Cardiovascular Disease Posttransplant

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Summary: Renal transplantation is currently the preferred treatment modality for virtually all suitable candidates with end-stage renal disease. Compared with dialysis, kidney transplantation improves both patient survival and quality of life. Nonetheless, posttransplant cardiac complications are associated with increased morbidity and mortality after renal transplantation. When compared with the general population, cardiovascular mortality in transplant recipients is increased by nearly 10-fold among patients within the age range of 35 and 44 and at least doubled among those between the ages of 55 and 64. Although renal transplantation ameliorates cardiovascular disease risk factors by restoring renal function, it introduces new cardiovascular risks derived, in part, from immunosuppressive medications. We provide an overview of the literature on conventional and unconventional cardiovascular disease risk factors after renal transplantation, and discuss an approach to their medical management.
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Successful kidney transplantation has been shown repeatedly to be associated with a reduction in mortality compared with dialysis. Studies suggest that this effect largely may be the result of the reduction in cardiovascular disease (CVD) associated with the improvement in renal function. In a retrospective analysis of the United States Renal Data System data consisting of more than 60,000 adult primary kidney transplant recipients transplanted between 1995 to 2000 and more than 66,000 adult wait-listed patients over the same time period, Meier-Kriesche et al[1] showed a progressive decrease in cardiovascular death rates by renal transplant vintage for diabetic and nondiabetic recipients of both living- and deceased-donor transplants.

In contrast, the CVD death rates in wait-listed patients appeared to increase steadily by dialysis vintage. Although the CVD death rates among transplant recipients were expectedly higher in the early postoperative period, they decreased significantly by 3 months posttransplant. On long-term follow-up evaluation, although there seemed to be a modest increase in CVD death rates in the second transplant year, the rates actually remained low even among high CVD risk groups such as those with end-stage renal disease secondary to diabetes mellitus or hypertension. This finding likely reflects the impact of deteriorating transplant function on CVD death rates and is consistent with the relationship between declining renal function and CVD risk observed in nontransplant chronic kidney disease.[2] Yet despite the well-established survival advantage of transplantation over dialysis, CVD death has emerged as the most frequent cause of late graft loss. Recognition of CVD risk factors and aggressive management of CVD risk factors should begin in the early posttransplant period and should remain an integral part of long-term care in renal transplant recipients.

CARDIOVASCULAR RISK FACTORS IN THE RECIPIENTS OF RENAL TRANSPLANTS

Although all the determinants of enhanced CVD risks in renal transplant recipients have not

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Table 1. CVD Risk Factors

Conventional		Unconventional	
Modifiable	**Nonmodifiable**	**Modifiable**	**Nonmodifiable**
Hypertension	Family history	Anemia*	Prior acute rejection episodes
Dyslipidemia	Diabetes mellitus	Proteinuria*	Pre-existing CAC
Obesity		Hyperhomocysteinemia*	
Smoking		Inflammatory cytokines*	
		Impaired allograft function†	
		CMV infection‡	
		Left ventricular hypertrophy§	
		CD4 lymphopenia‖	

*See text for more detail.
†Calcineurin inhibitor minimization or withdrawal at the discretion of the clinicians (variable results/difficult-to-modify risk factor).
‡Strict adherence to CMV prophylaxis protocol/CMV surveillance in high-risk candidates.
§Optimize BP control; use of ACE-I, angiotensin receptor AT1 blockers.
‖Assess risks and benefits of T-cell–depleting antibody treatment. Further studies are needed.

been well defined, both conventional and unconventional risk factors have been suggested to be contributory (Table 1). The former risks include diabetes mellitus, hypertension, dyslipidemia, obesity, smoking, and family history. The latter risks include pre-existing left ventricular hypertrophy, coronary artery vascular calcification, impaired allograft function, proteinuria, anemia, acute rejection episodes, hyperhomocysteinemia, and inflammatory cytokines.[3,4] More recently, CD4 lymphopenia and cytomegalovirus (CMV) infection also has been suggested to be associated with cardiac complications and atherosclerosis.[5-7] Selected CVD risks are discussed.

Hypertension

Hypertension is an independent risk factor for allograft failure and mortality and is present in 50% to 90% of renal transplant recipients.[8,9] The wide range in the frequency may reflect the variable definitions of hypertension, donor source, immunosuppressive medications, time posttransplantation, and level of allograft function. Systolic blood pressure (BP) is highest immediately after transplantation and declines during the first year.[8]

In a Collaborative Transplant Study registry analysis involving nearly 25,000 recipients of deceased-donor transplants, only 8% had a systolic BP of less than 120 mm Hg at 1 year, 33% had BP in the prehypertension range, 39% had stage 1 hypertension, and 20% had stage 2 hypertension despite antihypertensive therapy.[10] Pre-existing hypertension, tacrolimus, and to a greater degree cyclosporine, corticosteroids, quality of donor organ, delayed graft function, chronic allograft nephropathy, high body mass index or excess weight gain, acute rejection episodes, recurrent or de novo glomerulonephritis, and transplant renal artery stenosis all have been implicated in posttransplant hypertension. Excess renin output from the native kidneys also may contribute to posttransplant hypertension.[8]

The contributory role of calcineurin inhibitors and glucocorticoids in the development of posttransplant hypertension has been well established. In a large randomized trial consisting of more than 400 patients randomized to remain on sirolimus-cyclosporine-steroid (sirolimus-cyclosporine-steroid) or to have cyclosporine withdrawn (sirolimus-steroid) at 3 months, systolic and diastolic BP were significantly lower in the sirolimus-steroid compared with the sirolimus-cyclosporine-steroid groups at the 36-month follow-up evaluation (systolic BP, 131.3 versus 140.1 mm Hg, respectively, $P = .002$; and diastolic BP, 76.3 versus 81.2 mm Hg, respectively, $P = .006$). Moreover, this difference was observed despite significantly ($P = .001$) less use of antihyper-

tensive medication in the sirolimus-steroid group.[11] A 3-year observational follow-up evaluation of a European, multicenter, randomized, clinical trial comparing triple therapy with tacrolimus, steroids, and mycophenolate mofetil (MMF) with withdrawal of either steroids or MMF at 3 months after renal transplantation showed that steroid withdrawal was advantageous in reducing hypertension, hyperlipidemia, and diabetes mellitus.[12] The mean systolic BP was lower in the steroid-stop group compared with the steroid maintenance groups (steroid stop, 133.6 mm Hg; triple therapy, 136.2 mm Hg; MMF stop, 139.8 mm Hg; $P = .002$). The mean diastolic BP was similar in all groups. Renal function was maintained in all groups, and patient and graft survival at 3 years were not compromised by withdrawal of concomitant immunosuppression at 3 months from a tacrolimus-based regimen.

The results of the Collaborative Transplant Study registry suggest that BP control after transplantation is suboptimal. Management of posttransplant hypertension should include attempts to identify and treat the underlying cause, lifestyle modifications, and treatment of associated cardiovascular risk factors. Lifestyle modifications should be similar to those used in the nontransplant population. Potassium-based salt substitutes must be used with caution or should be avoided because of the high incidence of hyperkalemia among patients receiving cyclosporine or tacrolimus immunosuppression.

There is a paucity of controlled clinical trials to determine the superiority of one class of antihypertensive agents over the other in the transplant setting. In general, there are no absolute contraindications to the use of any antihypertensive agent in renal transplant recipients. All classes of antihypertensives have been used in various combinations with good results. Nondihydropyridine calcium channel blockers and diuretics are used frequently in the early posttransplant period, the former because of their beneficial effect on renal hemodynamics and the latter because of their ability to eliminate salt and water in these subjects who frequently are volume expanded. In a single-center retrospective study to identify ischemic heart disease risk after renal transplantation, Kasiske et al[13] unexpectedly found an association between the use of dihydropyridine calcium channel antagonists and an increased risk of ischemic heart disease. Of interest, the use of dihydropyridine calcium channel blockers in proteinuric chronic kidney disease patients also has been shown to be associated with an increased risk of renal disease progression and death, except when used in conjunction with angiotensin II blockade therapy.[5,14-16] Although the mechanism(s) for the potential adverse effects of dihydropyridine calcium channel blockers on the cardiovascular risk profile is unclear, the use of amlodipine has been reported to be associated with increased catecholamine levels.[17] Although further recommendations await results of large, ongoing, randomized, controlled trials in the general population, monotherapy with dihydropyridine calcium channel antagonists should be used with caution.

The use of angiotensin converting enzyme inhibitor (ACE-I) and angiotensin receptor blocker (ARB) alone or in combination has gained increasing popularity because of their safety, efficacy, and well-established renoprotective, antiproteinuric, and cardioprotective effects. Nonetheless, an increase in serum creatinine level (ie, >30% above baseline) associated with their use should alert the clinician of possible transplant renal artery stenosis. Caution should be exercised when used with diuretics because ACE-I or ARB may potentiate volume depletion–induced renal hypoperfusion. In patients with slow or delayed graft function, ACE-I and ARB generally are not recommended until allograft function has recovered. Mild to moderate renal allograft dysfunction, however, does not exclude their use if serum potassium and creatinine levels can be monitored closely. β-blockers should be considered in patients with known coronary artery disease or other atherosclerotic vascular disease whereas α-2 blockers may be beneficial in patients with benign prostatic hypertrophy and neurogenic bladder. Symptomatic bradycardia and blunting of hypoglycemic unawareness occasionally may limit the use of the former. Although aggressive blood pressure control is vital in reducing cardiovascular morbidities and

mortalities as well as improving graft survival, this is not recommended in the early perioperative period because of the risk of precipitating acute tubular necrosis and/or graft thrombosis.

NEW-ONSET DIABETES MELLITUS AFTER TRANSPLANTATION

New-onset diabetes mellitus after transplantation (NODAT) is a well-known complication after solid-organ transplantation and has been reported to occur in 4% to 25% of renal transplant recipients. The variation in the reported incidence may be owing to the lack of a universal agreement on the definition of NODAT, the difference in the duration of follow-up evaluation, and the presence of both modifiable and nonmodifiable risks factors. Kidney transplant recipients who developed NODAT are at 2- to 3-fold increased risk of fatal and nonfatal CVD events.[5] Potential risk factors for NODAT include African American and Hispanic ethnicity, obesity defined as a body mass index of 30 kg/m^2 or higher, age older than 40 years, male sex, family history of diabetes among first-degree relatives, impaired glucose tolerance before transplantation, recipients of deceased-donor kidneys, hypertriglyceridemia, hypertension, hepatitis C and cytomegalovirus infection, and immunosuppressive therapy including corticosteroids, tacrolimus, and, to a lesser extent, cyclosporine.[18] The presence of certain human leukocyte antigens (HLAs) such as A30, B27, and B42, increasing HLA mismatches, acute rejection history, and male donor also have been suggested to be associated with an increased risk for NODAT (Table 2).

Table 2. Potential Risk Factors for NODAT

African American and Hispanic ethnicities
Obesity defined as a body mass index of ≥30 kg/m^2
Increasing age >40 y
Male sex
Family history of diabetes among first-degree relatives
Impaired glucose tolerance before transplantation
Recipients of deceased donor kidneys
Hypertriglyceridemia
Hypertension
Hepatitis C and CMV infection
Corticosteroids, tacrolimus, and cyclosporine
Sirolimus*
The presence of certain HLA antigens such as A30, B27, and B42
Increasing HLA mismatches
Acute rejection history
Male donor

*Further studies are needed. Please see text for more detail.

The antimetabolites azathioprine and MMF have not been shown to be diabetogenic. On the contrary, the concomitant use of MMF has been suggested to mitigate the diabetogenic effect of tacrolimus.[19] It is conceivable that the use of azathioprine or MMF allows clinicians to use lower doses of other diabetogenic immunosuppressive medications.

Early clinical trials have suggested that sirolimus is devoid of a diabetogenic effect. However, recent studies in animal models and in recipients of renal transplants have suggested that sirolimus is associated with reduced insulin sensitivity and a defect in the compensatory β-cell response.[20,21] Studies in diabetic mice transplanted with islet cells have suggested that sirolimus is associated with reduced islet engraftment and impaired β-cell function in transplants.[21]

The management of NODAT should follow the conventional approach for patients with type 2 diabetes mellitus as recommended by many clinical guidelines established by well-recognized organizations including the American Diabetes Association. A global guideline for the management of type 2 diabetes mellitus is available through the International Federation Global Guideline website (available at: http://www.d4pro.com/diabetesguidelines/index.htm). Further intervention may include adjustment or modification in immunosuppressive medications and pharmacologic therapy to achieve a target hemoglobin A1C level of less than 6.5%. Corticosteroid dose reduction has been shown to improve glucose tolerance significantly during the first year after transplantation.[19] However, any dose reduction should be weighed against the risk of acute rejection. A steroid-sparing regimen or steroid-avoidance

protocol should be tailored to each individual patient. Tacrolimus to cyclosporine conversion therapy in patients who fail to achieve target glycemic control or in those with difficult-to-control diabetes has yielded variable results.

When lifestyle modification fails to achieve adequate glycemic control, medical intervention is recommended. Orally administered agents can be used either alone or in combination with other oral agents or insulin. Although oral hypoglycemic agents may be effective in many patients with corticosteroid-, cyclosporine-, or tacrolimus-induced NODAT, insulin therapy may be necessary in up to 40% of patients,[22] particularly in the early posttransplant period.

The choice of pharmacologic therapy is based on the potential advantages and disadvantages associated with the different classes of oral agents. Although metformin (a biguanide derivative) is the preferred agent for overweight patients, its use should be avoided in patients with impaired allograft function because of the possibility of lactic acidosis. Care also should be taken when the sulfonylurea derivatives are prescribed to patients with impaired allograft function or to elderly patients because of the increased risk of hypoglycemia. In general, it is best to start with a low dose and titrate upward every 1 to 2 weeks. The nonsulfonylureas meglitinides are insulin secretagogues with a mechanism of action similar to that of the sulfonylureas. Nonetheless, they have a more rapid onset and shorter duration of action and seemingly lower risks of hypoglycemia and the amount of weight gain.[23] These agents therefore are best suited for patients whose food intake is erratic, elderly patients, and patients with impaired graft function. They are best taken before meals and the dose may be omitted if a meal is skipped.

The thiazolidinedione derivatives are insulin sensitizers that may allow for a reduction in insulin requirement. Potential adverse effects of these agents include weight gain, peripheral edema, anemia, pulmonary edema, and congestive heart failure. The incidence of peripheral edema is increased when thiazolidinedione derivatives are used in combination therapy with insulin.

Drug-to-drug interactions also should be considered carefully. The meglitinide derivatives repaglinide and to a lesser extent nateglinide are metabolized through the cytochrome p450 isozyme CYP 3A4, and the glucose level should be monitored closely when the patient also receives a strong inhibitor (eg, cyclosporine, gemfibrozil, or the azole antifungal) or inducer (eg, rifampin, carbamazepine, phenytoin, or St John's wort) of the CYP 3A4 system.[23] The use of gemfibrozil, a CYP 3A4 inhibitor, and repaglinide combination therapy has been shown to dramatically increase the action of the latter, resulting in prolonged hypoglycemia. Co-administration of cyclosporine and repaglinide also has been shown to enhance the blood glucose–lowering effect of repaglinide and increase the risk of hypoglycemia.[24] In contrast, rifampin, a strong inducer of CYP 3A4, considerably decreases the plasma concentration of repaglinide and also reduces its effects.[25] Although tacrolimus also is metabolized via the CYP 3A4 system and should therefore be susceptible to many drug interactions similar to those of cyclosporine, these interactions are not as well documented.

Monitoring of patients with posttransplant diabetes mellitus should include measuring hemoglobin A1C level every 3 months, and screening for diabetic complications including microalbuminuria, regular ophthalmologic examinations, and regular foot care. In addition, the fasting lipid profile should be measured annually. In transplant recipients with multiple CVD risk factors, more frequent monitoring of the lipid profile should be performed at the discretion of the clinicians. The management of dyslipidemia is discussed later. Table 3 summarizes the suggested guidelines for the management of NODAT.

Posttransplant Dyslipidemia

Dyslipidemia is a common occurrence after transplantation. The hyperlipemic effect of immunosuppressive agents including corticosteroids, cyclosporine, tacrolimus, and sirolimus has been well documented. Although tacrolimus-based therapy has been suggested to be associated with better lipid profiles than cyclosporine-based therapy, sirolimus has been shown to be associated with a significantly greater incidence and severity of dys-

Table 3. Management of NODAT

Dietary modification
Dietitian referral
For diabetic dyslipidemia: a diet low in saturated fats and cholesterol and high in complex carbohydrates and fiber is recommended
Lifestyle modifications
Exercise
Weight reduction or avoidance of excessive weight gain
Smoking cessation
Adjustment or modification in immunosuppressive medications*
Rapid steroid taper, steroid-sparing, or steroid-avoidance protocols
Tacrolimus to cyclosporine conversion therapy
Pharmacologic therapy
Acute, marked hyperglycemia (may require in-patient management)
Intensive insulin therapy (consider insulin drip when glucose level $\geq$ 400 mg/dL)
Chronic hyperglycemia: treat to target $HbA_{1C} < 6.5\%$
Oral glucose-lowering agent monotherapy or combination therapy† and/or insulin therapy
Consider diabetologist referral if HbA1C remains $\geq$ 9.0%
Monitoring of patients with NODAT
Hemoglobin A1C every 3 months
Screening for microalbuminuria
Regular ophthalmologic examination
Regular foot care
Annual fasting lipid profile
Aggressive treatment of dyslipidemia and hypertension

Abbreviation: NODAT, new onset diabetes mellitus after transplantation.
*Clinicians must be familiar with the patients' immune history before manipulating their immunosuppressive therapy (please see text for more detail).
†The choice of a particular agent should be based on the characteristics of each individual patient (please see text for more detail).
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lipidemia than cyclosporine-based therapy, including higher total cholesterol and triglyceride levels. Other potential etiologic factors for posttransplant dyslipidemia include age, diet, rapid weight gain, hyperinsulinemia, pre-existing hypercholesterolemia, allograft dysfunction, proteinuria, and the use of β-blockers and diuretics (Table 4).

Although hyperlipidemia often improves within the first 6 months after transplantation as the doses of prednisone, cyclosporine/tacrolimus, or sirolimus are reduced, total and low-density lipoprotein (LDL) cholesterol goals as defined by the National Cholesterol Education Program guidelines (available at: http://www.nhlbi.nih.gov/about/ncep/index.htm) usually are not achieved and treatment frequently is required. Management of hyperlipidemia includes therapeutic lifestyle changes and pharmacotherapy.

Statins or the hydroxyl glutaryl (HMG)-CoA reductase inhibitors are the most widely used lipid-lowering agents in both the nontransplant and transplant settings. The clinical benefits of statins have been shown in several large randomized controlled trials including the Heart Protection Study and the Lescol Intervention Prevention Study.[26,27]

The Heart Protection Study, the largest study to date, randomized more than 20,000 individuals in the United Kingdom aged 40 to 80 years with total cholesterol levels of greater than 135 mg/dL to receive either simvastatin (40 mg/day) or placebo. At the 5.5-year follow-up evaluation there was a 12% reduction in total mortality, a 17% reduction in vascular mortality, a 24% reduction in CVD events, a 27% reduction in strokes, and a 16% reduction in noncoronary revascularizations.[26] The study further revealed

Table 4. Causative Factors for Posttransplant Dyslipidemia

Sirolimus, corticosteroids, cyclosporine, and tacrolimus
Age
Diet
Rapid weight gain
Hyperinsulinemia
Pre-existing hypercholesterolemia
Allograft dysfunction
Proteinuria
β-blockers and diuretic therapy

that statin therapy was beneficial in reducing major vascular events independent of baseline LDL in patients with known coronary artery disease, cerebrovascular disease, peripheral vascular disease, diabetes mellitus, or hypertension. Indeed, the beneficial effect of statins was greatest in the lowest LDL subgroups (LDL $<$ 60). Whether this effect can be extrapolated to renal transplant recipients awaits further studies.

Results of the Assessment of Lescol in Renal Transplantation study revealed that treatment of renal transplant recipients with fluvastatin over a 5- to 6-year period significantly and safely reduced LDL cholesterol levels. The incidence of major adverse cardiac events also was shown to be reduced, albeit not statistically significantly. However, further analysis showed a beneficial effect of early initiation of fluvastatin on outcome—the earlier the initiation of therapy, the greater the reduction in cardiac events. For patients initiated on therapy within the first 4 years posttransplant, there was a risk reduction of 64% compared with 19% for patients initiated on therapy after 10 years. No statin effect on graft loss or on doubling of serum creatinine level was observed.[28-30] This finding contrasts with that of Masterson et al,[31] who found better renal function at 12 months posttransplant in recipients who received statins compared with those who were not on statin therapy (Δ creatinine clearance 6.1 mL/min, $P < .00$; in addition, less interstitial fibrosis was seen on protocol biopsies).

Despite the well-established efficacy and safety of the use of statins in transplant recipients, clinicians should remain vigilant to the potential drug-drug interactions in transplant patients, who often require multiple medications. The use of statins in the presence of calcineurin inhibitors, particularly cyclosporine, often results in a several-fold increase in statin blood level and an increased risk for myopathy and rhabdomyolysis.[32] Cyclosporine increases plasma exposure to fluvastatin by approximately 2-fold, simvastatin (20 mg/day) by 3-fold, atorvastatin by approximately 6-fold, pravastatin by 5- to 23-fold, and lovastatin by up to 20-fold. Approximate therapeutic equivalencies are achieved by 10 mg of atorvastatin, 20 mg of simvastatin, 40 mg of pravastatin, 40 mg of lovastatin, and 80 mg of fluvastatin. At these doses, the LDL cholesterol decrease is approximately 34%, with very little change in high-density lipoprotein levels.[32] In addition to their lipid-lowering effect, statins may offer protection against CVD via their antiproliferative properties and effects on the reduction of circulating endothelin-1, C-reactive protein (CRP) levels, systolic and diastolic BP, and pulse pressure.

Other classes of lipid-lowering agents include fibric acid derivatives, nicotinic acid, bile acid sequestrants, and the newer lipid-lowering agent ezetimibe. Ezetimibe and statin combination therapy can significantly improve cholesterol control because of their complementary mechanism of actions. Ezetimibe blocks intestinal absorption of dietary cholesterol and related phytosterols whereas statin blocks hepatic cholesterol synthesis. The currently available ezetimibe/simvastatin [Inegy, Vytorin (MSP Singapore Company, LLC)] drug combination has been shown to markedly reduce LDL-cholesterol (LDL-C) levels and has been suggested to represent a valuable option for the management of hyperlipidemia across diverse patient populations.[33] In a cohort study consisting of 40 stable kidney transplant recipients with hypercholesterolemia, 4 weeks of ezetimide therapy significantly lowered total and LDL cholesterol levels.[34] In addition, the drug was found to be more effective when used in combination with a statin. LDL reduction was 24% $\pm$ 13% with ezetimide monotherapy ver-

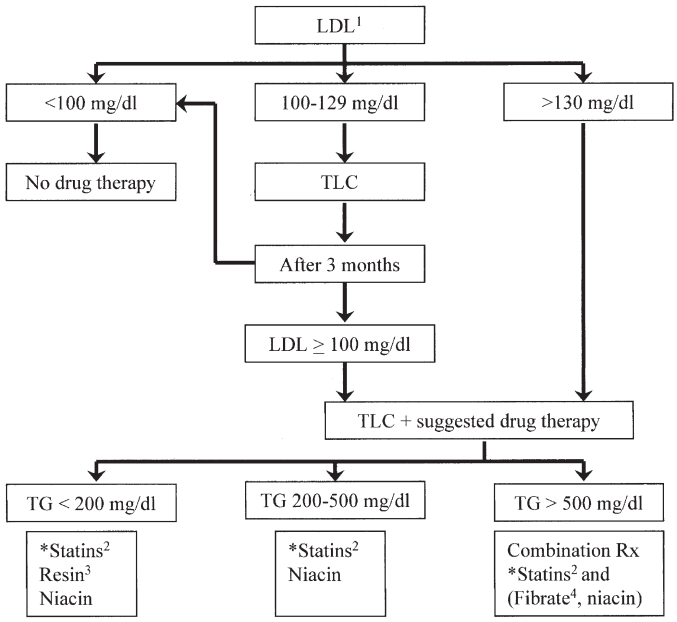

Figure 1. Suggested guidelines for the treatment of posttransplant dyslipidemia. All transplant recipients should be regarded as CHD risk equivalent. Goals: LDL < 100 mg/dL (optional < 70 mg/dL), TG < 200 mg/dL, HDL > 45 mg/dL. [1]LDL < 70 mg/dL has been suggested for very high-risk patients (NCEP, ATP III guidelines). [2]Statins are the most effective drugs and should be the agents of first choice. Start at low dose in patients on cyclosporine and tacrolimus. Monitor for myositis and transaminitis, particularly in those receiving combination therapy. [3]Bile acid sequestrans should probably not be taken at the same time as cyclosporine. [4]Extreme caution should be used with statin and fibrate combination therapy. [5]Consider cholesterol absorption inhibitors in patients intolerant to statins. TLC, therapeutic lifestyle change; TG, triglyceride. Adapted and reprinted with permission, Copyright Elsevier 2007.[18]

sus 41% ± 13% with the statin combination therapy. No significant adverse effects on serum creatinine level, drug level, body weight, or liver function test results were detected. It is likely that ezetimibe also can be used as adjunctive therapy with other lipid-lowering agents in renal transplant recipients with poorly controlled hyperlipidemia on statin monotherapy, although further recommendations await further studies. To date, no significant drug-to-drug interaction between ezetimibe and calcineurin inhibitors or sirolimus has been reported.

Severe hypertriglyceridemia (TG > 500 mg/dL) has been encountered more frequently since the introduction of sirolimus. Management includes sirolimus dose reduction, addition of a fibric acid derivative or nicotinic acid, and, in refractory cases, sirolimus to MMF or tacrolimus switch. Of the major fibric acid medications (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil), the first 3 have been reported to cause increases in the serum creatinine level in cyclosporine-treated patients, as well as higher plasma homocysteine levels. Although all fibrates in combinations with statins have been associated with creatinine kinase increases with or without overt rhabdomyolysis and myopathy, gemfibrozil may have a greater risk for the development of myopathy compared with bezafibrate or fenofibrate.[32] Niacin monotherapy has not been reported to cause myopathy, but its combined use with lovastatin, pravastatin, or simvastatin may be associated with rhabdomyolysis. Bile acid sequestrants must be used with caution because of their potential interference with the absorption of other medications vital to the renal transplant recipients. For a more complete list of drug-to-drug interactions of statins with other lipid-lowering agents, readers are referred to the article by Ballantyne et al.[32]

Suggested guidelines for pharmacologic treatment of dyslipidemia are summarized in Fig. 1.

Obesity

Obesity is a well-established risk factor for accelerated atherosclerotic heart disease and a potentially detrimental condition because of its associated comorbid conditions including hyperinsulinemia and insulin resistance, diabetes mellitus, dyslipidemia, and hypertension. Unfortunately, in the posttransplant setting, excessive weight gain or obesity may become a problem for many patients. For instance, patients on prednisone therapy may overeat because they often experience constant hunger or craving for sweets. In addition, the release from pretransplant dietary restrictions and habitual physical inactivity can result in rapid posttransplant weight gain. Studies in liver transplant recipients revealed that tacrolimus immunosuppression is associated with a lower likelihood of posttransplant weight gain compared with cyclosporine (27% versus 46%, respectively).[35] Nonetheless, cyclosporine has not been found consistently to be an independent predictor of posttransplant obesity.[36] Other suggested predictors for increased weight gain after transplantation include pretransplant obesity, greater donor body mass index, and higher cumulative doses of prednisone. It has been suggested that the steroid-sparing effect of tacrolimus may account for its lower likelihood of posttransplant weight gain compared with that of cyclosporine treatment.

Management of posttransplant obesity includes lifestyle and dietary modifications. Enrollment in a diet support group and/or exercise program can be invaluable. Steroid reduction or withdrawal must be balanced against the risk of allograft rejection and graft loss. The use of pharmacologic agents for weight reduction in the posttransplant period currently is not recommended because of unknown potential drug-drug interactions. In morbidly obese patients, gastric bypass surgery has been shown to be a safe and effective means for achieving significant long-term weight loss and relief of comorbid conditions after transplantation.[37] Data on the safety and efficacy of posttransplant gastric bypass surgery in ameliorating comorbid conditions such as hypertension, diabetes mellitus, or dyslipidemia currently are limited. However, with refinements in surgical techniques and advances in postoperative care, surgical management of posttransplant morbid obesity should be explored.

Hyperhomocysteinemia

Hyperhomocysteinemia occurs in about two thirds of renal transplant recipients. Studies in chronic renal transplant recipients have shown that the relative risk for cardiovascular complications is increased by 6% for every μmol/L increase in homocysteine level.[38] Important determinants of total plasma homocysteine levels include folate, vitamin B_6 (pyridoxine), vitamin B_{12} (cyanocolabamin), and impaired renal function. In a small, prospective, randomized, placebo-controlled study consisting of 56 stable hyperhomocysteinemic renal transplant recipients, vitamin supplementation with folic acid (5 mg/d), vitamin B_6 (50 mg/d), and vitamin B_{12} (488 μg/d) was shown to decrease the fasting homocysteine level significantly and to improve carotid intima-media thickening compared with placebo-treated patients.[39] Furthermore, the presence of carotid intima-media thickening has been shown to be a good marker of early atherosclerotic changes and an independent risk factor for myocardial infarction and stroke.[40]

In a single-center prospective study consisting of more than 700 renal transplant recipients who were seen for a routine visit in the transplant clinic, the baseline fasting plasma total homocysteine levels were shown to be associated independently with the risk of death and kidney allograft loss.[41] Nonetheless, plasma homocysteine-lowering treatment has not been shown consistently to be effective in the prevention of cardiovascular events in high CVD risk patients.

Results of the Norwegian Vitamin trial (a multicenter, prospective, randomized, double-blind, placebo-controlled trial consisting of more than 3,700 patients who sustained an acute myocardial infarction within 7 days of randomization) showed that homocysteine-lowering treatment with folic acid, with or without high doses of vitamin B_6, failed to lower the risk of recurrent CVD events or death. In contrast, there was a trend toward an increased risk in the treatment arm (relative risk, 1.22).[42]

The Folic Acid for Vascular Outcome Reduction in Renal transplantation study is an ongoing, multicenter, double-blind, randomized, controlled clinical trial to evaluate whether lowering the total homocysteine level with either a high-dose or low-dose of folic acid (5 or 0 mg), vitamin B_6 (50 or 1.4 mg), and vitamin B_{12} (1,000 or 2 μg) reduces CVD events in stable renal transplant recipients with increased total homocysteine levels. Further recommendations on the use of vitamin supplements to lower CVD risks await definitive results from the Folic Acid for Vascular Outcome Reduction in Renal transplantation study and other ongoing randomized clinical trials.

INFLAMMATION AND OXIDATIVE STRESS

Inflammation and oxidative stress, which are prevalent in patients with CKD, are not controlled effectively by dialysis. Simmons et al[3] have shown that pretransplant levels of the proinflammatory proteins interleukin-6, tumor necrosis factor-α, and CRP, as well as the oxidative stress markers plasma protein carbonyls and F2-isoprostanes, were increased significantly in CKD patients compared with healthy control subjects. After a successful kidney transplant, there was a rapid and sustained decline in all of these biomarkers, reaching levels of those of controls by 2 months posttransplant.

In a prospective study to determine the incidence and risk factors for ischemic heart disease in renal transplant recipients who were free of vascular disease at enrollment, coronary events were recorded in 7.8% of 344 consecutive renal transplant recipients at a mean follow-up period of 72 $\pm$ 14 months. In addition to traditional Framingham risk factors, CRP level (P = .009) and hyperhomocysteinemia (P = .01) were found to be independent risk factors for ischemic heart disease events.[43]

Increased CRP and other inflammatory markers also have been shown to be associated with an increased risk of all-cause mortality in renal transplant recipients. In a single-center prospective study consisting of more than 400 consecutive kidney transplant recipients followed up for a median of 7.8 years, Winkelmayer et al[44] showed that patients with a CRP of 0.5 mg/dL or higher had a 53% higher mortality risk compared with patients whose CRP was below that threshold [hazard ratio (HR) = 1.53; 95% confidence interval, 1.01-2.31; P = .04]. No associations between CRP and the risk of kidney allograft loss were detected.

Recent studies have established a link between inflammation, atherosclerosis, and other manifestations of cardiovascular disease. Hansson[45] illustrated the similarities between the role of T-cell activation on plaque inflammation and on the alloimmune response. It is conceivable that the dramatic reduction in CVD mortality posttransplant compared with remaining on dialysis is, in part, related to the use of immunosuppressive agents that also are anti-inflammatory.

The putative role of inflammation in the development of pretransplant and posttransplant morbidity and mortality raises intriguing therapeutic options. Grotz et al[46] hypothesized that aspirin protects allograft function and survival in the context of chronic renal allograft dysfunction because of the similarities between the inflammatory mechanisms underlying atherogenesis and chronic allograft nephropathy. In a retrospective multivariate analysis performed to assess the effect of low-dose aspirin treatment (100 mg/d) on allograft function and survival, the Grotz et al[46] found that low-dose aspirin substantially improved median allograft survival time compared with no aspirin treatment (low-dose aspirin versus no aspirin, 13.8 $\pm$ 2.6 years [n = 205] versus 7.8 $\pm$ 0.3 years [n = 625], respectively; adjusted relative risk, 0.443; $P < .0001$). In addition, renal allograft function was better preserved in aspirin-treated patients, who displayed a slower increase of serum creatinine level and less proteinuria and hematuria during the observation period. The investigators suggested that aspirin should be considered as part of the long-term posttransplant treatment regimen.

The failed or failing kidney transplant also has been suggested to be a potential source of chronic inflammation, which contributes to higher morbidity and mortality rates among patients who returned to hemodialysis after failure of their kidney transplant compared with nontransplanted dialysis patients. Lopez-Gomez et al[47] found that hemodialysis patients with a

failed kidney transplant in situ commonly suffered from a chronic inflammatory state and that transplant nephrectomy was associated with amelioration of markers of chronic inflammation, including improvement in serum albumin level, prealbumin level, ferritin level, fibrinogen level, CRP level, erythrocyte sedimentation rate, and erythropoietin resistance index. Transplant nephrectomy should be considered in patients with failed kidney transplants, particularly if they show clinical evidence of a chronic inflammatory state.

PROTEINURIA

Proteinuria has been reported to occur in 9% to 40% of kidney transplant recipients with a functioning allograft.[48] As in the nontransplant setting, posttransplantation proteinuria has been shown to be an independent risk factor for CVD.

In a retrospective study consisting of more than 500 Caucasian patients who received a deceased-donor renal transplant and had a functioning allograft for longer than a year, Fernandez-Fresnedo et al[49] found that compared with no proteinuria, the presence of persistent proteinuria (defined as urine protein excretion greater than 0.5 g/d for more than 6 months; mean follow-up period, 6.41 ± 3.6 y) was associated with increased mortality and graft loss (relative risk of death and graft loss [RR], 1.92 and 4.18, respectively), and a higher incidence of CVD (RR, 2.45). Similarly, Roodnat et al[50] reported a nearly 2-fold risk of death in renal transplant recipients with a functioning allograft and proteinuria at 1 year compared with those without proteinuria.

The literature on the link between proteinuria and increased CVD and related death, and its negative impact on patient and kidney allograft survival, has been increasingly recognized. It is suggested that proteinuria is a biomarker of systemic endothelial dysfunction inherent to the atherosclerotic process.[51] Unless contraindicated, ACE-I, ARB, or both should be considered in transplant recipients with microalbuminuria or overt proteinuria because of their well-established renoprotective, antiproteinuric, and cardioprotective effects. Whether the development of proteinuria associated with sirolimus[52] adversely affects CVD risks currently is unknown and warrants close monitoring.

ANEMIA

Anemia after renal transplantation has a reported prevalence of 20% to 80%.[53] The wide variation in the prevalence reported in part is owing to the variable definitions of anemia, immunosuppressive medications, time posttransplantation, duration of follow-up evaluation, and level of allograft function, among others.

In a retrospective study consisting of 92 renal transplant recipients with a functioning allograft at 1 year, posttransplant anemia, defined as a hemoglobin level of less than 13 g/dL for men and less than 12 g/dL for women, was found in 35.5% and 25% of patients at months 6 and 12, respectively.[54] In a multivariate analysis, the independent predictive factors of anemia at month 6 were erythropoietin level at day 0, cause of end-stage renal disease (polycystic kidney disease versus others), posttransplantation recombinant erythropoietin therapy, hematocrit level at month 3, platelets at day 7, and sirolimus therapy. Delayed graft function, renal function at month 12, and anemia at month 6 were independent risk factors for the presence of persistent anemia at 1 year.

In a retrospective study consisting of more than 200 transplant recipients receiving sirolimus, nearly 60% were found to be anemic, a frequency nearly twice that for patients receiving MMF.[55] It has been suggested that sirolimus inhibits erythropoiesis at the level of the erythropoietin receptor. The binding of erythropoietin to its cytoplasmic receptors leads to the activation of a cascade of phosphorylating enzymes including phosphoinositide 3-kinase, an enzyme responsible for controlling cell survival and cell-cycle progression in several cell lines including erythroid precursors. Sirolimus blocks p70S6-kinase, an enzyme downstream from phosphoinositide 3-kinase, and inhibits basal- as well as erythropoietin-stimulated proliferation. Sirolimus, however, does not interfere with the maturation of the J2E erythroid cell line.[56]

Suggested causative factors for posttransplant anemia include iron, folate, and B12 deficiency, impaired allograft function, acute rejection epi-

sodes, recent infection, and medications such as azathioprine, MMF, sirolimus, and ACE-I and ARB. Anemia also has been reported to be more common in African American and female transplant recipients. Similar to the general population and patients with chronic kidney disease, it has shown that anemia adversely affects CVD in kidney transplant recipients.

In a multivariate analysis of more than 400 recipients of kidney alone or simultaneous kidney-pancreas transplants, Djamali et al[57] found that diabetic transplant recipients with a hematocrit level greater than 30% were less likely to suffer from a CVD event (myocardial infarction, cardiovascular death, angina, and congestive heart failure) in the first 6 posttransplant months compared with those with a hematocrit level less than or equal to 30% (RR = .65, P = .22). Similarly, in a retrospective study involving consecutive de novo MMF-treated kidney recipients from the Hospital of the University of Pennsylvania between 1996 and 2002, Imoagene-Oyedeji et al[58] revealed that the cohort with anemia at 12 months, defined as a hemoglobin level of less than 12 g/dL, had inferior patient survival (P = .02, log rank) and a higher proportion of cardiovascular deaths (6.3% versus 2.2%; P = .017) compared with the nonanemic patients. In contrast, in a study involving more than 400 kidney transplant recipients, Winkelmayer et al[59] failed to show an association between anemia defined as a hemoglobin level less than 10 g/dL and mortality or graft loss. Among the iron parameters, only the percentage of hypochromic red cells was associated with greater all-cause mortality. The clinical significance and therapeutic implications of theses findings remain to be determined.

Darbepoetin alfa (Aranesp, Amgen Inc., Thousand Oaks, CA) is an effective and safe alternative to recombinant human erythropoietin treatment for anemic renal transplant recipients. However, it currently is not known whether erythropoiesis-stimulating agents have a beneficial effect on CVD risk factor reduction beyond correction of posttransplant anemia alone. Assessment of baseline iron stores at the time of transplantation may be invaluable because iron deficiency is not uncommon in the dialysis population. Profound iron deficiency should be treated with intravenous iron as tolerated. Refractory or severe anemia mandates aggressive evaluation to exclude the possibility of surgical postoperative bleeding, particularly in those with a rapid decrease in hemoglobin and hematocrit levels. Other possibilities include gastrointestinal bleed, tertiary hyperparathyroidism, underlying inflammatory conditions, or parvovirus B19 infection. Erythropoietin-resistant anemia has been described in patients receiving sirolimus immunosuppression.

CORONARY ARTERY CALCIFICATION

Coronary artery calcification (CAC) as measured by electron beam computerized tomography (EBCT) has been studied as a noninvasive technique to diagnose coronary artery disease and as a surrogate marker of coronary plaque load. CAC as detected by EBCT has a reported sensitivity and specificity of 97% and 72%, respectively, to detect 50% or more stenosis identified angiographically.[60] Studies have shown that CAC is highly prevalent in the dialysis population and the increased incidence has been suggested to be associated with older age, the presence of diabetes mellitus, higher body mass index, osteoporosis, and biochemical marker evidence of inflammation.

The prevalence of CAC in the dialysis population, not surprisingly, also is reflected in the transplant population. In a study to determine the extent and characteristics of CAC at the time of renal transplantation, Rosas et al[61] found that 65% (51 of 79) of asymptomatic renal transplant recipients had evidence of CAC, with a mean CAC score of 331.5 (562.4) and a median of 43.3. By univariate analysis, older age, presence of diabetes, exposure to dialysis before transplantation, deceased donor transplants, and hypercholesterolemia were found to be associated significantly with the presence of CAC. Median CAC scores were significantly higher in diabetics and in recipients of deceased-donor transplants, but lower in those who received pre-emptive transplantation. By multiple logistic regression analysis, age and time on dialysis were associated significantly with the presence of CAC at the time of transplant, a finding that is in concordance with

the documented negative impact of prolonged dialysis on posttransplant morbidity.

In a pilot study consisting of 19 young adults (mean age, 32 y) with stable allograft function who previously had received successful kidney transplants as children, nearly half were found to have CAC, with the quantity of calcification detected comparable with that of asymptomatic individuals from the general population 10 to 40 years older.[60] This finding is in keeping with the clinical observation of coronary heart disease in transplant recipients in their late 20s and 30s. Studies in children and adolescents aged 10 to 20 years with different stages of chronic kidney disease (CKD) and after renal transplantation have shown that thickening of intima-media of large arteries occurs early in the course of the disease, and is most marked in patients on dialysis.[62] Compared with dialysis patients, less marked arterial pathology was seen in recipients of renal transplants despite similar dialysis vintage, suggesting partial reversibility of CKD-associated arteriopathy in children, a finding that provides justification for expediting transplantation for this age group. To date, the value of the assessment of CAC by EBCT as an independent predictor of cardiac events and a replacement for more invasive monitoring remains to be determined. Nevertheless, transplant recipients with CAC should be regarded as suitable candidates for aggressive risk factor reduction.

Extracoronary vascular calcifications also are common in dialysis patients and are predictors of all-cause and cardiovascular mortality. Similar findings were observed among recipients of renal transplants. In a cohort of more than 1,000 renal transplant recipients, calcification in the aortoiliac region as assessed by plain radiography at the time of transplant was observed in 24.4% of patients, a finding that was an independent predictor of cardiovascular and all-cause mortality (relative risk, 1.8 for overall mortality and 2.6 for cardiovascular mortality).[63] Of interest, the effect of vascular calcifications on mortality was evident in nondiabetics but not in their diabetic counterparts. Mortality rates for nondiabetics with and without vascular calcifications were 21% and 9%, respectively ($P = .0001$). These differences were not observed in diabetic patients (16.5 versus 14.3%; $P = .656$). For patients in whom the transplant surgeon can identify the increased stiffness of pelvic vessels at the time of transplantation, it is advisable to confirm the presence of pelvic vascular calcifications with a plain radiograph and, if indicated, implement risk reduction strategies.

SUMMARY

Although there is no consensus on the optimal approach to the management of CVD risks in renal transplant recipients, the identification of the high-risk patient and implementation of primary prevention is probably the best treatment strategy. All transplant recipients currently should be considered at risk for coronary heart disease and, unless contraindicated, early treatment with statins, β-blockers, and antiplatelets should be considered. The beneficial effects of ACE-I or ARB on posttransplant patient and graft survival have not been shown consistently.[64,65] Further recommendations on their routine use in the posttransplant period await large, randomized, controlled, clinical trials. Target LDL concentrations should be maintained at less than 100 mg/dL. In addition to pharmacologic treatment, emphasis should be placed on lifestyle modifications including moderation of dietary sodium and saturated fat intake, regular aerobic exercise, weight reduction, and tobacco avoidance. The management of posttransplant CVD requires a multidisciplinary approach in which every potential complicating factor must be monitored closely and treated.

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