masked and sustained hypertension or altered day-night time BP profile. The start should be with thiazide diuretics with the addition of Calcium Channel Blockers (CCB), Angiotensin-II Receptor Blockers (ARB) and Angiotensin-II Converting Enzyme (ACE) inhibitors according to the KDIGO and JNC 8 recommendations [13], [15]. But the regulation and reaching of target BP level are far of an easy task. An average analyses of BP in kidney transplant recipients confirm that despite the whole spectrum of antihypertensives and careful BP measurements, the majority of the patients are still uncontrolled. Whenever we should start our pharmacological approach to the PTxH, hypertensive effects of CNI (especially Cyclosporine A) has to be taken into consideration. The use of other immunosuppressive protocols including mTOR inhibitors or Belatacept instead of CNI may provide better control and beneficial effects on long term graft and patients survival [27].

Invasive procedures

In patients with proven transplant renal artery stenosis, Percutaneous transluminal angioplasty (PTA) and surgery could be applied if the degree of a

stenotic lesion is more than 80%. However, it should be careful in decision because of polar infarcts, haematoma, intimal flaps, thrombosis and anastomotic re-stenosis [29], [30].

Renal denervation of the native kidneys is an interesting and probably promising therapeutic procedure which can be effective in some individual cases. A few reports confirmed a beneficial effect of this procedure, but it is still far of any definitive conclusion. Interestingly the effect was on nocturnal, and ABP was some of the non-dipper patients became dipper [31].

In the recent report from Dallas (USA), Lerman et al. performed laparoscopic bilateral nephrectomy in 5 cases of resistant hypertension in kidney and pancreas transplant recipients. Mean arterial pressure improved in the next six months after the surgery and renal function remained stable. Despite the beneficial results of this small report, there is no sufficient data to recommend this aggressive procedure. The future controlled studies should confirm the justification of surgical approach as a therapeutic measure [41].

Conclusion

The high prevalence of arterial hypertension in KTR contributes to chronic graft damage and significantly decreased graft and long-term patient survival. Despite the evidence of the adverse effects of hypertension, BP control has been poor despite the use of different combinations of antihypertensive drugs. Adequate diagnosis methods should be permanently implemented using classical office and home BP readings. Twenty-four hour ABPM allows very valuable information on circadian rhythm and nocturnal blood pressure. PTH remains a very important issue in clinical follow up of kidney transplant recipients.

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