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REVIEW

Hypertension in kidney transplant recipients

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Summary

Arterial hypertension is frequently observed in renal transplant recipients. Its pathogenesis is multifactorial in most cases. Calcineurin inhibitors (CNI) can increase peripheral vascular resistance by inducing arteriolar vasoconstriction and can cause extracellular fluid expansion by reducing the glomerular filtration rate (GFR), activating the renin–angiotensin system (RAS), and by inactivating the atrial natriuretic peptide. Glucocorticoids can impair urinary water and salt excretion. Poor graft function can lead to increased extracellular volume and inappropriate production of renin. Native kidneys, older age of the donor and transplant renal artery stenosis (TRAS) may also contribute to the development of hypertension. Arterial hypertension not only can increases the risk for cardiovascular events but can also deteriorate renal allograft function. A number of studies have shown that the higher the levels of blood pressure are, the higher is the risk of graft failure. On the other hand, a good control of blood pressure may prevent many cardiovascular and renal complications. Appropriate lifestyle modification is the first step for treating hypertension. Calcium channel blockers (CCB) and renin–angiotensin system (RAS) inhibitors are the most frequently used antihypertensive agents, but in many cases, a combination of these and other drugs is required to obtain good control of hypertension.

Introduction

One of the most frequent complications of renal transplantation is represented by arterial hypertension. About 70–90% of renal transplant recipients have either arterial hypertension or require antihypertensive therapy [1–3]. Studies reporting continuous ambulatory blood pressure measurements that provide a better assessment of the diurnal variation also showed a high rate of nondippers among renal transplant recipients [4,5]. In this article, we will review the pathogenesis, the main consequences and the possible management of post-transplant hypertension.

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 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 CNI and glucocorticoids (GCs) can exert hypertensive effects.

The hypertensive role of the CNI

These agents may increase systemic vascular resistance and cause renal vasoconstriction through several mechanisms, including activation of vasoconstrictor factors, such as renin–angiotensin system, endothelin, and thromboxane A2, while reducing the production of vasodilator compounds, such as nitric oxide and prostacyclin [6–10]. Cyclosporin, but not tacrolimus, can also cause an early rise in sympathetic tone that may contribute to the acute elevation of blood pressure. However, it is unlikely that sympathetic activity also contributes to the increase in blood pressure during chronic use because sympathetic activity is suppressed after 2 weeks of treatment [11]. CNI may also increase the levels of plasminogen activator inhibitor (PAI), an inducer of interstitial fibrosis and tubular atrophy and an inhibitor of matrix degradation. PAI may favour the recruitment of interstitial cells [12] and enhance the expression of mRNA transforming growth factor-beta1 (TGF-beta1), which is a central mediator of fibrogenic remodelling processes. TGF-beta is a biologically multi-potent regulatory protein implicated in regulation of cellular growth, differentiation, extracellular matrix formation and wound healing. This cytokine may induce trans-differentiation to myofibroblasts and extracellular matrix production either directly [13] or through the activation of the signal pathway of SMAD proteins that exert different roles in regulating cell growth, differentiation and apoptosis [14]. Cyclosporin and tacrolimus up-regulate the intracellular proteins SMAD-2 and -3 that increase the expression of alpha-smooth-muscle actin connective-tissue factor [15], whereas they down-regulate SMAD-7 and -8 that inhibit the signal pathway [16]. Important roles are also played by phosphatases that may inactivate SMAD phosphorylation [17] and by the molecular cross-talk between pro-fibrogenic TGF-beta and anti-fibrogenic interferon-gamma [18]. Over-expression or inadequate contra-regulation of TGF-beta can enhance the expression of platelet-derived growth factor, fibroblast growth factor, and endothelin, which can lead to cellular proliferation, hypertension and chronic allograft dysfunction [19]. As a consequence of these functional and pathological abnormalities, there is a reduction in glomerular filtration rate (GFR) and sodium retention. Moreover, CNI can increase sodium and water retention by activating the RAS and by inactivating the atrial natriuretic peptide [20]. These changes lead to an expansion of extracellular fluids and to an increased cardiac output. In many transplant recipients, renin plasma levels are normal, reflecting apparently a normal production by the allograft and by the native kidneys; however, these levels are inappropriately elevated in a setting characterized by extracellular fluid expansion, and can actually collaborate to the development of hypertension [21]. Finally, both cyclosporin and tacrolimus are neurotoxic and can alter sympathetic outflow, which plays an important role in the mediation of hypertensive adverse events [22].

Although cyclosporin and tacrolimus produce clinical post-transplant hypertension via similar mechanisms, hypertension is less common and severe in patients given tacrolimus than in those receiving cyclosporin. In healthy subjects treated with 2 weeks of tacrolimus and cyclosporin in randomized order, mean arterial blood pressure did not modify under tacrolimus, whereas it significantly increased under cyclosporin [23]. In a randomized trial comparing the two drugs in *de novo* renal transplant recipients, the incidence of hypertension was significantly more frequent in patients assigned to receive cyclosporin compared with those treated with tacrolimus [24]. Five-year follow-up results from a US randomized trial indicated that significantly fewer tacrolimus than cyclosporin recipients were receiving antihypertensive therapy [25]. In case of severe hypertension in cyclosporin-treated transplant, switching to tacrolimus resulted in a significant reduction in blood pressure [26]. Also, an early replacement of cyclosporin with sirolimus can significantly improve the mean blood pressure in *de novo* renal transplant patients [27]. Finally, hypertension may be easily controlled by minimizing the doses of cyclosporin. In one trial, renal transplant recipients were assigned to receive low-dose or minimal-dose cyclosporin associated with everolimus. After 1 year of follow-up, the mean levels of blood pressure were within normal values [28].

The hypertensive role of glucocorticoids

Logistic regression analyses showed that GCs are independently associated with post-transplant hypertension [29,30]. The hypertensive effect is mainly related to the sodium and water retention caused by the partial activation of mineralocorticoid receptors. However, also activation of GC receptors may play a role in steroid-related hypertension. In a mouse model of GC-induced acute hypertension, a critical role was played by vascular smooth muscle activated by GC receptors [31].The hypertensive effect of GC depends on the dosage. A maintenance dose of prednisone lower than 10 mg/day has little role in contributing to post-transplant hypertension [30]. To support the hypertensive role of GC, a recent meta-analysis of randomized controlled trials comparing a maintenance steroid group with complete avoidance or withdrawal of steroids showed that the incidence of

hypertension was significantly reduced in steroid-free patients [32].

Allograft dysfunction

Whatever its cause, the allograft dysfunction is strongly associated with arterial hypertension [29,30,33,34]. A poor kidney function may cause salt and water retention with increase in extracellular volume and cardiac output and inappropriate activation of the RAS with increased peripheral vascular resistance and further salt and water retention.

Native kidneys

The presence of native kidneys may contribute to post-transplant hypertension as suggested by a higher prevalence of hypertension in transplant recipients with native kidneys than in those who received bilateral nephrectomy [29,35]. As reported above, a possible explanation rests on the renin secretion by native kidneys which, although normal in absolute, might be inappropriately elevated in the presence of an increased extracellular volume [21].

Familial hypertension

Patients who received the kidney from a subject of a hypertensive family have a higher probability of developing arterial hypertension after transplantation than patients who received a kidney from a member of a normotensive family [36].

Age of the donor

The risk of post-transplant hypertension increases by 28% for each 10-year increase in donor age and is more than doubled if the donor carries aortorenal atheroma [37].

Transplant renal artery stenosis

Transplant renal artery stenosis (TRAS) accounts for 1–7% of cases of post-transplant hypertension [34]. However, the actual role of TRAS is difficult to assess as many cases detected by Doppler ultrasound are haemodynamically insignificant and cannot be considered responsible for hypertension. In TRAS, the evolution of the raised blood pressure can have three phases. In the first phase, blood pressure is raised by the direct pressor action of elevated peripheral plasma angiotensin II. In the second phase, circulating angiotensin II may be more modestly raised, but probably is still important in pathogenesis. Occasionally, in this phase, there is rapid elevation of renin, angiotensin II and aldosterone, and severe hypertension, with sodium retention and potassium depletion. In the later third phase, angiotensin II is not elevated and the renin system may no longer be concerned in the hypertension. In the first two phases, but not in the third phase, relief of the stenosis, removal of the affected kidney, or lowering of angiotensin II with converting enzyme inhibitors can correct the hypertension. In the affected kidney with renal artery stenosis, the intrarenal content of renin is raised and its distribution altered; these changes represent compensatory local actions [38]. There are three main locations for graft artery stenosis: (i) at the site of anastomosis, probably as a consequence of the surgical technique; (ii) at the distal site of anastomosis, the cause of which is still ill defined; (iii) at the distal arterial branches, where multiple stenoses can be seen, probably as an expression of a chronic rejection. Cytomegalovirus infection and delayed graft function were risk factors significantly associated with TRAS in a multivariate analysis [39]. The diagnosis of TRAS may be suspected in the presence of severe hypertension, if there is a bruit at the auscultation, and/or in the case of a rapid deterioration of renal function after administration of RAS inhibitors. The differential diagnosis between TRAS-related hypertension and other causes of hypertension is of major importance in view of the potential complications related to surgery and/or percutaneous transluminal angioplasty (PTA). Duplex Doppler of the allograft artery is the routine method for screening patients [40]. However, it may overestimate the significance of TRAS. Arteriography, magnetic resonance angiography, or computed tomography angiography, may confirm the diagnosis, but cannot predict the success of surgery or PTA. An increase in plasma renin activity of 260% 1 hour after administration of captopril [41] and a captopril renogram test [42] may help in identifying functionally significant stenosis.

Postbiopsy arteriovenous fistula

It is a rare cause of *de novo* hypertension. The diversion of blood flow from normal renal structures, caused by the abnormal communication between artery and vein, may result in local ischaemia and renin-mediated hypertension.

Consequences of post-transplant hypertension

Cardiovascular complications

Arterial hypertension is a strong risk factor for ischaemic heart disease [43], congestive heart failure [44], coronary heart disease [45] and stroke [46]. Angiotensin II, which is often elevated in patients with hypertension, can contribute to atherogenesis by stimulating the growth of smooth muscle cells and lipoxygenase activity which in

turn can increase inflammation and oxidation of low density lipoproteins. Hypertension also has pro-inflammatory actions on endothelium with increased formation of hydrogen peroxide and free radicals in plasma [47]. A major consequence of hypertension is left ventricular hypertrophy, which is an important risk factor for a variety of cardiovascular sequelae, such as angina pectoris, myocardial infarction, stroke, congestive heart failure, arrhythmias and sudden death.

Graft dysfunction

Hypertension can also be harmful for the long-term kidney graft outcome. Retrospective studies showed that increased levels of systolic blood pressure and diastolic blood pressure after transplantation were significantly associated with an increased risk of graft failure. Hypertension was an independent risk factor for graft failure, even when serum creatinine concentrations were normal and when patients had never been treated for rejection crisis [48,49]. This analysis confirmed that hypertension was an independent risk factor for graft failure, even when serum creatinine concentrations were normal and when patients had never been treated for rejection crisis [50]. Kasiske *et al.* [51] found that each increment in systolic blood pressure of 10 mmHg above 140 mmHg was associated with a 12% relative risk for graft failure and an 18% relative risk for patient death. These risks persisted even after adjusting for kidney allograft function and rejection episodes. Other investigators reported that high pulse pressure was associated with poor graft function [52,53] and emerged as the strongest blood pressure component influencing overall and death-censored kidney allograft survival [53].

Treatment

As transplant recipients with hypertension are at risk for cardiovascular morbidity and renal allograft dysfunction, aggressive means should be used to lower blood pressure. Two meta-analyses of hundreds of randomized trials in non transplant patients provided evidence that reducing blood pressure may decrease the risk of cardiovascular disease. [54,55]. A good control of blood pressure may also protect renal graft function in kidney transplant recipients. Opelz *et al.* [56] showed that lowering systolic blood pressure, even after 3 years of post-transplant hypertension, was associated with improved patient and graft survival. Other investigators reported a significantly longer graft survival in renal transplant recipients with a controlled blood pressure than in those with a non controlled blood pressure [57]. The last KDIGO guidelines recommend measuring blood pressure at each clinic visit and suggest maintaining blood pressure at <130 mmHg systolic and <80 mmHg diastolic if >18 years of age, and <90th percentile for gender, age, and height if <18 years old [58]. Other guidelines in non transplant patients recommend a blood pressure target of 125/75 mmHg in patients with proteinuria [59]. Unfortunately, however, in spite of treatment, as many as 50% of transplant patients have a systolic blood pressure >140 mmHg [53,60].

Lifestyle

Modifying the style of life is the first measure to be taken for treating hypertension in renal transplant recipients. The recommendations of the Canadian Hypertension Education Program [61] may be applied also to renal transplant recipients. Dietary sodium should be restricted to 1500 mg (65 mmol) per day in adults 50 years of age or younger and to 1300 mg (57 mmol) per day in adults 51–70 years of age; 30 min to 60 min of moderate aerobic exercise should be done 4–7 days per week; body mass index should be maintained between 18.5 and 24.9 kg/m^2 and waist circumference should be <102 cm for men and <88 cm for women; alcohol consumption should be limited to no more than 14 standard drinks per week for men or nine standard drinks per week for women; the diet should be low in saturated fat and cholesterol and should emphasize fruits, vegetables and low-fat dairy products, dietary and soluble fibre, whole grains and protein from plant sources.

Pharmacological treatment

Most patients require the use of anti-hypertensive agents (Table 1). The KDIGO guidelines recommend that transplant recipients should be treated with any class of antihypertensive agents [58]. We agree that any effort should be made to normalize or at least reduce blood pressure in hypertensive patients; however, some caution is needed in renal transplant recipients. The choice of drugs depends not only on their efficacy and tolerance in the single patient but also on their possible impact on renal graft function and on the pharmacological interference with immunosuppressive drugs.

A combination of two-first-line agents should be considered for initial treatment of hypertension if systolic blood pressure is 20 mmHg above target or if diastolic blood pressure is 10 mmHg above target [61]. First-line agents for isolated systolic hypertension in general population include thiazide diuretics, long-acting dihydropyridine calcium-channel blockers or RAS inhibitors. Although most hypertensive transplant recipients need a combined treatment, we will consider separately the different classes of antihypertensive agents.

Table 1. Main anti-hypertensive agents used in renal transplant recipients.

Drugs	Advantages	Adverse events
Calcium channel blockers (CCB)	Reduce arteriolar vasoconstriction Reverse ventricular hypertrophy	Peripheral oedema Gastro-oesophageal reflux Gingival hypertrophy Non-dihydropyridine CCB increase cyclosporin blood levels
ACE-inhibitors Angiotensin receptor blockers	Prevent heart failure Prevent intimal thickening Antiproteinuric effect	Small increase in creatinine Anaemia Hyperkalaemia Oligoanuria in transplant artery stenosis
Beta-blockers	Cardioprotective	Hyperlipaemia Increased risk of diabetes Poor correction of hypoglycaemia in diabetics
Alpha-antagonists	Control of benign prostatic hypertrophy	Increase cardiovascular risk?
Central agents	Rapid onset	Dry mouth Bradycardia Rebound hypertension Sedation
Diuretics	Reduce extracellular overload Synergize with other antihypertensive drugs	Hypokalaemia Hyperlipaemia Hyperuricaemia

Diuretics can exert an anti-hypertensive effect by reducing salt and water overload. Thiazide diuretics are often used as the initial treatment of hypertension in the general population [61,62]. However, diuretic therapy coupled with salt restriction may cause a drop in GFR because of the impaired capacity of haemodynamic adaption of the transplanted kidney [63]. Moreover, thiazide diuretics can cause electrolyte disorders, dyslipidaemia and may increase serum uric acid, which is an independent predictor of cerebrovascular or cardiac events [64,65]. Thus, the use of thiazide diuretics in association with other powerful antihypertensive agents should be restricted to selected cases of refractory hypertension. Loop diuretics are helpful in handling salt and water retention and in treating hyperkalaemia and hypercalcaemia. Some investigators reported that thiazides have better antihypertensive effects than loop diuretics [66], but others found that the mean arterial blood pressure decreased by the same amount with both diuretics [67].

As increased renal vascular resistance is a prominent feature of post-transplant hypertension, drugs that lower systemic blood pressure and increase renal blood flow may have a specific indication. Theoretically, calcium channel blockers (CCB) that reduce systemic vascular resistance by acting on the vascular smooth cells could be the drugs of choice as they may protect from vasoconstriction caused by CNI [68–70]. By modulating calcium flux, CCB may diminish the vascular smooth muscle reactivity to vasoconstrictor stimuli and hence reverse the increase in renal vascular resistance induced by CNI, particularly at the pre-glomerular level [71]. Cross *et al.* [72] identified 29 trials including 2262 patients that compared CCB with placebo or no treatment. CCB reduced graft loss (risk ratio 0.75) and improved GFR of 4.5 ml/min. Other studies showed that CCB could reverse ventricular hypertrophy in renal transplant recipients [2,73]. These data suggest that CCB may be preferred as first-line agents for hypertensive kidney transplant recipients. On the other hand, the management of post-transplant hypertension with these agents may be difficult. CCB can cause peripheral oedema and, relaxing smooth-muscle cells, constipation or gastro-oesophageal reflux; moreover, in combination with cyclosporin, may worsen gingival hyperplasia [74]. It is still a matter of controversy whether the use of dihydropyridinic CCB may cause an increased risk of cardiovascular events in high risk patients [75] as well as in renal transplant recipients [76]. Finally, it should be remembered that non-dihydropyridinic CCB, such as verapamil and diltiazem, and the dihydropyridinic nicardipine can increase the blood levels of cyclosporin [77–79]. It is still unclear if amlodipine does [80] or does not [81] interfere with the blood levels of cyclosporin while other dihydropyridine CCB do not interfere with the metabolism of cyclosporin [82–84].

Angiotensin converting enzyme inhibitors (ACE-i) and angiotensin II receptor blockers (ARB) are effective in reducing blood pressure in renal transplant patients [85–87]. ARBs are well tolerated and, unlike ACE-i, they do not interfere with bradykinin production and therefore cause dry cough less frequently than ACE-i. Both these agents may worsen renal function in patients with transplant artery stenosis [88] and also, rarely, in patients

without any evidence of the latter [89]. Moreover, ACE-i and ARB may cause hyper-kalaemia and may induce anaemia [90,91]. Therefore, an early initiation of RAS inhibitors is not recommended in patients with graft dysfunction, whereas it appears to be safe in transplant patients with good early function [92]. On the other hand, this class of drugs has demonstrated a number of effects that may be of benefit to transplant recipients. ACE-i reduce mortality following myocardial infarction, improve symptoms and prolong survival of patients with heart failure [93–95]. ARB and ACE-i may also prevent heart failure in patients with left ventricular dysfunction, and may favour the regression of left ventricular hypertrophy [96,97]. RAS-inhibitors in renal transplant recipients can also prevent an increase in the thickening of the intima–media complex of the carotid artery as measured by ultrasound, suggesting a role in prevention of atherosclerosis [98]. Finally, these agents may improve post-transplant erythrocytosis [99]. An additional benefit of these agents is their antiproteinuric effect. Hiremath *et al.* [100] conducted a systematic review of randomized trials to determine the effect of ACE-i or ARB use following kidney transplantation. ACE-inhibitor or ARB use was associated with a significant decrease in GFR (−5.8 ml/min), a lower haematocrit (−3.5%) and reduction in proteinuria (−0.47 g/day). Some studies reported that renal transplant recipients treated with either ACE-i or ARB had better patient and graft survival at 10 years in comparison with patient who did not receive these agents [101]. However, in a randomized controlled trial comparing CCB with ACE-i, patients receiving nifedipine but not lisinopril improved kidney transplant function over a period of 2 years [102]. Moreover, in an analysis of 17 209 kidney and 1744 heart transplant recipients, there was no patient or graft survival benefit for patients who received ACE-i or ARB, even when recipients of kidney from deceased and living donor, diabetics versus non diabetics, patients with or without cardiovascular disease or hypertensive nephropathy were considered [103]. Thus, RAS inhibition may improve arterial hypertension, proteinuria and erythrocytosis, but can cause hyperkalaemia, anaemia and deterioration of graft function. Clinical studies were unable to demonstrate a substantial benefit of RAS inhibitors when compared with other antihypertensive agents in slowing the progression of chronic allograft nephropathy [104,105].

Other antihypertensive agents can be useful in reducing post-transplant cardiovascular risk. Beta-blockers that inhibit beta-adrenergic receptors may be cardioprotective and should be considered as a first-line therapy for post-transplant hypertension in patients with concomitant coronary artery disease, stable heart failure and arrhythmias. However, the Canadian guidelines suggest limiting the use of beta-blockers to patients younger than 60 years [61]. These agents may contribute to adverse effects on lipids and glucose metabolism [106]. In a study on hypertensive patients, it was found that treatment with beta-blockers increased the risk of developing diabetes by 28% [107]. On the other hand, beta-blockers inhibit the catecholamine response to hypoglycaemia, hence avoiding the increase in glycaemia related to hepatic glycogenolysis [108]. It should be noted that the effects on lipid and glucose metabolism are more frequent and severe with non-vasodilator beta-blockers while vasodilator alpha-beta-adrenergic blockers are associated with more favourable effects on glucose and lipid profiles [109].

Centrally acting drugs stimulate alpha 2 receptors in the brain and reduce the sympathetic tone decreasing cardiac output and peripheral vascular resistance. These agents may be used in various combinations with other antihypertensive drugs.

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 [110]. However, these agents may cause postural hypotension and may increase the risk of cardiovascular disease in high-risk transplant recipients [49]. In the most severe cases of hypertension, the powerful vasodilator minoxidil may be added. Its administration requires also the use of diuretics and beta-blockers to prevent oedema and tachycardia that are the most frequent adverse events together with hypertrichosis.

In summary, there is no preferred antihypertensive agent to use in standard renal transplant recipients. What is important is that the chosen drug (or combination of drugs) is effective and does not cause adverse events. With this principle in mind, some suggestions may be proposed. In the early post-transplant period, dihydropyridinic CCB should be preferred, not only because they are among the more effective drugs in reducing blood pressure but also because they can induce renal arteriolar vasodilation so contrasting the vasoconstrictive effects of calcineurin-inhibitors. Instead, in patients with heart failure and in diabetics at risk of cardiovascular disease, RAS inhibitors and beta-blockers may be preferred to CCB, unless hypertension becomes difficult to control with these agents [61]. As pointed out by KDIGO guidelines [58], in proteinuric patients, ACE-i and ARB, either alone or in combination, remain the first-line drugs. A triple blockade of RAS with ACE-i, ARB, and the renin inhibitor aliskiren can offer a new therapeutic approach in selected hypertensive patients with severe proteinuria [111]. It should be noted, however, that the manufacturer states that concurrent use of aliskiren and cyclosporin is

not recommended as this combination increases the maximum concentration and area-under-curve of aliskiren in healthy subjects by 2.5-fold and 5-fold respectively (Tekturna or aliskiren US prescribing information. Novartis Pharmaceuticals Corporation February, 2010). If other measures are ineffective, reduction IN cyclosporin, tacrolimus, or GCs should be taken into account, whenever possible [103,112].

Invasive therapeutic procedures

Bilateral nephrectomy should be reserved primarily for patients with a history of severe hypertension before transplantation and for transplant recipients with refractory hypertension. Laparascopic technique is an effective method [113] which may be adopted also for patients with autosomal polycystic kidney disease [114]. In proven transplant artery stenosis, PTA or surgery may be indicated if stenosis narrows the artery by more than 80% [115]. It should be noted, however, that both these invasive manoeuvres may be complicated by polar infarcts, haematoma, intimal flaps, thrombosis and anastomotic re-stenosis. In the past, it has been reported that PTA may be associated with complications in about 28% of transplant patients with TRAS [116], but more recent studies outlined that PTA is safe and effective in most cases [117,118]. However, in spite of a high success rate, the mean dose of antihypertensive agents did not change in many patients after PTA [119] and an analysis of the United States Renal Data System registry reported that graft survival was not significantly different in patients treated with angioplasty compared with those without angioplasty [120]. For reasons of the risks of graft loss associated with surgical intervention, surgery should be considered a second option in patients in whom PTA or stenting has failed. However, successful surgery significantly reduces the risk of re-stenosis in comparison with PTA [121]. Embolization may repair arteriovenous fistulas with improvement of hypertension [122,123].

Conclusions

Arterial hypertension is frequent in renal transplant recipients. A number of factors may contribute to developing or aggravating hypertension after transplantation. Among them, a central role is played by CNI (particularly cyclosporin), GCs and allograft dysfunction. Hypertension may be responsible for severe and even life-threatening cardiovascular events and can exert deleterious effects on graft function and survival. There is emerging evidence that the impact of these complications may be prevented or at least attenuated by reducing the levels of blood pressure. Therefore, an early and aggressive treatment is mandatory. According to the recent guidelines, hypertensive patients should follow an appropriate lifestyle. In this regard, a dietary regimen poor in sodium, cholesterol and saturated fat and regular physical activity to maintain the body mass index <25 are recommended. Pharmacological treatment is often based on a combination of two or more antihypertensive drugs. CCB, ACE-i or ARB, often associated with loop diuretics, are the first-line agents. But in many cases, the addition of further drugs (beta-blockers, centrally acting drugs, and/or alpha-adrenergic antagonists) is required. As decreased incidence and severity of hypertension can be obtained in transplant recipients receiving low-dose cyclosporin and/or steroid-free immunosuppression, withdrawal or minimization of these drugs may be considered in patients with refractory hypertension.

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