6

Cardiovascular Diseases in Kidney Transplantation

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1. Introduction

Cardiovascular diseases that include atherosclerotic diseases; coronary artery disease, cerebrovascular disease and peripheral vascular disease, and cardiac functional diseases; congestive heart failure, left ventricular hypertrophy and arrhythmias, are very common in the general population and are the first cause of mortality (Wilson &Culleton, 1998, Culleton & Wilson, 1998). Moreover, patients with chronic renal failure have an increased risk of cardiovascular disease compared with the general population, and after stratification by age and gender, cardiovascular mortality is 10 to 20 times more frequent independently of treatment; predialysis, dialysis or after kidney transplantation (Foley et al, 1998). Kidney transplantation is the best therapy of end-stage renal disease by reducing cardiovascular mortality (McDonald &Russ, 2002, Ojo et al, 2000, Wolfe et al, 1999). But even after transplantation, a recipient of 25 to 35 years of age has a 10 times higher risk of cardiovascular mortality than an individual of similar sex and gender without renal failure (Foley et al, 1998). Among the cardiovascular diseases, atherosclerotic diseases are the most frequently studied and are associated with patient outcome. Ischaemic heart disease was the cause of 53% of total mortality in a study performed in Scandinavia 15 years ago (Lindholm et al, 1995) and these findings were still prevalent in a later report (Aakhus et al, 2004). However, several authors have recently emphasized the importance of functional cardiopathies such as congestive heart failure on patient outcome (Rigatto et al, 2002).

The high incidence of cardiovacular events and mortality in renal transplant recipients has been attributed to the increased presence of traditional (Ojo, 2006) and nontraditional risk factors (Ducloux et al, 2004, De Mattos et al, 2006). As traditional risk factors do not fully explain the high cardiovascular risk it has been postulated that some of these risk factors, age, diabetes and smoking, could have a higher deleterous impact in transplant recipients than in the general population (Kasiske et al, 2000a). Other authors consider that transplant related (De Mattos et al, 2006) and nontraditional or emergent factors, hyperhomcysteinemia and inflammation, could play a predominant role in the appearance of cardiovascular events (Ducloux et al, 2004). Progressive chronic graft dysfunction and death with functioning graft are the most important causes of graft loss (Matas et al, 2002, Collins et al, 2008) and cardiovascular diseases are the leading cause of mortality in renal transplant recipients dying with a functioning graft (Pilmore et al, 2010). Consequently decreasing

cardiovascular mortality could improve patient and graft outcomes (Howard et al, 2002, Marcén et al, 2001, Morales, 2008, Vanrenterghem et al, 2008).
The present chapter reviews the cardiovascular diseases which affect renal transplant recipients and their impact on patient mortality, the risk factors associated with these complications and the therapeutical strategies to improve patient and graft outcomes.

2. Cardiovascular diseases

Renal transplant recipients are not healthy individuals. They have a past history of chronic renal failure and dialysis therapy, both having negative impact on cardiovascular risk and they present variable chronic renal failure stages. All cardiovascular diseases; atheriosclerotic and functional cardiopathies can affect transplant recipients (Table 1).

Atheroesclerotic diseases	Functional cardiopathies
Coronary artery diseases	Congestive heart failure
Cerebrovascular diseases	Left ventricular hypertrophy
Peripheral vascular diseases	Arrhythmias

Table 1. Most common cardiovascular diseases affecting transplant recipients

As in the general population, cardiovascular diseases are important causes of morbidity and mortality in renal transplant recipients. Heart diseases and cerebrovascular diseases accounted for about 35% mortality in our Unit (Figure 1).

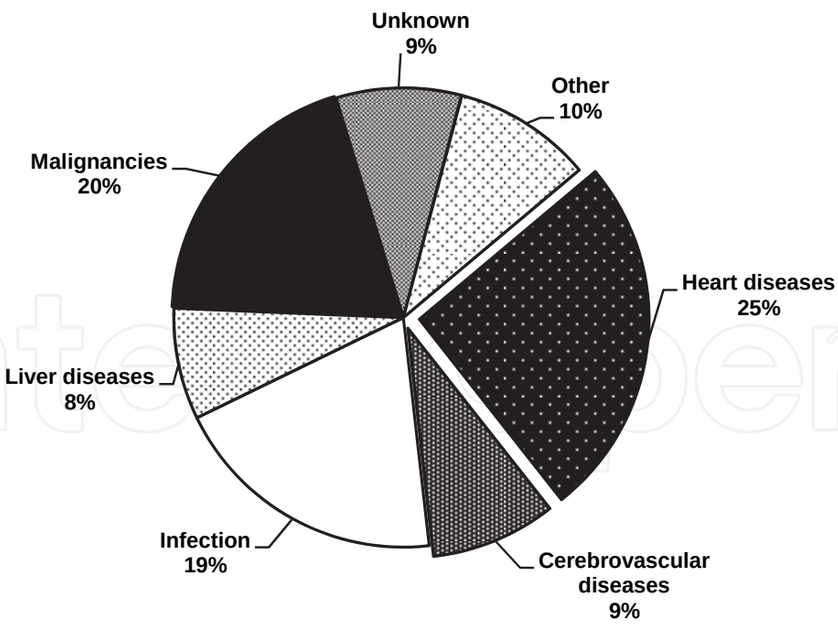

Fig. 1. Causes of mortality in 224 renal transplant recipients with functioning graft
(Ramón y Cajal Hospital)

2.1 Atherosclerotic diseases

2.1.1 Coronary artery disease

Coronary artery disease is the most frequent atherosclerotic disease in the general population and a leading cause of cardiovascular mortality. It is generally admitted that coronary artery disease is between 2 and 6 times more frequent in renal transplant recipients than in the general population (Aarkhus et al, 1999, Kasiske, 1988, Lentine et al, 2005a, Marcén et al, 2006, Massy, 2001). A very high number of events occurring during the first weeks after transplantation have been attributed to surgical stress, immunosuppression and silent disease while the patient was on dialysis (Kasiske et al, 2000, 2005, Lentine et al, 2005, Marcén et al, 2006). In a retrospective study from the USA, the prevalence of coronary artery disease, defined as acute myocardial infarction, coronary revascularization procedures, or death due to coronary disease, was 23% at 15 years of follow-up and it was the cause of 18.7% of mortality (Kasiske et al, 1996). In a multicenter, retrospective study performed in Spain, the prevalence of coronary artery disease was 6.8% at 5 years (Marcén et al, 2006) and very similar findings have been reported from France (Doucloux et al, 2004), two low risk countries. Data from the United Network for Organ Sharing (UNOS) and United States Renal Data System (USRDS) registry showed that the prevalence of acute myocardial infarction was between 6% to 11 % at 3 years a 17% lower than that observed on waiting list patients (Kasiske et al, 2006, Lentine et al, 2005). Moreover, myocardial infarction has a poor prognosis and is the cause of high mortality (Herzog et al, 1998, 2000, Morales, 2008).

The diagnostic criteria and therapeutical measures must be those used in the general population and in patients with chronic renal failure (Murphy et al, 1998). As a high percentage of events occur in the first weeks or months after the procedure, efforts have to be made to prevent and treat coronary artery disease before transplantation. Several algorithms have been proposed in which patients are classified according to cardiovascular risk (Lentine et al, 2008b, Wang & Kasiske, 2010), but we have not yet the ideal diagnostic procedure for asymptomatic patients.

2.1.2 Cerebrovascular diseases

Cerebrovascular diseases include transient cerebral ischaemia, when focal neurologic symptoms resolve in 24 hours, and persistent neurological deficits documented by computed tomography or nuclear magnetic resonance. Patients with chronic renal disease have more severe atherosclerotic lesions in carotic arteries than the general population (Kennedy et al 2001). This could explain the 5 to 10 times higher risk of having ischaemic or haemorragic events when compared with the general population (Seliger et al, 2002, 2003a,b). In renal transplant recipients the annual incidence was from 0.5% to 2.3% (Abedini et al, 2009a, Aull-Watschinger et al, 2008, Cosio et al, 2005, Lentine et al, 2008a, Oliveras et al,2003), and ischaemic events predominated in a proportion of 2-3:1 compared with haemorragic events (Aull-Watschinger et al, 2008, Oliveras et al, 2003). In a long-term study, by actuarial analysis, 15% of patients who survived with a functioning graft for 15 years experienced a major crebrovascular event (Kasiske et al, 1996). The evolution of cerebrovascular diseases is poor and a mortality rate around of 50% three months after the event has been reported (Oliveras et al, 2003). In retrospective studies, cerebrovascular diseases were the cause of 5% to 8% of total mortality (Aull-Watschinger et al, 2008, Howard et al, 2002). Only the Assessment of Lescol in Renal Transplantation (ALERT) study has prospectively investigated these complications, the incidence was 8.8% during the 6.7 year

follow-up period, and 21% of the cerebrovascular events, 48% of haemorragic and 8% of ischaemic, were fatal and accounted for 9.9% of total mortality (Abedini et al, 2009a).

2.1.3 Peripheral vascular disease

The incidence and clinical outcome of this complication have been seldom studied in renal transplant recipients. The diagnostic criteria include: intermitent claudication, ulceration with long-vessel disease on flow studies, amputations, by-pass or percutaneous angioplasty. The frequency reported was variable. In an old study, in which only amputation or revascularization procedures were included, the cumulative incidence was 15% at 15 years (Kasiske et al, 1996). In other studies, the incidence increased with the length of follow-up, from 2.1% at 1 year to 5.9% at 10 years (Sung et al, 2000). Data from the UNOS registry have shown a cumulative incidence of 20% in diabetic and 5% in nondiabetic patients at 3 years (Snyder et al, 2006). As the disease develops along years it is difficult to distinguish risk factors due to transplantation from those present before. The need of amputation is low about 2 to 3% (Sung et al, 2000). The disease by itself is not a cause of mortality but patients suffering from it have an increased risk of death with a functioning graft (Snyder et al, 2006, Sung et al, 2000).

3. Functional heart diseases

3.1 Congestive heart failure

Congestive heart disease is defined as dysnea plus at least two of the following characteristics; increased yugular venous pressure, basal lung rales, lung hypertension in radiography or pulmonary edema (Harnett et al, 1995). In dialysis patients, congestive heart failure is 36 times more frequent than in the general population and it is a mortality risk factor (Collins 2002, Stack &Bloemberg, 2001). Congestive heart disease has been studied less than coronary artery disease in the renal transplant population and it is associated with coronary artery disease in 30% of cases (Rigatto, 2003a,b). Its annual incidence was 3-5 times that of the general population, reached a cumulative incidence of 18.3% at 3years and was associated with poor graft function (Abbott et al, 2003b, Lentine et al, 2005, Rigatto, 2003a,b). It has a high impact on mortality, similar to that of coronary artery disease (Lentine et al, 2005).

3.2 Left ventricular hypertrophy

There are two types of left ventricular hypertrophy; concentric ventricular hypertrophy and dilatation with or without hypertrophy. The first one is associated with volume overload and the second with aortic insuficiency or severe anemia. Both types are more frequent in patients in renal failure than in the general population, reaching 20-50% in patients with chronic renal failure (Levin et al, 1996, Tucker et al, 1997) and up to 70% in those on dialysis (Foley et al, 1995, McGregor et al, 1998). Several prospective studies have shown that left ventricular hypertrophy improved during the first two years after transplantation but it was still present in about 40% of renal transplant recipients (Rigatto et al, 2000, Teruel et al, 1987). Factors related with no improvement were: age, left ventricular morphology, duration and severity of hypertension and time averaged pulse pressure (Rigatto et al, 2000). Moreover, renal transplant also improved ventricular function in most patients even in those with severe impairment (Parfrey et al 1995, Wali et al, 2005). However these findings have been recently questioned when cardiac structure was assessed by magnetic resonance

(Patel et al, 2008). Parameters of ventricular hypertrophy or impaired cardiac function were associated with increased risk of cardiovascular events and cardiovascular mortality in renal transplant recipients (Aull-Watschinger et al, 2008, McGregor et al, 2000). In a nonrandomized study, conversión from CNI to sirolimus regressed left ventricular mass thickness regardless of blood pressure changes, thus suggesting non-hemodynamic-effect mechanisms on the left ventricular mass (Paoletti et al, 2008).

3.3 Arrhythmias

Atrial fibrilation is the most common cardiac rythm disorder in the general population and in patients on dialysis (Harnett et al 1995, Zebe 2001). Data from renal transplant recipients, despite being a high risk population due to the pre-transplant history and the high prevalence of risk factors related to this complication such as hypertension and obesity, have only been recently reported. Registry studies from the USA have shown a cumulative prevalence around 7 % at 3 years (Abbott et al, 2003a, Lentine et al, 2006). Risk factors for postransplantation atrial fibrilation include older age, male gender, renal failure for hypertension, and coronary artery disease. As in the general population atrial fibrilation was associated with an increased cardiovascular mortality, up to 3 times higher than patients without the disease (Abbott et al, 2003, Lentine et al, 2006).

4. Cardiovascular risk factors

Three types of cardiovascular risk factors are generally identified in transplant recipients (Table 2). 1) Traditional risk factors are those which in the general population are associated with cardiovascular diseases, and their treatment decreases the incidence of these complications. They include; older age, hypertension, hypercholesterolemia, diabetes mellitus, tobacco smoking and obesity. Their incidence is mostly increased in advanced CKD stages (Ansell et al, 2007, Karthikeyan et al, 2004, Marcén et al, 2005). 2) Risk factors associated with the transplant; anaemia, graft dysfunction and related complications, proteinuria, and immunosuppression. Finally,3), non-traditional or emergent factors such as hyperhomocysteinemia and chronic inflammation.

Traditional risk factors	Transplant related factors	Nontraditional or emergent factors
Age Sex Hypertension Dislipidemia Diabetes Smoking Obesity	Anaemia Graft dysfunction Proteinuria Immunosuppression	Hyperhomocysteinemia Inflammation

Table 2. Cardiovascular risk factors

4.1 Traditional risk factors

4.1.1 Age and sex

Older age is a nonmodifiable cardiovascular risk factor in the general population. In renal transplant recipients it was associated with an increased risk for cardiovascular

atherosclerotic diseases; ischemic heart disease, cerebrovascular disease, and peripheral vascular disease (Kasiske et al, 1996, Kasiske et al, 2006, Marcén et al, 2006, Oliveras et al, 2003, Rigatto et al, 2002, Snyder et al, 2006), and also for functional heart diseases; congestive heart failure, left ventricular hypertrophy and arrhythmias (Abbott et al, 2003, Lentine et al 2006, Rigatto et al, 2000, Rigatto et al, 2002). Male gender is a risk factor for ischemic heart disease and peripheral vascular disease (Kasiske, 1988, Rigatto et al, 2002, Kasiske et al, 2006, Marcén et al, 2006, Snyder et al, 2006) and female gender for cerebrovascular disease and congestive heart failure (Abbott et al, 2003, Lentine et al, 2008a).

4.1.2 Hypertension

It is a common complication in renal transplant recipients. Its prevalence varies between 70 and 90%. There are several causes and mechanisms of high blood pressure and many patients have several of them. A previous history of hypertension, artery graft stenosis, the own recipient kidneys, overweight, chronic graft dysfunction and immunosuppressive agents such as calcineurin inhibitors (CNIs), cyclosporine and tacrolimus, are the conditions generally associated with post-transplant hypertension (Koomans & Ligtenberg, 2001, Zhang et al, 2003). Among CNIs, cyclosporine seems to increase blood pressure more than tacrolimus (Ligtenberg et al, 2001). It has been associated with an increased risk of ischemic heart disease, congestive heart failure, left ventricular hypertrophy (Rigatto 2002) and with mortality (Kasiske et al 2004, Fernández-Fresnedo et al, 2005).

One characteristic of post-transplant hypertension is the lack of control despite treatment. In a study of 1295 patients, only 12.4% had a normal blood pressure one year after grafting and more than 95% of them were on antihypertensive therapy (Kasiske et al, 2004). Others found in their series a higher number of patients with normal blood pressure without therapy (26.0%) but they also reported that 32.0% of patients had uncontrolled blood pressure while they were on treatment (Tutone et al, 2005). Cross-sectional studies have shown that between 60 to 100% of patients according to the stage of graft failure had a blood pressure above 130/80 mm Hg and most of them were on antihypertensive therapy (Karthikeyan et al, 2004, Marcén et al, 2009a).

There are not specific blood pressure levels for renal transplant recipients and the reference values are those of the general population. As the renal transplant recipients are considered a high risk population for cardiovascular diseases, a blood pressure of 130/80 mm Hg has been recommended. Treatment includes changing life style, reducing the diet sodium intake, physical activity, low consumption of alcohol and antihypertensive agents (Choubanian et al, 2003). There are no specific antihypertensive agents to treat post-transplant hypertension and all agents can be used. The prescription has to be done taking into account the characteristic of each patient (KDIGO, 2009, Park & Luan, 2005). Most patients need to be treated with several antihypertensive agents. Studies in which angiotensin converting enzyme inhibitors or angiotensin receptor blockers have been compared with other antihypertensive agents have shown controversial results, and there are no studies in which the superiority of one agent over the others on patient survival has been definitively established (Opelz et al, 2006, Hiremath et al, 2007). There are not randomized, prospective studies that have demonstrated the beneficial effects of controlling blood pressure in renal transplant recipients, but it has been assumed that they would be similar to those obtained in the general population. However, retrospective registry studies have shown that decreasing blood pressure even several years after hypertension appearance was associated with a better patient outcome (Opelz et al, 2005).

4.1.3 Dyslipidemia

Lipid disorders are more common in renal transplant recipients than in the general population and include high levels of cholesterol and triglycerides. Also frequent are high levels of LDL-cholesterol, lipoprotein (a) and apolipoprotein B, while HDL-cholesterol can be high, normal or low. Hypercholesterolemia, total serum cholesterol above 200 mg/dl and LDL-cholesterol above 100 mg/dl, have been observed in up to 90 % of patients (Aakhus et al, 1996, Hricik et al, 1994). Several factors have been associated with hyperlipidemia; genetic predisposition, body weight gain, graft dysfunction, proteinuria, diabetes, immunosuppressive and antihypertensive agents (Massy & Kasiske, 1996).

Among immunosuppressive agents, corticosteroids, CNIs and mammalian target of rapamycin inhibitors (mTORs), sirolimus and everolimus, are those most frequently associated with hyperlipidemia. The mechanisms of corticosteroid-induced hyperlipidemia are through promoting insulin resistence and hyperinsulinism, reduction of lipoprotein lipase activity, overproduction of triglycerides and secretion of VDLD-cholesterol (Hricik et al, 1994). CNIs inhibit bile acid synthesis and binding of the drugs to the LDL-cholesterol receptor with reduction of its activity. Also a decrease in lipoprotein lipase activity and impairment of LDL-cholesterol catabolism may be involved (Moore et al, 2001). These effects seem to be more prominent with cyclosporine than with tacrolimus (Ligtenberg et al, 2001, Moore et al, 2001, Vincenti et al, 2002). mTORs are the agents with stronger hyperlipidemic effect (Kasiske et al, 2008), which is more accentuated in those patients also treated with cyclosporine than in those treated with tacrolimus (Ciancio et al, 2004). The pathogenesis of mTOR dyslipidemia is unclear. A reduced catabolism of apo B100 could be the cause of increased triglycerides and cholesterol and decreased lipoprotein lipase activity and increased free fatty acid levels may be contributing factors. Their effects are dose dependent and rapidly reversible (Kasiske et al, 2008, Webster et al, 2006).

As in the general population, hypercholesterolemia and low HDL-cholesterol levels are associated with ischemic heart disease (Kasiske, 1988 Kasiske et al, 1996, Kasiske et al, 2006, Marcén et al, 2006, Rigatto et al, 2002). The treatment of this complication may follow the recommendations given to the general population and confirmed by the transplant guidelines (KDIGO, 2009). It is important to begin with a rich diet of monosaturated fats, but diet therapy does not control hyperlipidemia and lipid-lowering agents have to be added. 3-Hydroxy-3methylglutaryl coenzyme A reductase inhibitors (statins) are the elective pharmacologic agents in hypercholesterolemic patients. Fluvastatin, pravastatin and atorvastatin seem to have a more favourable safety profile over simvastatin and lovastatin. In patients with hypertriglyceridemia, gemfibrocil is the pharmacological agent of choice. Some observational studies have shown an association between statin therapy and better patient outcome (Cosio et al, 2002a, Wiesbauer et al, 2008). However, the Assessment of Lescol in Renal Transplantation (ALERT) study did not show differences in the primary compound end point, despite a reduction of 32% in the LDL-cholesterol blood levels at 5 years follow-up, between recipients treated with fluvastatin compared with those on placebo (Holdaas et al, 2003). A later evaluation of the study showed the benefits of the treatment but only when statin therapy started in the first two years after transplantation and in low-risk recipients (Holdaas et al 2005, Jardine et al 2004). In case of statin intolerance or hyperlipidemia of difficult control, ezetimibe that blocks the cholesterol absorption in the brush border, alone or combined with statins, is an efficient and safe alternative (Buchanan et al 2006, Langone & Chuang, 2006).

4.1.4 Diabetes

In the renal transplant recipients, two types of diabetes mellitus can be distinguished, diabetes mellitus as the cause of end-stage renal disease and new onset diabetes mellitus (NODAT). The prevalence of diabetes mellitus as the cause of renal failure is variable among countries. In the USA, more than 20% of the patients on the waiting list or transplanted have diabetes mellitus as the cause of renal failure (Collins et al, 2008). The incidence of NODAT varies between 2% to 50% in the first posttransplantation year according to the criteria used in its definition (Montori et al, 2002). When the American Diabetes Association criteria were used, the incidence of NODAT at 12 months was 13% and of glucose intolerance of 33% in a study performed at the Mayo Clinic (Cosio et al, 2005). Similar findings have been observed in a prospective study from Spain (Marcén et al, 2006). As the term NODAT does not include states of impaired fasting glucose and impaired glucose tolerance which pose a cardiovascular threat similar to overt diabetes, the term transplant associated hyperglycemia (TAH) has been proposed (Crutchlow & Bloom, 2008). The most common risk factors associated with NODAT or TAH include: race, blacks or hispanics, older age, obesity, family history, hepatitis C virus infection and some immunosuppressive agents such as corticosteroids, CNIs (tacrolimus) and mTORs (Crutchlow & Bloom, 2007, Montori et al, 2002).

The effects of immunosuppresive agents on glucose metabolism have been widely reviewed (Heisel et al, 2004, Miller, 2002, Morales & Dominguez, 2006). Both CNIs, cyclosporine and tacrolimus, cause NODAT by inducing insulin resistance or by impaired insulin secretion (Hornum et al, 2010). Early trials designed to compare the efficacy and security of cyclosporine and tacrolimus, and registry data showed a higher incidence of NODAT in patients treated with tacrolimus (Kasiske et al, 2003, Mayer et al, 1997, Vincenti et al, 2002) and more recent studies have confirmed these findings (Vincenti et al 2007). Also mTORs are associated with an increased risk of NODAT (Johnston et al, 2008). These agents induce hyperglucemia by impairing insulin-mediated suppression of hepatic glucose production, by ectopic triglyceride deposition leading to insulin resistance, or by direct β cell toxicity (Crutchlow & Bloom, 2007).

Single centre and registry studies have shown the association of NODAT with acute myocardial infarction, cerebrovascular events and mortality (Cosio et al 2002b, 2005, 2008, Kasiske et al 2003, Lentine et al, 2005, 2008). The treatment has the objective of preventing the symtoms due to uncontrolled hyperglucemia and the microvascular complications as the transplant recipients develop identical complications as the nontransplanted diabetic patients (Burroughs et al, 2007). The guidelines of the American Diabetes Association and the Joint Nacional Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for patients with type 2 diabetes have been recommended (Haffner SM 2003).

4.1.5 Tobacco

The effects of tobacco on the health in the general population are well known. It is a risk factor of cardiovacular diseases, malignancies and respiratory diseases (Bartecchi et al, 1994). About 25% of the renal transplant population are active smokers after transplantation (Cosio et al 1999, Kasiske & Klinger, 2000, Zitt et al, 2007). In transplant recipients, tobacco was associated with cardiovascular diseases and mortality (Kasiske & Klinger, 2000). It has been reported that the negative impact of tobacco on health disappeared after five years, and some authors emphasize that efforts have to be made to convince the patients about the

benefits of avoiding smoking. There are few data about the influence of transplant on toxic habits, but some studies suggest that transplantation constituted a strong reason to give up smoking (Banas et al, 2008).

4.1.6 Obesity

Obesity is a growing health problem in the general population. Epidemiological studies have shown its association with a higher morbidity and mortality due to cardiovascular diseases (Allison et al, 1999). Transplant recipients have a tendency to gain body weight mostly in the first year after grafting. In a study performed in our Unit, the mean body weight gain in the first year was 5 kg or 8.7 % of the body weight at the time of transplantation and the percentage of obese patients increased nearly two fold, from 6.5% to 11.7% (Marcén et al, 2007). Inappropriate dietary habits, decreased physical activity, and increased appetite as a result of well-being and corticosteroid therapy are among the causes of owerweight and obesity after transplantation.

Both body weight gain and obesity (body mass index >30 kg/m2) are associated with an increased risk for NODAT, hypertension, hyperlipidemia and metabolic syndrome which are cardiovascular risk factors (Armstrong et al, 2005, El-Agroudy et al 2004). The effects of weight gain and obesity on graft and patient outcome are controversial. Some authors do not find that the complication has any impact on patient mortality (Chang et al 2007, Marcén at al, 2007, Massarweh et al, 2005). However, other studies and registry data have shown their negative impact on patient survival due to an increased cardiovascular and infectious mortality (Aalten et al, 2006, El-Agroudy et al 2004, Meier-Kriesche et al, 2002). In our opinion, controlling weight gain and weight reduction in patients with marked obesity seems to be a goal to improve well-being and outcomes in renal transplant recipients.

4.2 Risk factors associated with transplantation

4.2.1 Anaemia

Post-transplant anaemia is a common complication that has only been recently studied and considered. Its prevalence depends greatly on the definition criteria and the time post-transplant. Nowadays, there is a trend toward the use of the World Health Organization criteria which define anaemia as serum haemoglobin less than 12 g/dl in women and less than 13 g/dl in men. The prevalence of anaemia is about 90% during the first posttransplant weeks and decreases to 25% to 35% at 12 months and remains stable or slightly increases thereafter (Kamar et al, 2008, Vanrenterghem et al, 2003, Yorgin et al, 2002). In cross-sectional studies the prevalence of anaemia reached more than one third of patients and it was severe, serum haemoglobin below 11 g/dl, in about 10% (Karthikeyan et al, 2004, Marcen et al, 2009a, Molnar et al, 2007, Vanrenterghem et al, 2003). The origen of anaemia is multifactorial and graft function is the most important factor (Shah et al, 2006, Vanrenterghem et al, 2003, Yorgin et al, 2002). However, it does not completely explain post-transplant anaemia, as renal transplant recipients have more severe anaemia for each chronic renal disease stage when compared with nontransplantation subjects (Chadban et al, 2007). Several immunosuppressive agents such as azathioprine, mycophenolate mofetil (MMF), enteric coated mycophenolic acid (EC-MPA) and mTORs may cause anemia due to bone marrow toxicity or to disorders on iron homeostasis (Augustine et al, 2004, Fishbane et al, 2009, Vanrenterghem et al, 2003, Wang et al, 2004). The combination of MMF or EC-MPA with mTORs is specially toxic for the bone marrow (Hricik, 2003, Rigatto, 2006). Other

medications as angiotensin converting enzyme inhibitors and angiotensin receptor blockers are known to cause anaemia and should be cautiously used.

Recent studies have shown an association between anaemia and graft survival, cardiovascular diseases and mortality. Post-transplant anaemia seems to be a risk factor of congestive heart failure and of left ventricular hypertrophy but not of ischaemic heart disease (Borrow et al, 2008, Rigatto et al, 2002, 2003b). In addition, anaemia has been associated with increased mortality in some studies (Chhabra et al, 2008, Imoagene-Oyedeji et al, 2006, Kamar et al, 2008, Molnar et al, 2007) but not in others (Winkelmayer et al, 2006). The treatment of anaemia must follow the recommendations given for patients with chronic kidney disease in the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (KDIGO, 2009). Iron supplementation and erythropoiesis stimulant agents should be administered to maintain serum haemoglobin between 11 and 12 g/dl.

4.2.2 Graft dysfunction

Renal function measured by the estimated glomerular filtration rate (eGFR) is a cardiovascular risk factor in the general population (Go et al, 2004). An important number of renal transplant recipients have different stages of renal failure (Figure 2), and at least two thirds have chronic renal failure defined by an eGFR below 60 ml/min/1.73m2 (Ansell et al, 2007, Karthikeyan et al, 2004, Marcén et al, 2005). As cardiovascular diseases are the leading cause of renal transplant recipient mortality, it seems logical to think in the existence of some links between premature cardiovascular death and poor graft function. Registry and prospective studies have demonstrated a correlation betwen serum creatinine and cardiovascular events or cardiovascular mortality (Fellstrom et al, 2005, Meier-Kriescheet al, 2003, Pilmore et al, 2010, Soveri et al, 2006). However, for other authors the increased cardiovascular risk of patients with poor graft function is mostly due to the effects of hypertension and anaemia than to graft failure itself (Rigatto et al, 2002). Moreover, uncontrolled hyperparathyroidism mostly in recipients with poor graft function may be a risk factor for progression of coronary artery calcification (Mazzaferro et al, 2009). The treatment of renal dysfunction includes the control of hypertension and dyslipidemias (Arias et al, 2005, Opelz et a, 2005, Wiesbauer et al, 2008) as well as the use of non-nephrotoxic immunosuppressive agents as MMF, EC-MPA and belatacept and dose reduction or withdrawal of CNIs.

The prevalence of proteinuria in the renal transplant recipients is between 7.5 and 45% (Knoll, 2009). It is a risk factor of progressive renal function loss and of cardiovascular disease in nontransplantation patients. Retrospective studies have reported that proteinuria is an important predictor of cardiovascular events and mortality in renal transplant recipients (Fernandez-Fresnedo et al, 2002, Roodnat 2001). It is important to note that proteinuria is frequently associated with graft dysfunction, hypertension and obesity and the effects of proteinuria on cardiovascular events could be mediated by these conditions or viceversa. Treatment of proteinuria includes control of hypertension, maintaning blood pressure levels below 120/80 mm Hg, of dyslipidemias and of overweigth, and avoiding immunosuppressive agents associated with proteinuria as mTORs (Amer & Cosio, 2009). Angiotensin converting enzime inhibitors and angiotensin receptor blockers are the elective agents of treatment of hypertension in patients with proteinuria because of their antiproteinuric effects. However, these agents can deteriorate graft function and increase the severity of anaemia, both cardiovascular risk factors as well. Moreover, there are no definitive studies which support the effectiveness of this treatment.

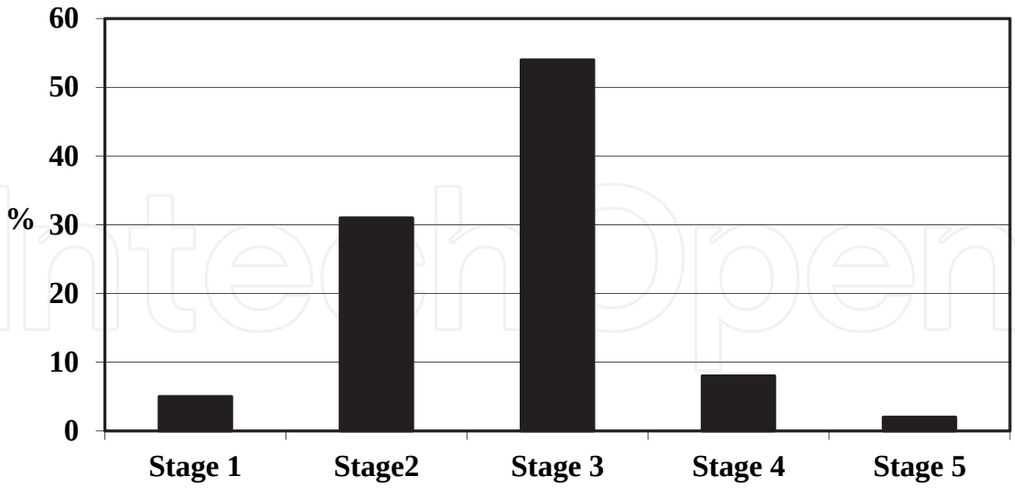

Fig. 2. Distribution of chronic kidney disease stages at 12 months in 447 renal transplant recipients (Ramón y Cajal Hospital)

4.2.3 Immunosuppression

The effects of immunosuppressive agents in cardiovascular risk factors have been previously reviewed (Miller, 2002, Marcén, 2009b, Morales & Dominguez-Gil, 2006). In addition, the impact of these agents on each cardiovascular risk factor has already been described. Corticosteroids and CNIs are the agents with worst cardiovascular risk profile, increasing the incidence and severity of traditional risk factors such as hypertension, hyperlipidemia, diabetes and obesity. CNIs also are nephrotoxic and cause graft function impairment. mTORs increase the risk of anaemia, hyperlipidemia, diabetes and proteinuria (Webster et al, 2006, Schena et al, 2009). MMF and EC-MPA may increase the risk of anaemia but have no impact in the other cardiovascular risk factors. Combinations of CNIs with MMF and EC-MPA or with mTOR allow corticosteroid withdrawal without harm. On the other hand, MMF and EC-MPA and mTORs alone or in combination can be used for CNI dose reduction or withdrawal. All these strategies have been shown to be effective in improving cardiovascular risk but there are no prospective studies in which this improvement is followed by a lower incidence of cardiovascular events or mortality (Schena et al, 2009). Among the new immunosuppressive agents, belatacept improved short-term cardiovascular risk profile and graft function when compared with cyclosporine (Vincenti et al, 2010, Durrbach et al 2010). However, phase II trials with tasocitinib have shown no improvement in hyperlipidemia and blood pressure when compared with patients who received tacrolimus (Busque et al, 2009).

4.3 Emergent risk factors

4.3.1 Hyperhomocysteinemia

Homocystein is a sulfur amino acid produced in all cells, and hyperhomocysteinemia has been considered a cardiovascular risk factor in the general population. Hyperhomocysteinemia is present in around 60% to 70% of renal transplant recipients. Homocystein levels are related with graft function, folic acid levels, serum albumin, age,

and treatment with CNIs (Bostom et al, 1999, Ducloux et al, 2000, Friedman et al, 2002). The impact of homocystein levels on cardiovascular events is controversial. Some authors found an association between the homocystein levels and cardiovascular diseases (Ducloux et al, 2000, 2004) and a prospective study has shown that homocystein levels above 12 μmol/l were associated with 2.44 times increased mortality (Winkelmayer et al, 2005). Other authors have not found this association (Hagen et al, 2001). The treatment consists in the administration of folic acid supplements (5 mg/day) even with normal folic acid levels (Fernandez-Miranda et al, 2000). The efficacy of this therapy in the prevention of cardiovascular events has been examined in the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT). This trial should contribute to answer this question (Bostom et al, 2009).

4.3.2 Inflammation

C-reactive protein (CRP) is an acute phase marker of inflammation. It is produced by the liver under control of several citokines. In the general population, C-reactive protein is associated with obesity and poor renal function (Stuveling et al, 2003). It is also a negative predictor of acute myocardial infarction, cerebrovascular disease and cardiovascular mortality (Ridker et al, 1997). In renal transplant recipients, its levels are associated with graft function, waist circumference and smoking (Van Ree et al, 2005). The association between graft function and C-reactive protein levels could be explained by the situation of chronic low-grade inflammation, by being a marker of graft-mediated immune response or by a decreased renal excretion. As in the general population, it has been considered a risk factor of cardiovascular disease and mortality (Ducloux et al 2004, Winkelmayer et al 2004). Data from the ALERT study have confirmed the previous findings, baseline levels of CRP as well as of IL-6, another inflammation marker, were independently associated with major cardiovascular events and all-cause mortality (Abedini et al, 2009b). Results from a retrospective study have shown an association between MMF therapy and less inflammation than other immunosuppressive agents (Wong et al, 2007).

5. Therapeutical strategies

The management of each particular cardiovascular disease in renal transplant recipients should be similar to that used in the general population. In addition, clinical trials have demonstrated that cardiovascular events and cardiovascular mortality have been reduced by controlling blood glucose, lipid levels and blood pressure in the general population. As interventional studies are lacking in the transplant population, it seems reasonable to extrapolate these findings to transplant recipients. However, transplant recipients present differences from the general population, one of them is the high incidence of graft dysfunction. Preserving graft function has to be a goal in the management of transplant recipients and this could be partly accomplished by controlling the traditional cardiovascular risk factors and by a prudent use of immunosuppressive agents. CNIs minimization or withdrawal may be individually considered. Additional interventions such as treatment of anaemia with erytropoyesis stimulating agents could help in the prevention of cardiovascular diseases but the optimal haemoglobin threshold has to be determined. The benefits of lowering homocysteine levels have not been proved. In addition, long-term interventional studies should be performed in order to improve graft and patient outcomes (Table 3).

Control of cardiovascular risk factors	Preserving graft function	Treating emergent factors
Blood pressure Dislipidemias Diabetes Smoking Obesity Anaemia	Minimization/avoidance of CNIs Control of proteinuria	Folic acid supplements Aspirin

Table 3. Prevention and treatment of cardiovascular diseases after transplantation.

6. Summary

Cardiovascular diseases are common after transplantation. Coronary vascular disease, cerebrovascular disease and congestive heart failure are the diseases most commonly associated with mortality. The increased incidence of cardiovascular events could be partly explained by the high prevalence of traditional risk factors which are not adequately controlled and by the presence of renal dysfunction. Pretransplant evaluation of candidates, control of traditional risk factors and preservation of graft function should be the measures taken to improve patient outcome. The control of traditional risk factors has been effective in the reduction of cardiovascular events in the general population and there are no reasons to believe that it does not work in the transplant population. In addition, adequate control of traditional risk factors could preserve progression of graft failure. A prudent use of immunosuppressive agents could also help to improve the cardiovascular risk profile and graft function. The benefits of additional interventions need to be proved.

7. References

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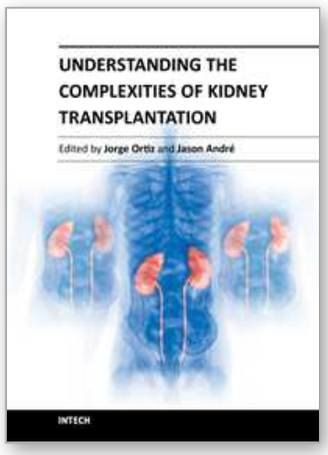

Understanding the Complexities of Kidney Transplantation
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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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