Long-Term Complications in Renal Transplantation

JOHN R. SILKENSEN
Division of Nephrology, Hypertension, and Transplantation, University of Florida, Gainesville, Florida.

The preferred modality for renal replacement is renal transplantation, and its superiority in prolonging the longevity of patients with end-stage renal disease is well established (1). In the United States, more than 12,000 kidney transplants were performed in 1998 and the waiting list for transplants has increased threefold, from approximately 13,000 in 1988 to 43,000 in 1999 (2). Economically, transplant is a more feasible method of replacement therapy, an important factor when considering the increasing health care costs and the government’s continued commitment to providing coverage of end-stage renal disease therapies. In many countries, nephrologists and technicians trained in dialytic techniques are relatively scarce and transplantation remains the only feasible option. In terms of quality of life, patient surveys have consistently indicated a clear preference for transplantation over other replacement therapies.

The series of cadaveric renal transplants performed in the early 1950s by Hume in Boston, as well as similar operations in Paris, marked the first successes in the field (3). In the mid-1950s, expertise in the science of cell-mediated immunity provided a foundation for the understanding of the immune response. Around this time, transplants using identical twins served to propel the field forward from a technical standpoint and fueled hope that transplants from nonidentical donors would someday become feasible. Where radiation-induced bone marrow suppression had been used for some of the early transplants in Boston and Paris, the introduction of 6-mercaptopurine (6-MP) in 1953 spawned one of the mainstays in the immunosuppressive regimen. Azathioprine, a less toxic derivative of 6-MP introduced in 1960, and corticosteroids remained the primary immunosuppressive drug regimen over the next two decades. During this time, technical expertise in the transplant procedure as well as proficiency in the care of the transplant recipient rapidly grew, and the advent of dialysis provided an option for individuals awaiting transplantation and for those in whom transplantation was unsuccessful. The field of transplantation was revolutionized by the introduction of cyclosporine in the early 1980s, and this agent remains the mainstay of immunosuppression at most centers. Cyclosporine is derived from fungi and works by inhibiting the transcription of interleukin-2 (IL-2) mRNA, leading to decreased production of IL-2 and other cytokines critical to T cell activation and proliferation. Cyclosporine and other immunosuppressive drugs have lowered the incidence of acute rejection and have improved long-term survival. The median cadaveric graft survival improved from 5.2 years in 1986–1987 to 10.2 years in 1994–1995. This twofold increase is largely attributable to cyclosporine, since a dramatic decrease in first-year allograft loss rate occurred after the introduction of the drug in 1983. Median living donor graft survival also improved over the same periods from 10 years to 16.2 years, and steady increases in both cadaveric and living donor graft survival also occurred (4). Patient survival has also improved, but has been associated with medical complications that both impair the quality of life of transplant recipients and substantially add to societal health care costs. Long-term complications of renal transplantation can arbitrarily be thought of as those occurring more than 3 months from the time of surgery. Certainly there are a number of complications in the early perioperative period, including delayed graft function due to tubular necrosis, acute allograft dysfunction from a variety of causes (acute rejection, ischemic tubular necrosis, nephrotoxic drugs, infection), untoward side effects from drugs at higher doses, and a variety of infections more common early in the transplant course. However, long-term medical complications of renal transplantation have become increasingly important. The most important of these include infection, malignancy, bone disease, and cardiovascular disease. Additionally, hypertension, posttransplant diabetes mellitus, cataracts, postransplant erythrocytosis, chronic rejection, and recurrent disease all account for increased morbidity in the transplant recipients and deserve special consideration.

Infection

Infection has long been one of the most important medical complications of transplantation of all types. Over time, however, the pattern and severity of the various infections has changed, with a general trend toward a reduction in severity. In fact, the incidence of infection has dropped from 70% in the early days of renal transplantation to 15 to 44% more recently. Mortality due to infection in these same series ranged from 11 to 40% in the former to less than 5% in the latter (5). This trend is probably attributable to a number of factors, including refinement of the actual surgical technique, better and more appropriately tailored immunosuppressive regimens, the use of prophylactic antimicrobial agents, improved methods for diagnosis, and more effective therapies. In the early postoperative period, the most common infections are bacterial and involve the urinary tract, the wound, the respiratory tract, and intrave-
nous lines. These problems are not unique to the transplant patient and many can be avoided by common-sense measures such as prompt removal of the bladder catheter, prophylactic intraoperative antibiotics with meticulous wound management, and avoidance of prolonged intravenous lines.

Urinary tract infection is the most common infection in the transplant recipient with an incidence of more than 30% in the first 3 months following transplantation (6). The clinical presentation is variable, from asymptomatic bacteriuria or pyuria to pyelonephritis and septicemia. Graft dysfunction is not uncommon as the major presenting feature. Because an anatomic and functionally intact kidney is important as a primary host defense against infection, it is not surprising that urinary tract infections would be more common in patients who must undergo implantation of a donor ureter into their own bladder. Many centers encourage the use of trimethoprim-sulfamethoxazole as prophylaxis against urinary tract infections as well as *Pneumocystis carinii*, *Listeria*, and *Nocardia*.

Community-acquired infections such as the common cold, influenza, pneumococcal pneumonia, diarrheal syndromes, and sexually transmitted diseases can all affect the transplant recipient. It is necessary that these routine infections be considered carefully, because there is a temptation to focus on some of the more unusual opportunistic infections, sometimes to the exclusion of those that are more common. When prescribing antibiotics, it is important to be aware of the drug interactions that may result with other drugs of the immunosuppressive regimen, particularly cyclosporine. Erythromycin and other macrolide antibiotics inhibit cytochrome P450-I1IA, resulting in elevated levels of cyclosporine and a tendency toward nephrotoxicity. When treating an organism such as *Legionella* with azithromycin, for example, cyclosporine dose adjustments may become necessary.

Opportunistic infections can occur at any time following transplantation but tend to occur after the first month when the immunosuppressive effect is at its peak. The degree of immunosuppression is clearly linked to the development of opportunistic infections, and patients who have been treated for multiple rejection episodes or who have received a more aggressive regimen are definitely at higher risk. A recent study dividing patients into three groups based on the presence of acute rejection and subsequent therapy showed a significant increase in the number of infections during the first 6 months posttransplant in patients treated with high-dose corticosteroids for acute rejection compared to those without rejection (71% versus 52%). The addition of cytolytic therapy, either OKT3, an anti-CD3 monoclonal antilymphocyte preparation, or a polyclonal antilymphocyte preparation resulted in a further increase in the incidence of infections that rose to 86%. Not all infections were opportunistic, however; urinary tract infection was the most common in all groups (7). Additional studies will be necessary to establish the risk in the use of some of the newer agents, including the humanized monoclonal antibody daclizumab and the chimeric monoclonal antibody basiliximab.

Cytomegalovirus (CMV) is one of the most common infections encountered in the renal transplant patient population with an incidence of 34 to 55% (6). The typical onset of disease is within the first 1 to 4 months after transplant. Transmission can occur through transplantation of an infected organ or through transfusion of blood products from a seropositive donor. Clinically significant disease with CMV can evolve in three ways: (1) Primary infection can occur when a seronegative recipient receives an organ from a seropositive donor. This group of patients represents those at highest risk and it is this group for which prophylaxis is deemed most important. (2) Seropositive individuals can reactivate latent virus and develop clinically significant disease. (3) Reactivation of donor virus can occur in a seropositive recipient and has been labeled superinfection. Prophylaxis with acyclovir has been used historically, although the efficacy of this therapy in the prevention of disease is questionable. Some transplant physicians believe that it does attenuate disease severity and that its use is justified for that reason as well as its prophylactic effect on herpes simplex virus. Many centers now, however, favor the use of oral ganciclovir as prophylaxis, and evidence supports the fact that it is superior to acyclovir in providing effective CMV prophylaxis for recipients of seropositive donor kidneys (8). A recent study demonstrated the effectiveness of valacyclovir, a prodrug of acyclovir, in the prevention of CMV disease compared to placebo. Interestingly, the use of valacyclovir was associated with a reduction in the number of acute rejection episodes, a finding that supports the association of CMV with acute rejection (9). Additional studies will be necessary to compare valacyclovir to ganciclovir and other agents.

The most common clinical presentation for CMV is fever, malaise, and leukopenia. Other manifestations include chorioretinitis, pneumonitis, and gastrointestinal involvement (esophageal discomfort, abdominal cramping, diarrhea, and hepatitis). As mentioned, those at highest risk include CMV seronegative recipients of CMV seropositive donor kidneys. Reactivation disease in a seropositive recipient is generally less severe clinically, and superinfection is generally rare. Disease can range from asymptomatic to severe, the latter characterized by sight-threatening retinitis or life-threatening systemic involvement (pulmonary, gastrointestinal, or hematologic). In this group, therapy with intravenous ganciclovir is initiated and immunosuppression is occasionally reduced. Because CMV infection can lead to an intensified immunosuppression of host defenses, concomitant superinfection with other opportunistic pathogens (*Pneumocystis, Aspergillus*, and *Listeria*) should be considered (5).

Epstein-Barr virus (EBV) plays a central role in the development of posttransplant lymphoproliferative disorder (PTLD), although milder manifestations of infection include a mononucleosis syndrome consisting of fever, malaise, leukopenia, and atypical lymphocytosis. Because EBV is responsive to acyclovir, many centers have continued to use this drug as a prophylactic medication.

Reactivation of herpes simplex virus is frequently seen in transplant recipients during the first several months. The incidence is markedly reduced when prophylactic acyclovir is used. Ganciclovir also has activity against herpetic lesions. Orofacial, esophageal, and genital involvement can be seen,
and treatment consists of acyclovir or famiciclovir. More severe disease may be manifested by pneumonitis or hepatitis.

Varicella-Zoster virus (VZV) can cause a reactivation infection characterized by zoster lesions in a localized dermatomal pattern, as well as a more disseminated cutaneous presentation. Primary disease in a seronegative transplant recipient exposed to VZV can be especially severe, with life-threatening pneumonia, encephalitis, hepatitis, and disseminated intravascular coagulation possible. Prompt administration of varicella-zoster immune globulin early in the postexposure period can prevent serious illness (5).

The major causes of liver disease in the renal transplant population are hepatitis B (HBV) and hepatitis C (HCV) viruses. Due to the dependence on blood transfusions prior to the availability of recombinant erythropoietin, HBV has long been an important pathogen in transplant patients. Viral replication and rate of disease progression are markedly increased with the use of posttransplant immunosuppressive drugs, and 50% of transplanted carriers will develop end-stage liver disease or hepatocellular carcinoma within 10 years (10). Although controversial, most centers consider HBV infection a contraindication to transplantation. Vaccination prior to transplantation is advocated for individuals without antibodies to HbsAg, and is a routine requirement for patients with end-stage renal disease on dialysis. With the availability of a vaccine, better infection control, and stringent transplantation requirements, HBV accounts for only a small fraction of renal transplant recipients with chronic liver disease. In contrast, HCV accounts for virtually all of the 10 to 15% of transplant recipients who develop chronic liver disease. The clinical course of HCV in the transplant population is more indolent, with generally no major impact on mortality until 5 years after transplant. From that point on, however, progressive liver failure and hepatocellular carcinomas are observed (11). Treatment with interferon-α has been disappointing, and allograft rejection is a major concern through elaboration of cytokines (12). Therefore, some experts have recommended the consideration of therapy prior to transplant when an allograft is not at risk and reduction of immunosuppression for significant disease after transplantation.

In most centers, HIV infection in a candidate is considered a contraindication to transplantation. Although some patients have done well, many develop AIDS and die of infections shortly after the transplant surgery. Whether the newer antiretroviral therapies provide an improvement in longevity after transplantation is still unclear.

Parasitic diseases include *Toxoplasma* and *Strongyloides*. In transplant candidates from endemic areas (Asia and Latin America), *Strongyloides stercoralis* must be excluded by antibody detection before transplantation, as life-threatening disseminated infection can occur in the immunocompromised state. Stool specimens are generally not adequate for detection despite the ability of the organism to live asymptotically in the gastrointestinal tract for decades (10).

Pneumocystis is uncommon in patients who receive prophylaxis with trimethoprim/sulfamethoxazole. In sulfa allergic patients, a combination of trimethoprim and dapsone or aerosolized pentamidine can be substituted. When eliciting a history from a transplant recipient, emphasis on travel and exposures may yield some clues regarding the ultimate diagnosis, especially with fungal and mycobacterial infections. Infection with geographically restricted systemic mycoses such as *Histoplasma, Coccidioides*, and *Blastomyces* should be considered in a transplant recipient with a history of travel to endemic areas. Because serologic studies may not be helpful in the evaluation of an immunosuppressed individual, isolation of the organism through tissue diagnosis or culture of specimens may be necessary. The most common fungal infection in the renal transplant recipient is candidiasis, with *Candida albicans* the most frequently isolated pathogen. Various alterations such as suppression of normal gut flora by antibiotics, metabolic derangements favoring fungal growth (diabetes and corticosteroid use), and perturbation of host barriers with intravenous lines and bladder catheters all serve to foster growth of candidal species. Other fungal organisms that exhibit a similar pattern of opportunistic disease in immunocompromised patients include *Aspergillus, Cryptococcus*, and mucormycosis. Worldwide, tuberculosis remains a significant problem in the transplant recipient and occurs either through primary infection or reactivation of quiescent disease. Many centers give isoniazid (INH) for prophylaxis for 6 to 12 months in individuals with a positive purified protein derivative, placing them in the medically high-risk group denoted by the American Thoracic Society and Centers for Disease Control and Prevention. Concern for liver toxicity in this group seems to be unfounded and should not prevent therapy (13).

All prospective transplant patients should receive vaccinations against hepatitis A and B, tetanus, diphtheria, and pneumococcal disease. Because these diseases have the potential to be much more serious in the immunosuppressed individual, the benefit of prevention is obvious. There is no vaccination at present for hepatitis C, and this disease has become an increasingly significant problem in the renal failure and renal transplant populations.

**Malignancy**

Several factors have been postulated to play a role in the increased incidence of malignancy in transplant recipients, including posttransplant viral infections, possible transfer of malignancy with the donor organ, and a cadre of drugs that induce alterations in the immune system. Historically, one can track the presence of malignancy and note associations with various drug changes and additions. An increased incidence of lymphomas was seen in the late 1960s with the introduction of polyclonal antibody preparations to the regimen that then consisted of azathioprine and corticosteroids. With the introduction of cyclosporine in the early 1980s, another wave of lymphomas was seen. Finally, when attempts to further improve graft function in the late 1980s encouraged the use of multiple immunosuppressive drugs, additional increases were noted (14). It appears that total cumulative immunosuppressive dose is well correlated with the development of malignancy, and it has long been realized that the number of episodes of acute rejection was predictive. In a comparison of three groups of
transplant recipients, the first without rejection, the second treated with corticosteroids for acute rejection, and the third treated with cytolytic therapy in addition to steroids, there was a clear increase in the incidence of lymphoma with each addition to the immunosuppressive regimen (7).

Although there has been no demonstrated increase in the incidence of lung, breast, and colon cancer when compared with the general population, transplant recipients are far more likely to develop skin cancer. In fact, skin cancer is the most common malignancy in renal transplant recipients and tends to be aggressive in nature and present at multiple sites. Although the insults predisposing an individual to skin cancer are cumulative and may precede the transplant by years, it is important to educate the transplant patient about avoiding sun exposure and wearing sunscreen at all times. In contrast to the general population, squamous cell carcinoma rather than basal cell carcinoma is the most common type of skin cancer in transplant recipients. Interestingly, melanoma is not found at a rate higher than in the general population. Risk factors for skin cancer include skin color, amount of sun exposure, increased age, and length of time with a transplant. In addition to careful prevention, the use of retinoids has been shown to prevent the formation of new skin cancers and keratotic skin lesions (15).

PTLD is the most feared of malignancies following solid organ transplantation. An increased incidence of PTLD has clearly been shown in individuals receiving more marked immunosuppression, especially cytolytic therapy. PTLD accounts for 21% of all malignancies in the transplant population compared to 5% in the general population. The characteristics of PTLD are different from non-Hodgkin’s lymphoma seen in the general population. The percentage of non-Hodgkin’s lymphoma in the transplant population is higher than that of the general population (93% versus 65%), extranodal involvement is more common in the transplant population, and central nervous system involvement is fairly common as an extranodal site (16). The pathogenesis of PTLD appears to be related to EBV-induced B cell proliferation, although uncommonly the PTLD can originate from T cells. The spectrum of disease in EBV-related PTLD ranges from a benign mononucleosis-type syndrome characterized by polyclonal B cell proliferation, a similar polyclonal B cell proliferation but with evidence of malignant transformation, and an aggressive monoclonal B cell proliferation with malignant characteristics and extranodal distribution (17). The incidence of PTLD is highest in the first year, probably related to the increased level of immunosuppression. Treatment consists of a reduction in immunosuppression in the two polyclonal forms of the disease, and this alone is successful in the majority of patients. Some have advocated the use of acyclovir or ganciclovir, however, the efficacy of these antiviral agents is unclear. The malignant, monoclonal form is less amenable to immunosuppressive reduction and may require antineoplastic agents. Morbidity for this group remains high. One of the most important goals with PTLD is prevention. Patients at low risk for rejection immunologically should have their immunosuppressive regimens tailored accordingly. When cytolytic therapy is used, coadministration of either acyclovir or ganciclovir may be beneficial (18).

Kaposi’s sarcoma occurs at a rate higher than in the general population and has a risk ratio of 224.7 among transplant recipients compared with 7.4 for PTLD and 6.2 for squamous cell carcinoma (19). Like PTLD, a viral etiology is suspected (20). Other malignancies occurring more frequently in transplant recipients include carcinomas of the cervix, uterus, vulva, perineum, and hepatobiliary system. General health screening similar to that with the general population is important in transplant recipients, although Pap smears in particular are a necessity on a yearly basis. Although probably not related to increased immunosuppression, renal cell carcinoma occurs at a higher rate in the transplant population. The reason likely relates to the presence of acquired cystic disease in the native kidneys, a finding correlated with length of time on dialysis and associated with an increased incidence of carcinoma in the end-stage renal disease population. In addition, analgesic nephropathy, a known cause of tumors throughout the urinary tract, is a common cause of renal failure (21).

Bone Disease
Osteoporosis, a disease characterized by low bone mass and a subsequent increase in fracture risk, is recognized as an important health problem in the United States and throughout the world. Primary osteoporosis is a problem in the general population and is associated with postmenopausal estrogen deficiency and age-related bone loss. Secondary causes include a variety of metabolic derangements as well as the therapeutic use of corticosteroids. The detrimental effects of corticosteroids are well known and occur through both direct and indirect effects. The direct effects include inhibition of bone formation through decreased osteoblast recruitment and differentiation as well as increased bone resorption through enhancement of osteoclast activity. Indirect effects include reduced calcium absorption by the gut and increased renal calcium excretion. All of these effects on bone and mineral metabolism result in rapid bone loss, especially during the first 12 to 18 months of therapy (22). It is probably safe to assume that corticosteroid-induced bone loss is superimposed upon that sustained by aging and estrogen deficiency. In a recent study, female gender was associated with an elevated risk of fracture in a group of renal transplant recipients (23). Although corticosteroids are probably the major immunosuppressive agent causing bone disease, the effects of cyclosporine and tacrolimus (FK506) have more recently been implicated by rat studies of Epstein and colleagues. Increased bone resorption is seen with both agents, and the resorption is greater than a possible counteracting bone formation, which is reflected by elevated serum bone Gla protein (BGP or osteocalcin) concentrations. Some controversy exists, however, because the rat model is not believed to be an entirely suitable analogy for humans, and because most human studies of bone disease in transplant recipients also include corticosteroids in the regimen (24). In one series, patients treated with cyclosporine alone had a significant improvement in bone density, suggesting that cyclosporine does not interfere with bone mineralization (25).

Most patients undergoing renal transplantation have some evidence of renal osteodystrophy prior to surgery. Hyperpara-
thyroidism, osteomalacia, and adynamic bone disease are all included under this general category, and likely contribute in an additive manner to bone disease that is observed posttransplantation. Furthermore, persistent hyperparathyroidism posttransplantation may contribute to osteopenia and mandate parathyroidectomy, generally when serum calcium levels remain persistently above 13 mg/dl.

The clinical management of patients with posttransplant osteoporosis is not clearly delineated, and systematic analysis of available data has been unclear. However, it is obviously important to limit bone disease prior to transplantation. Aggressive treatment of hyperparathyroidism and avoidance of aluminum-containing agents is critical, and pretransplant bone densitometric screening can identify those who already have osteoporosis. Posttransplantation, corticosteroid-sparing drug regimens have generally been unsatisfactory because of an increased incidence of rejection, although a more rapid reduction of corticosteroids may be considered in any patient at low risk for rejection. Several studies are currently under way using newer immunosuppressive drugs in an effort to limit corticosteroid use. Estrogen replacement for postmenopausal women and calcium supplementation are certainly reasonable interventions at this time, but the effect of calcium on the fracture rate has not been studied. Some investigators have demonstrated a decreased rate of vertebral fractures with calcitriol, although this drug should be used cautiously in patients with persistent hyperparathyroidism and a risk of hypercalcemia. The efficacy of drugs that reduce calcium mobilization (bisphosphonates) from bone remains to be seen in the transplant population, but three studies have shown that cyclical etidronate therapy prevents corticosteroid-induced bone loss. A randomized trial of patients receiving two intravenous infusions of pamidronate immediately 1 month after renal transplantation did prevent lumbar spine and femoral neck bone loss. More data are required with these agents, and it also is important to remember that the renal excretion of aluminum-containing agents is critical, and pretransplant bone densitometric screening can identify those who already have osteoporosis. Posttransplantation, corticosteroid-sparing drug regimens have generally been unsatisfactory because of an increased incidence of rejection, although a more rapid reduction of corticosteroids may be considered in any patient at low risk for rejection. Several studies are currently under way using newer immunosuppressive drugs in an effort to limit corticosteroid use. Estrogen replacement for postmenopausal women and calcium supplementation are certainly reasonable interventions at this time, but the effect of calcium on the fracture rate has not been studied. Some investigators have demonstrated a decreased rate of vertebral fractures with calcitriol, although this drug should be used cautiously in patients with persistent hyperparathyroidism and a risk of hypercalcemia. The efficacy of drugs that reduce calcium mobilization (bisphosphonates) from bone remains to be seen in the transplant population, but three studies have shown that cyclical etidronate therapy prevents corticosteroid-induced bone loss. A randomized trial of patients receiving two intravenous infusions of pamidronate immediately 1 month after renal transplantation did prevent lumbar spine and femoral neck bone loss. More data are required with these agents, and it also is important to remember that the renal excretion of bisphosphonates limits their use in patients with moderate or severe renal insufficiency. Calcitonin, another antiresorptive drug, has been used to treat corticosteroid-induced osteoporosis and also has shown promising results in a trial comparing intravenous calcitonin and oral etidronate in patients after liver transplantation.

Osteonecrosis is a major concern, caused to a large degree by the use of corticosteroids. Several series of patients have failed to illustrate a correlation between steroid dose and propensity for osteonecrosis, but some investigators have suggested a correlation with total methylprednisolone dose and acute rejection episodes. The clinical presentation of osteonecrosis is pain exacerbated by weight bearing. The femoral head is the most common site of involvement. Magnetic resonance imaging is probably the most sensitive test for detection of osteonecrosis and can permit early diagnosis. A variety of surgical approaches are available.

Cardiovascular Disease

Cardiovascular disease is now the most common cause of death following renal transplantation. Deaths over the years have not abated, and it is likely that the same epidemiologic risk factors for coronary artery disease in the general population are operational in renal transplant recipients. Furthermore, factors unique to the transplant population may contribute to, and perhaps increase, the risk of coronary artery disease. Kasiske and colleagues followed 403 renal transplant recipients (1977 through 1986) for up to 4 years, revealing an incidence of ischemic heart disease of 15%, more than four times greater than expected in the general population. Reasons for the higher incidence of cardiovascular disease are not entirely clear, although significant associations noted by different groups provide some insight into the problem. Several groups have shown that pretransplant cardiovascular disease is the strongest predictor of posttransplant disease. Other independent risk factors noted by Kasiske have included diabetes, age, male gender, serum cholesterol, tobacco use, and the number of acute rejection episodes. The latter factor is intriguing and suggests the possibility that corticosteroids are a major contributor. Furthermore, renal disease itself should now be considered a cardiac risk factor, primarily due to the increased presence of the usual risk factors for atherosclerosis, especially hypertension and diabetes. Factors fairly unique to the uremic patient may also play a role, and these include hyperparathyroidism, abnormal vascular calcification, and deranged calcium and phosphorous metabolism. Because many transplant patients have been exposed to the uremic milieu for considerable amounts of time, they assume this particular risk factor. Progressive graft dysfunction often accompanied by proteinuria is one more insult to which many of these patients are exposed, and hyperlipidemia can result from the proteinuria. Hyperlipidemia itself is a known cardiac risk factor that likely contributes to disease in both the end-stage renal disease and transplant patient populations. The lipid abnormalities in dialysis patients involve hypertriglyceridemia, normal total cholesterol levels, and low levels of HDL. In contrast, transplant recipients demonstrate hypertriglyceridemia, hypercholesterolemia, an elevated LDL, slightly increased HDL values, and elevated VLDL cholesterol.

Hyperlipidemia is a remarkably common problem posttransplant, and immunosuppressive agents such as corticosteroids and cyclosporine have been clearly associated with hyperlipidemia, independent of renal disease. In multiple studies, posttransplant hyperlipidemia has been identified as a major risk factor for ischemic heart disease. Although intuitive to assume a benefit with therapy, no studies have addressed the efficacy of treating hyperlipidemia in the posttransplant population. Nevertheless, most centers do treat hyperlipidemia. Historically, there was probably an inordinate fear of the hydroxymethylglutaryl-CoA reductase inhibitors since high-dose lovastatin has been associated with an increased incidence of rhabdomyolysis in cardiac transplant patients. If the patient is aware of the symptoms of myositis and periodic screening tests such as liver function tests and a creatine phosphokinase are performed, use of these drugs should be acceptable.

Because diabetes is the most common cause of end-stage renal disease in the United States and the incidence of cardiac disease is much higher in this group, special attention should
be given to the proper evaluation of these patients before transplantation. It has been clearly demonstrated that diabetic patients have a high incidence of asymptomatic coronary artery disease (30) and that many noninvasive stress tests in this group are not optimal (31). The appropriate cardiac evaluation, therefore, is somewhat controversial. There is reasonable support for obtaining a coronary angiogram in all type I diabetic patients over age 45, even if asymptomatic. In patients younger than 45 years, the presence of multiple cardiac risk factors, a heavy smoking history, or an abnormal electrocardiogram should prompt the cardiologist to perform an angiogram, even in the absence of classic symptoms (32). The evaluation of nondiabetic patients can probably be accomplished with the use of noninvasive tests based on patient history and associated conventional cardiac risk factors. Most transplant physicians would agree that modification of known cardiac risk factors is a reasonable endeavor given the significant morbidity and mortality of cardiac disease in transplant recipients. For example, all patients should be strongly encouraged to refrain from tobacco use, postmenopausal women should be given estrogen, and hypertension should be aggressively treated. Other less conventional factors in the renal transplant population include hyperhomocysteinemia, posttransplant erythrocytosis, and the effect of viral infections such as CMV. Hyperhomocysteinemia, occurring with high prevalence in the renal transplant population, has been clearly associated with premature atherothrombotic events. Whether modification of homocysteine levels with folic acid, vitamin B6, and vitamin B12 results in a reduction in these atherothrombotic events is unknown (33).

In some series, erythrocytosis, which is seen in 10 to 20% of transplant recipients, has been associated with increased thromboembolic events. The treatment of choice at this time consists of an angiotensin-convert ing enzyme inhibitor or angiotensin II type I receptor antagonist. Finally, CMV has been associated with atherosclerotic plaques. Whether the incidence of cardiovascular disease is positively correlated with CMV infection is unclear, but raises an intriguing point with regard to the multiple adverse effects of immunosuppression.

References


