Hyperlipidemia and Glucose Intolerance in the Post-Renal Transplant Patient

Mariana S. Markell,1 Vincent Armenti, Gabriel Danovitch, and Nabil Sumrani

M.S. Markell, Division of Nephrology, SUNY Health Science Center at Brooklyn, Brooklyn, NY
V. Armenti, G. Danovitch, UCLA Medical Center, Los Angeles, CA
N. Sumrani, Department of Transplant Surgery, SUNY Health Science Center at Brooklyn, Brooklyn, NY
(J. Am. Soc. Nephrol. 1994; 4:537–S47)

ABSTRACT
This review examines the relationship between renal transplantation and two important metabolic consequences: hyperlipidemia and glucose intolerance. Before cyclosporine, hypertriglyceridemia and hypercholesterolemia were common abnormalities that worsened in the cyclosporine era. In addition to obesity, steroid use, and reduced renal function, cyclosporine plays an independent role in elevating cholesterol levels, with particular reference to the modulation of the low-density lipoprotein receptor. Management includes maintaining low levels of steroid, manipulation of cyclosporine appropriately, diets low in fat and cholesterol, and an exercise program. Pharmacologic management in general revolves around the HMG-CoA reductase drugs, which can be used safely if liver function tests and muscle enzymes are monitored. The unmasking of clinically important glucose intolerance occurs in 5 to 10% of patients in the cyclosporine era, not different from the earlier experience. Steroids and cyclosporine independently can worsen glucose tolerance to unmask a genetic predisposition to Type II diabetes in some and to even create glucose intolerance in otherwise normal individuals. Management is based on dietary and immunosuppressive drug dosing manipulations and the judicious use of oral hypoglycemic agents. Half of these recipients may ultimately need insulin. In summary, hyperlipidemia and glucose intolerance remain important metabolic consequences of renal transplantation that affect long-term patient survival unless recognized and treated.

Key Words: Hypertriglyceridemia, hypercholesterolemia, steroids, cyclosporin A, glucose intolerance, coronary artery disease, renal transplantation

Several metabolic disturbances that may contribute to long-term morbidity and mortality occur with increased frequency after renal transplantation. The cause of these disorders is multifactorial, resulting from an interaction of inherent genetic susceptibility, effects of immunosuppressant and antihypertensive drugs, and weight gain, as well as other factors. This review will focus on the pathogenesis and management of two of the most common posttransplant metabolic disorders—hyperlipidemia and glucose intolerance.

HYPERLIPIDEMIA

In a study published in 1973, before the introduction of cyclosporine, 32 renal transplant recipients were noted to have a mean cholesterol value of 252 ± 7.9 mg/dL, which was significantly higher than that of the control population (1). Other authors reported a prevalence rate of posttransplant hypercholesterolemia between 27 and 70% for patients treated with azathioprine and prednisone alone (2-5). Hypertriglyceridemia was also a common finding, with a prevalence of >50% in one report (6). Posttransplant hypercholesterolemia was reported to be independent of the length of time posttransplant, with a prevalence of 27 to 30% in a retrospective study that monitored several hundred azathioprine-prednisone–treated patients for up to 5 yr (5).

With the introduction of cyclosporine and the use of steroid-sparing regimens, it was hoped that the prevalence of hyperlipidemia would decline. Although the prevalence of hypertriglyceridemia decreased after the introduction of cyclosporine, the prevalence of hypercholesterolemia remained at or above 50% (Table 1) (7-9). In a prospective study of 43 cyclosporine-treated renal transplant patients, posttransplant hypercholesterolemia was apparent as early as 3 months after transplantation (7) and did not appear to remit spontaneously, despite a reduction in immunosuppression doses over a 4-yr follow-up period (10). In a study comparing the effects of conventional therapy with cyclosporine treatment,
TABLE I. Prevalence of hypercholesterolemia in renal transplant recipients

<table>
<thead>
<tr>
<th>Author (Ref. No.)</th>
<th>No. of Patients</th>
<th>Immunosuppression</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibeis et al., 1975 (2)</td>
<td>175</td>
<td>AZA/Pred</td>
<td>60</td>
</tr>
<tr>
<td>Ponticelli et al., 1978 (3)</td>
<td>76</td>
<td>AZA/Pred</td>
<td>29</td>
</tr>
<tr>
<td>Chan et al., 1981 (4)</td>
<td>54</td>
<td>AZA/Pred</td>
<td>52</td>
</tr>
<tr>
<td>Kasiske and Uman, 1987 (5)</td>
<td>201</td>
<td>AZA/Pred</td>
<td>23–30</td>
</tr>
<tr>
<td>Markell et al., 1989 (7)</td>
<td>43</td>
<td>CSA/Pred/AZA</td>
<td>50</td>
</tr>
<tr>
<td>Vathsala et al., 1989 (8)</td>
<td>500</td>
<td>CSA/Pred</td>
<td>37.6</td>
</tr>
<tr>
<td>Divakar et al., 1991 (9)</td>
<td>62</td>
<td>CSA/Pred</td>
<td>16</td>
</tr>
</tbody>
</table>

* Abbreviations: AZA, azathioprine; Pred, prednisone; CSA, cyclosporine.

Cyclosporine-treated patients were observed to have higher cholesterol levels at 90 days posttransplant when compared with azathioprine-treated patients (11). Evidence that cyclosporine treatment can contribute to hyperlipidemia was suggested by studies that monitored lipid profiles after the conversion of patients from cyclosporine to azathioprine therapy—a significant drop in cholesterol and triglyceride levels was documented (12,13). In patients receiving cyclosporine monotherapy for the treatment of nonrenal diseases, a significant rise in cholesterol occurred after the initiation of therapy (14). Also, in studies of patients who were receiving cyclosporine monotherapy or cyclosporine and azathioprine alone after steroid withdrawal, the mean cholesterol levels did not fall into the “desirable” range, as defined by the National Cholesterol Education Program (see below (15,16), suggesting that cyclosporine is contributing to the suboptimal lipid profile observed in these patients (17).

Lipoprotein Subtypes

Hemodialysis and continuous ambulatory peritoneal dialysis patients commonly develop hypertriglyceridemia and, less commonly, hypercholesterolemia (18). When lipid fractionation is performed, the very low-density lipoprotein (VLDL) fraction is elevated, with low-density lipoprotein (LDL) normal or elevated and high-density lipoprotein (HDL) generally decreased, resulting in a highly “atherogenic” lipid profile (18).

Renal transplant recipients who are treated with azathioprine and prednisone alone also have elevated VLDL cholesterol, as well as elevated LDL (5,19). HDL cholesterol values are reported as elevated or normal (19–22). Cyclosporine-treated patients have elevated LDL cholesterol, normal or elevated HDL cholesterol, and normal or minimally elevated VLDL values, unless they have concomitant diabetes (7–9). These latter lipid abnormalities occur as early as 3 months after transplantation and do not remit spontaneously (11). The influence of transplantation on lipoprotein(a) [Lp(a)], which is an LDL-like particle to which an additional protein, “apoprotein (a)” is bound, and which has been independently implicated in conferring atherogenic risk, is unclear, with some authors reporting no effect or decreased Lp(a) levels after transplantation (23) and others, increased levels (24). Whether these changes reflect the restoration of renal function, the effects of immunosuppression, or other factors related to transplantation is not known at this time.

**Pathogenesis of Posttransplant Lipid Disorders**

Factors that have been associated with the development of posttransplant lipid disorders are listed in Table 2. Obesity and poor dietary habits are factors that are found to correlate with hypercholesterolemia in the general population and are not specific to transplanted patients. Nephrotic syndrome is commonly associated with hypercholesterolemia (25) and may occur in the posttransplant setting secondary to chronic rejection or recurrent or de novo renal disease. Patients may also have a genetic predisposition to hypercholesterolemia that is “unmasked” because of stresses occurring in the posttransplant period (26).

**TABLE 2. Factors that have been associated with posttransplant lipid disorders**

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes/glucose intolerance</td>
</tr>
<tr>
<td>Poor diet: excessive intake of calories and simple sugars</td>
</tr>
<tr>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Use of glucocorticoids</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Hypocholesterolemia</td>
</tr>
<tr>
<td>Poor diet: excessive intake of saturated fats and cholesterol</td>
</tr>
<tr>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Use of glucocorticoids</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Use of diuretics and β-blockers (minor contribution)</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Menopause of ovarian failure</td>
</tr>
</tbody>
</table>

* Factors marked with an ** are potentially remediable and should be addressed or ruled out before starting pharmacologic therapy.
When predictive factors for the development of post-transplant elevations in LDL, including cause of renal disease, age, length of time on dialysis, and lipid profile, were examined by regression analysis in group of hypercholesterolemic renal transplant recipients, only pretransplant LDL was significantly associated with posttransplant LDL level (8), suggesting that genetic factors strongly influence the posttransplant lipid profile.

Finally, it is clear that immunosuppressive agents, specifically prednisone and cyclosporine, affect lipid metabolism adversely. Corticosteroid hormones can affect lipid metabolism in two ways. Corticosteroids create an insulin-resistant state, with secondary hyperinsulinemia occurring as a sequela (27). Hyperinsulinemia results in increased uptake by the liver of free fatty acids, which in turn serve as a substrate for the production of triglycerides and VLDL (triglyceride-rich) lipoproteins, leading to hypertriglyceridemia and elevated VLDL (29). VLDL is converted to intermediate-density lipoprotein (IDL) and LDL via the actions of hepatic triglyceride lipase, leading to increased LDL cholesterol. Insulin resistance also results in decreased action of peripheral lipoprotein lipase, which is responsible for the clearance of triglyceride available to the liver for the synthesis of VLDL (29,30). Corticosteroid hormones may also raise HDL levels through interference with cholesterol-ester transfer protein via a mechanism that is not well understood (31). This finding may explain the rise in HDL observed after transplantation (8) or the treatment of nephrotic syndrome with corticosteroids (31) and the fall in HDL observed after steroid withdrawal (15). Whether these changes in HDL affect cardiovascular risk in renal transplant recipients is not known.

The mechanism by which cyclosporine affects lipid metabolism is less well understood. Cyclosporine is a cyclic undecapeptide that is highly lipophilic; 35% of the absorbed dose is transported in the blood in association with lipoproteins, predominantly HDL. Biosynthesis could occur through the alteration of LDL configuration by cyclosporine, leading to an abnormal interaction of LDL with its receptor (34). Because 75% of LDL clearance is accomplished through receptor-mediated LDL uptake by the liver and LDL uptake serves as a feedback control both on cholesterol biosynthesis by the liver and expression of LDL receptors (35), abnormal LDL-LDL-receptor interaction could result in hypercholesterolemia.

An alternative explanation is suggested by in vitro evidence that cyclosporine alters bile acid synthesis. Liver cells in culture demonstrate abnormal bile acid side chain synthesis when exposed to cyclosporine (36). The secretion of bile acids serves a feedback control on cholesterol metabolism, and decreased production of bile acids could exacerbate hypercholesterolemia by causing down-regulation of LDL receptor expression and thus decreasing cholesterol clearance from the peripheral circulation.

Cyclosporine may also influence lipid metabolism by alteration of glucose tolerance through interference with the peripheral actions of insulin, which has been observed in animal models, (37) or by a directly toxic effect on pancreatic β cells, observed in vitro (38) or in animal models (39), resulting in decreased insulin secretion.

Evaluation of Posttransplant Hyperlipidemia

There are no formal guidelines established for the work-up or the treatment of hyperlipidemia in the posttransplant recipient, nor have intervention trials been performed in order to evaluate whether the treatment of hyperlipidemia will affect long-term outcome in this population. As such, it has been the policy at our center(s) to follow the guidelines of the National Cholesterol Education Program (NCEP) for the treatment of lipid disorders in the general population, as outlined in Table 3 (15,16). Lipid profiles are performed on all patients with total cholesterol greater than 200 mg/dL, all patients with diabetes mellitus, and all patients with a history of cardiovascular disease.

The lipid profile should be drawn after an 8- to 12-h fast and repeated within a 2-wk period. The mean LDL value should be used to determine the course of therapy, and if the results vary by more than 30 mg/dL, a third value should be measured and the mean of all three values used to determine risk (16). There are several remediable factors that can affect the lipid profile adversely (Table 4). For patients with hypertriglyceridemia, the measurement of postprandial triglycerides is necessary.

**TABLE 3. 1991 guidelines for the treatment of hypercholesterolemia as proposed by the National Cholesterol Education Council (1993 guidelines are in parentheses)**

<table>
<thead>
<tr>
<th>Cholesterol Value</th>
<th>Action</th>
<th>LDL Cholesterol Value</th>
<th>Action</th>
<th>HDL Cholesterol Value</th>
<th>Action</th>
<th>Triglyceride Value</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200—desirable range</td>
<td>Pharmacologic therapy indicated</td>
<td>&lt;130 (&lt;100**)—desirable</td>
<td>Pharmacologic therapy indicated</td>
<td>&gt;35—desirable</td>
<td>Pharmacologic therapy indicated</td>
<td>&gt;200—high</td>
<td>Pharmacologic therapy indicated</td>
</tr>
<tr>
<td>200-239—borderline high**</td>
<td></td>
<td>130-159—borderline high**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;240—high</td>
<td></td>
<td>&gt;160—high</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pharmacologic therapy indicated, after 3-month dietary trial: * patient with no other cardiac risk factor, ** patient with one or more cardiac risk factors, *** patient with history of cardiac disease (secondary prevention).
### TABLE 4. Classes of pharmacologic lipid-lowering agents and their side effects (see Text for references)

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Side Effects</th>
<th>Concerns:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile-acid resin</td>
<td>Cholestyramine, colestipol</td>
<td>Constipation, flatulence</td>
<td>Alteration of cyclosporine pharmacokinetics, interference with coumadin, digitoxin, thyroid hormone absorption</td>
</tr>
<tr>
<td>Fibric acid derivatives</td>
<td>Gemfibrozil, clofibrate, bezafibrate, fenofibrate</td>
<td>Gastrointestinal upset, loose stool, myositis (especially in patients with decreased renal function), increased transaminases</td>
<td>Increased incidence of gallstones, myalgias, and rhabdomyolysis when used with HMG-CoA reductase inhibitors, no studies in cyclosporine-treated renal transplant recipients</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Nicotinic acid, sustained release, acipimox</td>
<td>Flushing, pruritis, altered glucose tolerance and uric acid secretion, elevated transaminases</td>
<td>Increased incidence of gout in cyclosporine-treated patients, life-threatening hepatitis in patients treated with sustained-release preparation</td>
</tr>
<tr>
<td>Probucol</td>
<td>Probucol</td>
<td>Flatulence, loose stools</td>
<td>Prolonged QT-interval on electrocardiogram, decreased HDL levels of unclear significance</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>Lovastatin, pravastatin, simvastatin, fluvastatin</td>
<td>Abdominal pain, flatulence, constipation, headache and insomnia, elevation of transaminases</td>
<td>Myositis, rhabdomyolysis in patients treated with cyclosporine or fibric acid derivatives</td>
</tr>
</tbody>
</table>

Dial blood glucose or the performance of an oral glucose tolerance test should be considered because a high prevalence of glucose intolerance has been reported in this group of patients, often with normal fasting blood glucose levels (40). Once glucose intolerance has been corrected, hypertriglyceridemia often remits. Hypercholesterolemia may be caused by hypothyroidism or nephrotic syndrome, and thyroid function tests as well as 24-h urine protein should be measured and treatment should be planned on the basis of the findings of these tests. In postmenopausal women, there is evidence that estrogen replacement improves the lipid profile (41), but there have been no studies of estrogen replacement in renal transplant recipients.

Finally, immunosuppression doses must be reevaluated. There is evidence that steroid withdrawal improves total cholesterol values; however, as mentioned previously, the administration of steroids may improve HDL levels, and conversely, the withdrawal may result in decreased HDL, with little improvement in the overall lipid profile (15). Although it is not recommended to routinely withdraw steroids on the basis of lipid profile alone, it is important to minimize steroid dose, especially in patients with hypertriglyceridemia.

### Treatment of Posttransplant Hyperlipidemia

It is unclear whether minimal to moderate hypertriglyceridemia (200 to 500 mg/dL) increases cardiovascular risk. The only population in whom risk has been established for this disorder is the patient with diabetes (42), in whom improvement of glucose control often dramatically improves hypertriglyceridemia. All hypertriglyceridemic patients should be placed on a diet that restricts the intake of simple sugars and alcohol, in addition to limiting fat intake to less than 30% of total daily calories. In obese patients, caloric restriction with weight loss may result in the resolution of hypertriglyceridemia. There are no specific drug therapies that are recommended for hypertriglyceridemia alone; however, patients with severe non-diet-responsive life-threatening hypertriglyceridemia (fasting triglyceride value > 1,000 mg/dL), which can lead to pancreatitis, hepatic steatosis, and hepatosplenomegaly, can be treated with either niacin or a fibric acid derivative (29),
as described below, with the understanding that the risks of using these drugs in a transplant recipient outweigh the dangers of persistently and extremely elevated levels of triglycerides.

Multiple studies have documented increased risk of cardiovascular death in nontransplanted patients with elevated LDL cholesterol (43). There are presently no large population studies of cardiovascular risk in renal transplant recipients; most centers follow the NCEP guidelines for the use of pharmacologic lipid-lowering agents in the post–renal transplant population. All patients are given a 3-month trial of an American Heart Association Step I (or II) cholesterol-lowering diet: <300 (<200) mg of cholesterol/day, 30% (10%) of total caloric intake from fat, and maintenance of a 1:1 ratio of saturated to polyunsaturated or monounsaturated fats. Dietary therapy alone is rarely successful in normalizing lipid profile, with success rates ranging from 10 to 20% in published studies (44, 45). After 3 months of dietary therapy, the fasting lipid profile is redrawn. If the patient has an LDL value > 160 mg/dL, or in the patient with any two cardiac risk factors (including hypertension, diabetes, positive family history of cardiovascular disease, age > 55 yr in a male, or age > 65 yr in a female), if the LDL value is > 130 mg/dL, the patient should be started on lipid-lowering therapy (16). The current recommendation for secondary prevention in nontransplanted patients with a previous history of cardiac disease is to aim for a target LDL value of < 100 mg/dL; however, this level may be very difficult to achieve in transplanted patients, especially those receiving cyclosporine, because of the complications associated with high-dose lipid-lowering therapy in this patient population (see below).

The five classes of lipid-lowering agents currently available are listed in Table 4. Each class of therapy works at a slightly different step in cholesterol metabolism, and each one has specific problems when used with cyclosporine-treated renal transplant recipients. The first class of agents is the bile acid-binding resins, e.g., cholestyramine or colestipol. These drugs act by increasing bile acid excretion, thus forcing more cholesterol to be used for the production of bile acids by the liver. This causes increased LDL receptor expression with resultant increased clearance of LDL from the peripheral circulation (35). Because cyclosporine undergoes enterohepatic circulation, however, bile acid–binding resins may alter the pharmacokinetics of the drug in an unpredictable fashion. A study of heart transplant recipients reported that although peak cyclosporine levels did not change, time to peak absorption and therefore area under the curve values did change after the ingestion of the bile acid resins (46), and it is recommended that these agents not be administered within 1 to 2 h of a cyclosporine dose. In addition, the bile acid–binding resins can cause severe constipation and flatulence and alter the absorption of other bile-dependent drugs including thyroid hormones, coumarin, and digitoxin (47).

The second class of agents is the fibric acid derivatives, e.g., clofibrate, gemfibrozil, bezafibrate, and fenofibrate (the latter two drugs are not presently available in the United States). These agents act through increased activity of lipoprotein lipase and reduction of VLDL synthesis, with resultant increased VLDL catabolism and increased HDL synthesis (35). One effect of the fibrates is increased cholesterol saturation of the bile, with increased risk of gallstones in patients taking the drugs for long periods (48). In addition, early studies of clofibrate-treated patients suggested an increased rate of biliary carcinoma (49). Other side effects of the fibrates include gastrointestinal upset and loose stools, increased transaminases, myositis, and rhabdomyolysis, especially in patients with renal insufficiency, because the drugs are cleared primarily by the kidney (50). Myalgias and rhabdomyolysis have been reported when the fibrates are used in conjunction with HMG-CoA reductase inhibitors (51), and these two classes of lipid-lowering agents should not be coadministered. There are no large-scale studies of fibrates in renal transplant recipients, and it is not known whether drugs of this class alter cyclosporine kinetics. There is one anecdotal report that bezafibrate and several of the newer fibric acid derivatives cause elevations of creatinine in cyclosporine-treated renal transplant recipients through an unknown mechanism (52). Because little is known regarding the use of these drugs in cyclosporine-treated transplant patients, it is recommended that they be used with caution and that liver function tests and creatinine phosphokinase be closely monitored.

The next class of agents is nicotinic acid and its derivatives (e.g., acipimox). The exact mechanism by which nicotinic acid affects plasma lipoproteins is unclear; however, the ingestion of 3 to 6 g/day causes decreases in the lipolysis of adipose tissue, resulting in a fall in plasma free fatty acid concentration, direct inhibition of LDL synthesis by the liver, alteration in HDL synthesis, and decreased synthesis of Lp(a) (29). Side effects of nicotinic acid include generalized flushing and pruritis immediately after drug ingestion, which can be lessened by slowly titrating the dose from 100 mg three times daily to the target dose of 1 to 3 g daily. In addition, the administration of aspirin before the ingestion of nicotinic acid may be helpful; however, the administration of aspirin to renal transplant patients with compromised renal function may have negative effects on GFR, as is true of patients with chronic glomerulonephritis (53). More serious side effects include worsening of glucose tolerance and alteration of uric acid secretion.
Metabolic Complications of Transplantation

with the appearance of de novo or acute gouty arthritis. In the experience of one center, 100% of cyclosporine-treated renal transplant patients who were treated with full-dose nicotinic acid developed gout over the course of 1-yr follow-up (unpublished observation, M.S. Markeli). Finally, time-release preparations of nicotinic acid have been reported to cause severe, sometimes life-threatening hepatitis (54). When nicotinic acid is used in a cyclosporine-treated renal transplant recipient, liver function tests, glucose tolerance, and uric acid levels should be frequently monitored.

The fourth class of agents currently available includes probucol and its derivatives. Probucol is similar in structure to butylated hydroxytoluene and has potent antioxidant properties, as well as lipid-lowering characteristics. The drug decreases LDL through increased clearance of LDL via its receptor and perhaps through enhancing bile acid secretion as well (55). This agent also causes decreased HDL levels, either through decreased HDL synthesis or an increase in reverse cholesterol transport (56). Probucol has been used in the treatment of heart transplant recipients without adverse consequences (57). The most frequently reported side effect is flatulence or loose stools. There are rare reports of prolonged QT-interval on the electrocardiograph, and it is recommended that routine electrocardiographs be performed before the initiation of therapy and 6 months after therapy has been initiated.

The fifth and final class of agents are the HMG-CoA reductase inhibitors, including lovastatin, pravastatin, simvastatin, and fluvastatin. These agents work by inhibiting the rate-limiting enzyme in cholesterol biosynthesis that results in a secondary increase in LDL receptor expression and increased LDL clearance. Treatment with HMG-CoA reductase inhibitors results in decreases in LDL and total cholesterol, with minimal decreases in triglycerides and a slight increase in HDL levels (58). In patients with primary hyperlipidemia, this class of agents is effective in lowering LDL cholesterol from 20 to 25% when used at the lowest dose recommended, administered with the evening meal or twice daily. Minor side effects include abdominal pain, flatulence, and constipation. A small percentage of patients complain of headache and insomnia, which may be worse with the lipophilic drugs lovastatin and simvastatin as compared with pravastatin, which is water soluble (58). Major side effects of the HMG-CoA reductase inhibitors include elevated transaminases of more than three times the upper limit, which occurred in 1% of patients with primary hyperlipidemia taking lovastatin over a 1-yr period; elevated creatinine phosphokinase levels (CKP), which occurred in 29 to 30% of patients but did not differ from levels in placebo-treated controls; and occasional myositis. Rhabdomyolysis has been reported in heart transplant recipients receiving high doses of lovastatin (40 to 80 mg/day) concomitantly with cyclosporine (59,60); however, more recently, several reports suggest that, at low doses, the HMG-CoA reductase inhibitors are safe in the heart transplant population (61). Several small uncontrolled studies, including one in which lovastatin was used at low dose (10 to 20 mg) for a short period of time in six patients (62) and one in which pravastatin was used in 24 patients, at 10 mg/day for 6 months (63), suggest that these drugs are safe for use in renal transplant recipients; however, many patients will not achieve target lipid levels as recommended by NCEP at the doses of drug used in these studies and combination therapy may be needed.

Recommendations for the use of HMG-CoA reductase inhibitors in cyclosporine-treated renal transplant recipients include the use of low doses and frequent (every 4 to 6 wk) follow-up of liver function tests and creatinine phosphokinase levels, with dose reduction or discontinuation of the drug if elevations in these levels of more than three times normal are observed. The use of other potentially hepatotoxic drugs is discouraged, and the drugs should not be used in combination with fibric acid derivatives. At present, there is one small study using lovastatin in 11 patients treated with azathioprine and prednisone alone. The study was a double-blind crossover design, and at the dose of drug used (20 mg), total cholesterol fell by 21% but the mean LDL level did not fall into the "desirable" range after 12 wk of therapy. There were no episodes of rhabdomyolysis, but the authors noted an increase in white blood cell count in lovastatin-treated patients that they felt might represent reduced azathioprine bone marrow suppression and which they felt deserved further investigation (64). In dialysis patients, both lovastatin and simvastatin have been used safely in doses from 10 to 40 mg/day (65).

POSTTRANSPLANT GLUCOSE INTOLERANCE

Background

Posttransplant glucose intolerance, ranging from subclinical hyperinsulinemia to postprandial hyperglycemia and clinically evident diabetes mellitus, is a frequently recognized problem after kidney transplantation. In the era before the introduction of cyclosporine, the prevalence of diagnosed diabetes varied from 5 to 10% of patients studied, depending on the series (66–68). After the introduction of cyclosporine, it was hoped that steroid sparing would result in fewer cases of posttransplant diabetes; however, the prevalence of diabetes is higher in most series of cyclosporine-treated patients (Table 5) (69–73). Routine screening of transplanted patients for
TABLE 5. Selected studies of prevalence rates for posttransplant diabetes

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Type of Immunosuppression</th>
<th>Prevalence Rate (%)</th>
<th>Author (Ref. No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>Azathioprine/prednisone</td>
<td>10.6</td>
<td>McGeown et al., 1980 (66)</td>
</tr>
<tr>
<td>835</td>
<td>Azathioprine/prednisone</td>
<td>14.3</td>
<td>Friedman et al., 1985 (67)</td>
</tr>
<tr>
<td>353</td>
<td>Azathioprine/prednisone/cyclosporine/prednisone</td>
<td>5</td>
<td>Yasigawa et al., 1986 (68)</td>
</tr>
<tr>
<td>173</td>
<td>Cyclosporine/azathioprine/prednisone</td>
<td>11.6</td>
<td>Boudreux et al., 1987 (69)</td>
</tr>
<tr>
<td>31</td>
<td>Cyclosporine/azathioprine/prednisone</td>
<td>13</td>
<td>Yamasaki et al., 1988 (70)</td>
</tr>
<tr>
<td>463</td>
<td>Azathioprine/prednisone/cyclosporine/prednisone</td>
<td>3.3</td>
<td>Mejia et al., 1989 (71)</td>
</tr>
<tr>
<td>314</td>
<td>Azathioprine/prednisone/cyclosporine/prednisone</td>
<td>9.1</td>
<td>Roth et al., 1989 (72)</td>
</tr>
<tr>
<td>337</td>
<td>Cyclosporine/azathioprine/prednisone</td>
<td>11.6</td>
<td>Sumrani et al., 1991 (73)</td>
</tr>
</tbody>
</table>

more subtle types of glucose intolerance was not done in any of these studies; the true prevalence is undoubtedly much higher.

Pathogenesis and Risk Factors

The majority of patients with posttransplant diabetes produce insulin, but not in amounts adequate to overcome their insulin resistance, creating a situation similar to the non-insulin-dependent, Type II diabetic patient. Corticosteroids have a twofold effect on glucose metabolism, altering insulin secretion by the pancreatic β cell and producing peripheral insulin resistance by an as yet undefined postreceptor effect (74,75), resulting in decreased nonoxidative glucose disposal. The suppression of hepatic glucose production is reportedly normal (76), with the result that patients may have normal fasting blood glucose levels with markedly abnormal postprandial blood glucose values (40). In a small study of the effects of steroid withdrawal on posttransplant diabetes, complete steroid withdrawal was successful in ameliorating posttransplant diabetes in seven out of eight patients; however, two of these patients later had rejection and required reinstitution of steroid therapy with recurrence of diabetes (77).

Cyclosporine use has been associated with altering glucose tolerance in animal models and in human studies, both by altering peripheral insulin sensitivity (37,78) and by decreasing βcell function (38,39). Studies in human kidney transplant recipients (79) suggest that the effect is minor when cyclosporine is used as monotherapy, but that it may be additive when used in conjunction with corticosteroids (69,72).

Risk factors for the development of posttransplant diabetes (Table 6) are similar to factors that increase risk for Type II diabetes in the general population (73). In a study of 337 renal allograft recipients whose grafts survived for more than 1 yr, increased risk was not associated with type of induction or immunosuppressant therapy, incidence of rejection, total steroid or cyclosporine dose, percentage of body weight gain, serum creatinine concentration, or patient sex (72). Increased risk was associated with race (73), advanced age (69,72,73), recipient of a cadaveric kidney (71,72), and presence of HLA-A 30 and Bw42 antigens (73). Additional risk factors have been described as weight over 70 kg and elevated cyclosporine trough level (69).

Diagnosis and Treatment

Most series report that the majority of cases of posttransplant diabetes occur within the first year after transplantation, primarily within the first 3 months (69–71). A diagnosis of diabetes is made following the criteria established by the American Diabetes Association (80); fasting plasma glucose >140 mg/dL on more than one occasion; 2-h plasma glucose and one other timed sample >200 mg/dL after a 75-g glucose load or mixed meal. Patients with a fasting plasma glucose <140 mg/dL and 2-h postglucose challenge or postprandial glucose >140 mg/
TABLE 6. Factors that have and have not been associated with increased prevalence of posttransplant diabetes mellitus (see Text for references)

<table>
<thead>
<tr>
<th>Associated Factors</th>
<th>Unassociated Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Type of induction therapy</td>
</tr>
<tr>
<td>Obesity</td>
<td>Incidence of rejection</td>
</tr>
<tr>
<td>Glucocorticoid use</td>
<td>Total steroid or cyclosporine dose</td>
</tr>
<tr>
<td>Cyclosporine use</td>
<td>Serum creatinine</td>
</tr>
<tr>
<td>HLA type</td>
<td>Sex</td>
</tr>
<tr>
<td>Cadaveric kidney</td>
<td>Percentage of body weight gain</td>
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</tbody>
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dL and <200 mg/dL, but with a plasma glucose of >200 mg/dL at less than 2 h after a glucose challenge, are classified as having impaired glucose tolerance (80). As mentioned above, renal transplant recipients with diabetes may have normal fasting blood glucose levels with markedly abnormal postprandial or post-glucose challenge blood values. The administration of oral glucose tolerance tests should be considered in patients with hypertriglyceridemia because many of these patients fall into this group.

Once a diagnosis of diabetes has been established, the patient should be referred for nutritional counseling to learn the American Dietetic Association diabetic diet, with its system of "exchanges" and limitation on simple sugars and caloric intake. In addition, if appropriate, weight loss should be encouraged, because obesity worsens insulin resistance. Very few, if any, patients can be managed with diet therapy, and if the patient has moderate hyperglycemia (fasting plasma glucose <250 mg/dL or normal fasting plasma glucose with postprandial hyperglycemia), an oral hypoglycemic agent can be used. Short-acting oral hypoglycemic agents that undergo extensive hepatic metabolism, e.g., glipizide, may be preferable in order to avoid unpredictable effects in patients with impaired renal function, in whom insulin action may be prolonged because of decreased renal catabolism. Several oral hypoglycemic agents (chlorpropamide, tolbutamide) may impair water excretion via an ADH-like effect (81), and patients should be monitored for hyponatremia if these agents are used.

In most series, oral hypoglycemic agents do not control blood glucose adequately in 40 to 50% of patients and insulin must be used (70,73). The decision regarding the use of regular insulin in addition to NPH insulin and whether the total insulin dose should be given as a single shot or in divided doses must be made on an individualized basis, because insulin requirements will vary depending on the patient's diet, level of exercise, degree of insulin resistance, renal function, and other factors. If the patient is receiving tapering doses of corticosteroids, the dose of insulin will usually require adjustment (decrease) as the steroid dose is decreased. A nurse educator who is trained to teach diabetes management and who is familiar with the complications associated with renal disease and transplantation is invaluable for teaching patients to perform blood glucose self-monitoring, which simplifies insulin adjustment and allows for better glucose control in the long term. Patients can be asked to keep a "glucose diary" in which all monitored blood glucose levels are entered, and therapy is adjusted at each clinic visit as necessary. In addition, glycosylated hemoglobin values should be measured every 2 months in order to assess the degree of overall glucose control.

Finally, patients whose grafts function for a prolonged period (10 yr or greater) are at risk for long-term diabetic complications, including retinopathy, neuropathy, and nephropathy. Ophthalmologic and podiatric follow-up is therefore an important ongoing concern that should be stressed to the patient, and proteinuria, which occurs late in the posttransplant course, may warrant a renal biopsy to differentiate de novo diabetic glomerulosclerosis from chronic rejection.

CONCLUSIONS

As long-term survival of renal allografts becomes commonplace, the metabolic derangements that occur secondary to immunosuppressive agents become important considerations. Although at this time, there are no large-scale population studies that address cardiovascular risk in renal transplant recipients, cardiovascular disease remains the leading cause of death in this population (82). Both hypercholesterolemia and diabetes are considered "classic" risk factors for cardiovascular disease, and it is likely that the increased prevalence of these diseases contributes to the high prevalence of cardiovascular disease in the post-transplant population.

In addition, hypercholesterolemia has been associated with acceleration of renal disease in animal models of nephrosis (83,84). Although a 4-yr follow-up of 43 patients in whom lipid profiles had been determined at 3 months did not demonstrate excessive graft loss in the patients with early hyperlipidemia (11), increased cholesterol could play a role in potentiating renal loss once renal injury has occurred from other factors (e.g., immune attack, cyclosporine). On the other hand, most series have demonstrated inferior graft survival in patients with post-transplant diabetes (69,72,73), although the cause of
graft loss was not specified in these series and diabetes may be a coexisting condition, rather than an exacerbating factor in graft loss.

The management of these posttransplant metabolic disorders is complex and must be individualized to the specific patient. Diet control for both hypercholesterolemia and diabetes is not successful in most patients, and they must be placed on pharmacologic agents. The optimal treatment regimen for posttransplant hypercholesterolemia has not been established, and the clinician should be aware of the risks of the individual agents discussed above. The control of diabetes is complicated by changes in immunosuppressive medications and the patient's renal function. The treatment of posttransplant hypercholesterolemia and diabetes should benefit the patient in the long run, with the aim of prolonging not only graft survival, but patient survival as well.

REFERENCES


