Transplantation in the Diabetic Patient With Advanced Chronic Kidney Disease: A Task Force Report

Robert S. Gaston, MD, Giacomo Basadonna, MD, PhD, Fernando G. Cosio, MD, Connie L. Davis, MD, Bertram L. Kasiske, MD, Jennifer Larsen, MD, Alan B. Leichtman, MD, and Francis L. Delmonico, MD
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• On May 7 to 8, 2003, more than 60 physicians, surgeons, nurses, and allied health professionals met in Chicago, IL, to discuss state-of-the-art approaches to transplantation in the clinical management of patients with diabetes and advanced chronic kidney disease. Four work groups addressed pretransplantation evaluation and management, therapeutic alternatives for treatment of patients with chronic kidney disease, posttransplantation diabetes mellitus, and improving long-term kidney transplant outcomes in patients with diabetes. This report summarizes the deliberations and recommendations of the task force. Am J Kidney Dis 44:529-542.

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INDEX WORDS: Diabetes mellitus; kidney transplant; chronic kidney disease (CKD); pancreas transplant; hypertension.

Diabetes mellitus is reaching almost epidemic dimensions in the United States, with 16 million currently afflicted and nearly 29 million Americans projected to have diabetes by 2050.1,2 Accordingly, the incidence of stage 5 chronic kidney disease (CKD) as a result of diabetes has doubled during the last decade, with even steeper trends among minority patients.3 Diabetes now causes almost half of all new cases of end-stage renal disease (ESRD), and patients with diabetes comprise 46% of referrals to a large transplant center in 2002.4 Fully one quarter of all kidney transplant recipients have preexisting diabetes mellitus, representing a 33% increase since 1992.3,5 Among patients without diabetes at the time of transplantation, at least 15% to 20% will develop significant glucose intolerance afterward.6-8 Patients with diabetes have a greater risk for death while on dialysis therapy and after kidney transplantation.

In response to these trends, the National Kidney Foundation commissioned a task force of specialists in nephrology, transplantation, and diabetes mellitus to consider the implications of recent clinical advances and interpret current standards regarding transplantation in patients with diabetes. Participants were charged with generating a report to document the deliberations and recommendations of the task force. Cosponsored by Merck and Company, Novartis Pharmaceuticals, and the United Resources Network, the meeting brought together in Chicago, IL, 60 physicians, surgeons, nurses, and other allied health professionals on May 7 to 8, 2003. A steering committee (Appendix) outlined issues in the clinical management of patients with diabetes to be addressed by 4 work groups: pretransplantation evaluation and management, choosing among therapeutic alternatives for treatment of patients with CKD, minimizing the occurrence of posttransplantation diabetes mellitus (PTDM), and optimizing long-term kidney transplant outcomes. Each group was asked to offer therapeutic recommendations within the purview of its assigned topic and to delineate unresolved issues that might serve as foci for future research. Given the nature of the process involved, this report should be perceived as reflecting only the expertise and consideration of the participants. It

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should in no way be misconstrued as comprehensive, peer-reviewed, evidence-based guidelines. However, deliberations of the task force may provide the underpinnings for future guideline development in this important diagnostic and therapeutic area.

Compared with dialysis therapy, successful transplantation imparts a substantial survival benefit to patients with diabetes with ESRD. Likewise, the consequences of kidney allograft failure are dire: morbidity and mortality increase after returning to dialysis therapy, and chances for retransplantation are limited. Thus, paramount among the concerns expressed by participants in all work groups were the promotion of early transplantation (ideally preemptive or before the institution of maintenance dialysis therapy) and preservation of renal allograft function.

WORK GROUP 1: REFERRAL, EVALUATION, AND MANAGEMENT OF PATIENTS WITH DIABETES BEFORE TRANSPLANTATION

Work Group 1 examined issues associated with the care of patients with advanced CKD (stages 3, 4, or 5) and type 1 or 2 diabetes. Optimal care involves active collaboration among primary care physicians, cardiologists, diabetologists, nephrologists, and transplant surgeons.

Renal transplantation offers the best long-term survival for patients with diabetes and advanced CKD, and the best outcomes occur when transplantation is performed before implementation of long-term dialysis therapy (preemptively). Unfortunately, patients with diabetes are less likely to be referred for transplantation than patients with ESRD with other diagnoses. In addition to implementing treatment regimens to preserve native kidney function, management of patients with diabetes and CKD should include early referral to a transplant center. The National Kidney Disease Education Program, designed to increase general awareness of kidney disease at early stages, should help further this objective. Absolute contraindications to transplantation in patients with diabetes and advanced CKD are few, limited to those with unresolvable infection, recent malignancy, and severe unremediable coronary disease. These contraindications do not differ substantively from those in the nondiabetic setting.

Current Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend referral of patients with CKD to a transplant center when glomerular filtration rate (GFR) decreases to less than 30 mL/min. For patients with diabetes and CKD, earlier referral (GFR, 30 to 40 mL/min, or late stage 3 CKD) may allow more time to explore transplant options (vide infra) and complete the more extensive pretransplant evaluation usually required, although such a recommendation may not be appropriate for individuals documented to have slowly progressive CKD. Angiographic procedures are safer if performed earlier in the course of CKD, and outcomes of cardiovascular interventions also may be enhanced.

The ultimate objective of early referral is preemptive transplantation. Delayed graft function and rejection are reduced by more than half with preemptive kidney transplantation compared with transplantations performed after a year or more of dialysis therapy, with corresponding increments in graft and patient survival.

Ishani et al recently found that native-kidney GFR (5 to 20 mL/min) did not influence outcome in individuals undergoing preemptive transplantation, indicating that the benefits of avoiding dialysis therapy are evident in all such transplant recipients. The preemptive approach may be particularly beneficial for patients with diabetes, whose mortality on the waiting list is more than twice that of others.

Issues in Pretransplantation Evaluation

Pretransplantation evaluations of patients with CKD with and without diabetes address many similar issues, including malignancy, hepatic disease, and adequacy of urinary outflow. However, autonomic neuropathy resulting in bladder dysfunction, orthostasis, and gastrointestinal dysmotility is more problematic in patients with diabetes, as are complications related to cardiovascular disease (CVD). Although CVD prevalence is high in dialysis patients as a whole (35% to 50%), it affects as many as 50% to 85% of patients with diabetes older than 45 years, increasing mortality both before and after transplantation. None of these complications, however, should be perceived as a contraindication to
renal transplantation in patients with diabetes because therapeutic options are available to minimize the impact of each.23 Goals of the pretransplantation cardiovascular evaluation are to reduce perioperative morbidity and mortality, determine who (because of imminent mortality risk) should not be a transplant candidate, and provide a basis for modifying future risk.26-29

Because severe coronary disease often is asymptomatic in patients with diabetes, clinical history may be of limited utility. Most CVD evaluations begin with noninvasive studies to detect coronary ischemia, including electrocardiography, echocardiography, and/or stress testing. Each can be helpful, but in this population, variability in predictive accuracy is high, and electron-beam computed tomography cannot be recommended (Table 1).30,31 At most centers, the choice of study to be implemented may best be determined according to local expertise. Although some centers advocate angiography in most (if not all) transplant candidates with diabetes, many pursue cardiac catheterization only in candidates with positive screening examination results or those considered high risk because of age (≥45 years) or other risk factors.29,32 Patients with a previous myocardial infarction, angina, documented peripheral vascular disease, or wall motion abnormalities by echocardiography or with stress imaging may benefit from coronary angiography. If beta cell replacement is contemplated, angiography may be implemented more routinely.

In patients with significant coronary lesions, revascularization before transplantation is encouraged. However, despite several small studies indicating benefit, it is unknown whether this strategy changes immediate or long-term posttransplantation outcomes. Although associated morbidity can be high, the ultimate benefit of revascularization can be striking.33 In general, surgical revascularization has been considered clearly superior to catheter-based approaches in terms of restenosis and longevity of benefit.19,34,35

Very recent data indicate that long-term results with percutaneous transluminal coronary angioplasty lately have improved dramatically.36 Overall, the value of drug-eluting stents and postprocedure administration of antiplatelet agents in patients with advanced CKD is not yet determined. Nonischemic cardiomyopathy, which may improve with aggressive dialysis and/or resolve after transplantation, should not be considered an absolute contraindication to renal transplantation.37

Peripheral vascular disease is common in patients with diabetes with advanced CKD and can be severe even without symptoms. Noninvasive Doppler screening for hemodynamically significant and potentially correctable lesions is included in many evaluation protocols. Invasive studies are indicated for symptomatic patients, and surgical revascularization or angioplasty is warranted, when appropriate. It is not common to screen for cerebrovascular disease in the absence of clinical symptoms or suggestive physical findings.38

**Patients With Diabetes on the Waiting List**

Although no specific evidence exists to document that glycemic control and CVD risk factor reduction improve outcomes before or after transplantation, management of patients with diabetes on the waiting list should follow established National Cholesterol Education Program and American Diabetes Association (ADA) guidelines (Table 2).39,40 Although large clinical trials are lacking in this population, smaller studies

<table>
<thead>
<tr>
<th>Table 1. Noninvasive Evaluation of Coronary Artery Disease</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Meta-analysis of exercise electrocardiography</td>
</tr>
<tr>
<td>Thallium scintigraphy</td>
</tr>
<tr>
<td>Exercise echocardiography</td>
</tr>
<tr>
<td>Persantine thallium</td>
</tr>
<tr>
<td>Dobutamine echocardiography</td>
</tr>
<tr>
<td>Electron-beam computed tomography</td>
</tr>
</tbody>
</table>

Data from Ashley et al.31
Table 2. Proposed Management Goals in Patients With Diabetes and CKD Before and After Transplantation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic blood pressure</td>
<td>130/80 mm Hg</td>
</tr>
<tr>
<td>Glycosylated hemoglobin (A1c)</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>&lt;100 mg/dL</td>
</tr>
</tbody>
</table>

NOTE. To convert cholesterol in mg/dL to mmol/L, multiply by 0.02586.
Adapted from the National Cholesterol Education Program\(^{39}\) and ADA\(^{40}\) guidelines.

have documented a beneficial impact of statin use in patients on dialysis therapy.\(^{41,42}\) Smoking cessation, exercise, and weight control are desirable, as well. In addition, anemia correction with erythropoietin and aggressive management of hyperphosphatemia and renal osteodystrophy are important.\(^{43-45}\) Definitions of dialysis adequacy do not differ for patients with ESRD with and without diabetes. Maintenance of a functioning vascular access is essential; arteriovenous fistulae provide the best option. Unless preemptive transplantation from an identified living donor (LD) is certain, arteriovenous fistula creation before ESRD is desirable and consistent with recent K/DOQI guidelines.\(^{43,46}\) Recent clinical recommendations indicate that patients with diabetes with ESRD awaiting a suitable kidney should undergo cardiac reevaluation annually.\(^{28,47,48}\)

WORK GROUP 2: CHOOSING AMONG THERAPEUTIC OPTIONS FOR PATIENTS WITH DIABETES WITH CKD

Options for renal replacement therapy in patients with diabetes include hemodialysis, peritoneal dialysis, kidney transplantation (from either an LD or deceased donor), and simultaneous pancreas/kidney (SPK) transplantation. Timely institution of dialysis therapy or preemptive transplantation is essential to avoid uremic complications.

For patients with type 1 diabetes mellitus, LD and SPK transplants offer superior and approximately equivalent long-term patient and renal allograft survival.\(^{5,49}\) LD and SPK transplantation reduce mortality by almost two thirds compared with remaining on dialysis therapy, with 10-year patient survival rates of 67% and 65%, respectively. Mortality rates on the waiting list are high for all patients with diabetes and ESRD (up to 58%). Inasmuch as LD transplantation may obviate or decrease time on dialysis therapy awaiting a suitable organ, it is the preferred option for most candidates with type 1 and type 2 diabetes. However, the advantages of glycemic control offered by SPK transplantation may be important enough in some candidates with type 1 diabetes to necessitate frank and open discussion by transplant teams and patients, even when LD transplantation is an option. Availability of potential LDs (related or unrelated) should be reassessed periodically in candidates with diabetes on the waiting list.

Although patient and graft survival after deceased donor kidney transplantation are lower than with the LD or SPK transplantation options, outcomes for diabetic recipients of these kidneys are superior to remaining on dialysis therapy.\(^{3}\) Even after allograft failure, retransplantation (from any donor), which decreases mortality rates by 45% compared with maintenance dialysis therapy, offers the best hope for long-term survival.\(^{16}\) Timely retransplantation should be the norm for any patient with diabetes with a failed allograft.

Beta Cell Replacement

Although of potential benefit, aggressive glycemic control can be difficult to maintain in patients with diabetes and stage 3 or 4 CKD and hypoglycemic unawareness who also have, as a consequence of CKD, diminished insulin clearance and poor or inconsistent oral intake. After kidney transplantation, recipients with diabetes are prone to hyperglycemia resulting from weight gain and immunosuppressant-induced insulin resistance. Nonetheless, the recognized systemic benefits of meticulous glucose control justify efforts to achieve stringent targets by using intensive insulin regimens. For some patients, this may be achieved best with beta cell replacement. Successful pancreas transplantation protects from both hyperglycemia and hypoglycemia and normalizes glycosylated hemoglobin values.\(^{50,51}\) It obviates needs for adherence to a diabetic diet, blood glucose monitoring, and insulin injections. Importantly, it allows patients with diabetes the opportunity for spontaneity in diet and exercise. A recent study from Leiden, The Netherlands,
Table 3. Adjusted Pancreas Graft and Recipient Survival for SPK and PAK Transplantation, 1996 to 2001

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>3 Years</th>
<th>5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graft survival (pancreas) (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAK</td>
<td>79.7</td>
<td>67.4</td>
<td>44.9</td>
</tr>
<tr>
<td>SPK</td>
<td>85</td>
<td>76.8</td>
<td>70.2</td>
</tr>
<tr>
<td>Patient survival (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAK</td>
<td>95.3</td>
<td>92.9</td>
<td>82.2</td>
</tr>
<tr>
<td>SPK</td>
<td>95.9</td>
<td>92.7</td>
<td>88.9</td>
</tr>
</tbody>
</table>

Data from United Network for Organ Sharing/Scientific Registry of Transplant Recipients.57

Documented that during 4 years, recipients of simultaneous pancreas/kidney transplants with functioning pancreas grafts showed less progression of coronary disease (with frank regression in some) compared with recipients of SPK transplants with failed pancreas transplants.62 In addition, pancreas transplantation may prevent the recurrence of diabetic nephropathy and improve neuropathy and retinopathy.50-56

The greatest experience and best outcomes are with SPK transplantation. However, since 1996, there has been little growth in SPK transplantations performed because of the limited availability of deceased donor kidneys, whereas the number of pancreas after kidney (PAK) transplants has doubled.5 Although patient and pancreatic allograft survival with PAK transplantation have improved in recent years (particularly in selected centers), there remains a slight benefit in favor of SPK transplantation (Table 3).57,58 Candidacy requirements for SPK and PAK transplantation vary from center to center. Although some contend that any patient thought to be a candidate for SPK transplantation should be considered for a pancreas after successful kidney engraftment, recent data regarding intermediate-term patient survival after PAK transplantation indicate that no specific recommendations regarding candidacy can be made at this time.59

Enthusiasm for islet transplantation is growing rapidly, and greater numbers of patients are achieving insulin independence with single islet infusions. However, islet recipients are typically thin and of small stature, with minimal insulin requirements before transplantation; insulin independence often requires islets from 1 to 3 donors, and long-term insulin-free intervals (>5 years) have not yet been shown.51,60,61 Thus, solid-organ pancreas transplantation, either SPK or PAK transplantation, currently must be considered the treatment of choice for suitable patients with type 1 diabetes, especially those with high insulin requirements and larger body habitus.62 At the current time, islet transplantation should be reserved for patients with diabetes with excessive surgical risk and low insulin requirements.

Allocation Issues

Currently, as with all kidney transplant candidates, patients with diabetes cannot accrue points for time on the waiting list until GFR has decreased to 20 mL/min or less.53 Inasmuch as patients with diabetes and CKD characteristically develop uremic symptoms earlier in their disease course than those without diabetes, they may be disadvantaged by current policies. In addition, a patient with type 1 diabetes with a GFR between 20 and 50 mL/min can derive substantial benefit in reducing metabolic complications from either solitary pancreas or SPK transplantation. However, the former is precluded by renal function inadequate to support the use of calcineurin inhibitors, and the latter by policies requiring a lower GFR for wait listing. These policies were created to preserve equity in allocation by not disadvantaging those without diabetes.17 However, in light of new data indicating better patient survival and greater posttransplantation benefits from early kidney transplantation, this work group recommends reevaluation of current policy, recognizing that broad analyses of current data and future implications may be necessary.12,13

WORK GROUP 3: MINIMIZING PTDM

New-onset diabetes mellitus after transplantation is common, compromises patient and graft survival, and appears to be increasing in frequency.6-8,64-66 The precise incidence of PTDM is difficult to determine because of variable criteria used to diagnose this syndrome. Although it develops most often during the first 3 to 6 months after transplantation, patients remain at risk for PTDM during the life of the allograft.6-8 It now appears that PTDM may exert the same adverse effect on outcomes during 8 to 10 years as preexisting diabetes, primarily as a consequence of enhanced cardiovascular risk.57,68
Table 4. ADA Guidelines for Diagnosis of Diabetes and Impaired Fasting Glucose Levels

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>Fasting blood glucose level ≥ 126 mg/dL (≥7.0 mmol/L) or symptoms + casual blood glucose level ≥ 200 mg/dL (≥11.1 mmol/L) or 2-h postprandial glucose level ≥ 200 mg/dL after 75-g glucose load</td>
</tr>
<tr>
<td>Impaired fasting glucose</td>
<td>Fasting blood glucose level &gt; 100 and &lt;126 mg/dL.</td>
</tr>
<tr>
<td>Impaired glucose</td>
<td>2-h postprandial glucose ≥ 140 and &lt; 200 mg/dL.</td>
</tr>
</tbody>
</table>

NOTE. An abnormal test result should be confirmed by the same or another test on a different day. To convert glucose from mg/dL to mmol/L, multiply by 0.05551.

Data from the American Diabetes Association.40

Defining and Diagnosing PTDM

One of the difficulties in understanding PTDM is the absence of widely accepted diagnostic criteria for this disorder. Consequently, the reported incidence of PTDM varies widely among studies.7,8,69,70 Although not well established in the transplant population, it nonetheless seems reasonable to use ADA/World Health Organization diagnostic criteria to define PTDM (Table 4), a standard consistent with recently published international consensus guidelines.56,71,72 The oral glucose tolerance test and measurement of glycosylated hemoglobin levels are not recommended as routine screening tests for diabetes because of cost, inconvenience, and lack of sensitivity. Recent guidelines for monitoring plasma glucose levels from the American Society of Transplantation are reasonable to screen for new-onset diabetes after transplantation (Table 5).73 However, because of increasing risk beyond the first year, fasting plasma glucose should be measured with every determination of kidney function (usually every 3 to 4 months), rather than once a year. Given the stringency of the ADA/World Health Organization definition relative to those presently used in the literature, it seems likely that the incidence and prevalence of PTDM are greater than reported. Although the additional diagnostic categories identified by the ADA (impaired fasting glucose level and impaired glucose tolerance) have implications for CVD risk in the general population, their meaning in transplant recipients is as yet undetermined.

Yet another diagnostic inaccuracy arises from the implication that PTDM develops de novo after transplantation. It is likely that some patients with a diagnosis of PTDM had significant preexisting glucose intolerance that was clinically undetected or unrecognized.74 Others have truly de novo diabetes mellitus. PTDM compromises graft and patient survival during a relatively short interval (8 to 10 years).75,66,67 Whether the negative impact of PTDM is caused solely by hyperglycemia after transplantation or also may reflect the atherogenic effects of longstanding insulin resistance is uncertain. Furthermore, although it has long been presumed that PTDM is an expression of peripheral insulin resistance, it also is likely that some patients have low insulin production, at times as a direct toxic effect of immunosuppressive medications.64,75,76 PTDM thus appears to be the clinical manifestation of several pathophysiologic influences, rather than a single entity. Whether differences in the cause or manifestations of diabetes mellitus have prognostic and/or therapeutic implications for transplant recipients is unknown.73

Assessing Risk for PTDM

Several characteristics, identifiable in patients before transplantation, have been linked to a greater risk for developing PTDM (Table 6). Additionally, events occurring after transplantation heighten preexisting risk. Increasing doses of corticosteroids (and length of exposure) have been linked to greater risk for PTDM.77,78 Calcineurin inhibitors as a class increase glucose intolerance, and because PTDM is related to drug exposure, more efficient microemulsion preparations may have increased risks in recent years.77,79 PTDM also appears more frequently in patients treated with tacrolimus than in those administered cyclosporine in some, but not all, studies.7,8,66,70,80 There are significant interactions between pretransplantation risk factors and

Table 5. Frequency of Obtaining Fasting Blood Glucose Levels After Kidney Transplantation

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Days after transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least weekly months</td>
<td>1 to 3 posttransplantation</td>
</tr>
<tr>
<td>At least semimonthly</td>
<td>months 4 to 6 posttransplantation</td>
</tr>
<tr>
<td>At least monthly</td>
<td>months 6 to 12 posttransplantation</td>
</tr>
<tr>
<td>At least every 3 to 4</td>
<td>months thereafter</td>
</tr>
</tbody>
</table>

Data from Kasiske et al,73 with modifications (see text).
the diabetogenic effects of immunosuppressive medications. For example, both tacrolimus and cyclosporine are associated with significantly greater risk for PTDM in African Americans. Likewise, among patients administered tacrolimus, PTDM is substantially more common in those with hepatitis C. Again, comparing the impact of various immunosuppressant medications on PTDM is difficult because of the absence of standardized diagnostic criteria.

Preventing PTDM

Can PTDM be prevented by risk-factor modification? Some pretransplantation variables, such as age and ethnicity, are not modifiable. Recent studies have shown that weight reduction, increased exercise, and dietary changes reduce the risk for developing type 2 diabetes mellitus in the general population. Although similar studies of patients with ESRD do not exist, it is reasonable to assume that beneficial effects can be expected in transplant recipients. Thus, patients who are overweight before transplantation (body mass index >25 and <30 kg/m²) or obese (body mass index >30 kg/m²) should be encouraged strongly to modify their lifestyle to reduce the likelihood of PTDM. In the presence of significant risk factors, transplant candidates should be informed of their increased risk for developing PTDM and experiencing untoward cardiovascular events.

After transplantation, selection of immunosuppressant regimens may influence the development of PTDM. Unfortunately, risk for PTDM has not been the primary end point of prospective trials, and any recommendations must be based on observational studies of the incidence of new-onset diabetes in groups of patients treated with different immunosuppressive protocols. Protocols that avoid or minimize corticosteroid use are becoming more widely accepted and clearly reduce risk for PTDM. However, follow-up periods for most of these trials remain short, and their long-term safety and efficacy remain unproven. In some patients, use of cyclosporine, rather than tacrolimus, and targeting lower blood levels of both may reduce the immediate risk for PTDM. Any benefit of calcineurin inhibitor avoidance in reducing PTDM must be weighed against the possibility of increased risk for rejection and greater need for corticosteroids.

Managing PTDM

All general recommendations applicable to the management of patients with preexisting diabetes apply to patients with PTDM (Table 2). Given the contribution of immunosuppressive medications to the pathogenesis of PTDM, modifications in the dose or selection of these medications is an option for clinically stable patients at least 6 to 12 months posttransplantation. A seemingly small reduction in corticosteroid dose (from 10 to 5 mg/d) appears to have beneficial effects on glucose metabolism. It is more difficult to provide specific recommendations regarding modification of calcineurin inhibitor dosage or preparation. However, observational data indicate that, in some patients, hyperglycemia improves after conversion from tacrolimus to cyclosporine therapy. It appears appropriate to reserve the term “resolution” of PTDM for patients who no longer require hypoglycemic agents to achieve normal blood glucose levels. It is unclear whether those with resolution of PTDM have particular characteristics and whether resolution is long lasting and associated with reduced CVD risk. In all cases, provision of immunosuppression adequate to prevent immunologic injury and maintain allograft function must remain the primary consideration.
WORK GROUP 4: IMPROVING OUTCOMES FOR TRANSPLANT RECIPIENTS WITH DIABETES

Increased risk for graft loss after transplantation among recipients with diabetes is caused primarily by increased death from CVD. Although recognizing that significant differences exist between patients with type 1 and type 2 diabetes, management goals should apply to both, as well as to transplant recipients who develop PTDM. In reality, the impact of implementing these recommendations may be compromised by morbid events occurring before transplantation. Effective management of patients with diabetes during progressive CKD and dialysis therapy promotes optimal outcomes after transplantation. 11,43,44,46

Immunosuppression

As noted, the first goal in selecting an immunosuppressive protocol is minimizing rejection to optimize graft survival. Implemented protocols may be center specific. For example, some institutions may achieve outstanding results with steroid avoidance, whereas the same approach at other centers may yield unacceptable rates of rejection and graft loss. Given the consequences of transplant failure in this population, application of new and experimental immunosuppressive protocols in patients with diabetes must be approached with caution.

Data indicating superiority of any specific immunosuppressive regimen in transplant recipients with diabetes do not exist. Although calcineurin inhibitors can be toxic to islet cells, 76 there is little or no evidence to indicate a differential effect of tacrolimus or cyclosporine on glycemic control in patients with preexisting diabetes. Likewise, although some contend that maintenance steroid therapy may increase insulin requirements among patients with type 2 diabetes, there is little evidence that corticosteroids at low doses worsen either glycemic control or other outcomes. It also was noted that most steroid-avoidance protocols require greater doses of other agents (eg, calcineurin inhibitors, sirolimus) that themselves may adversely affect islet cell function, glycemic control, or CVD risk. Using high doses of corticosteroids to treat or prevent acute rejection often alters glycemic control and requires close monitoring of blood glucose levels and insulin dosing.

Other considerations may impact on immunosuppressant choices in transplant recipients with diabetes. Patients with diabetic enteropathy may have difficulty with mycophenolate mofetil, especially in combination with tacrolimus 90. The impact of sirolimus on wound healing may be especially problematic in obese or poorly nourished transplant recipients with diabetes. Sirolimus, calcineurin inhibitors, and corticosteroids also can cause or exacerbate dyslipidemia. 91 It is increasingly obvious that immunosuppressive management requires acceptance of certain trade-offs, for which there is little guiding evidence. For example, is the increased glucose intolerance noted in blacks with tacrolimus an acceptable trade-off for less rejection in this high-risk population? Likewise, is the risk for hyperlipidemia offset by the immunosuppressant efficacy and potentially beneficial vascular effects noted with sirolimus?

Glycemic Control

The general assumption must be that glycemic control after transplantation is as important to patients with diabetes as in other settings, and 2 persuasive lines of evidence support such an approach. First, large population-based trials of patients with type 1 and type 2 diabetes indicate that glycemic control is important in reducing diabetic complications; there is no reason to assume these findings are not applicable to transplant recipients. 92,93 Second, pancreatic transplantation in kidney recipients (SPK or PAK transplantation), with restoration of euglycemia, may reduce the recurrence of diabetic nephropathy, retinopathy, neuropathy, and progression of CVD. 50,62 Improved glycemic control also reduces infectious risks and improves wound healing.

Current treatment standards emphasize tight glycemic control using whatever means will achieve recommended goals. These include aggressive use of new insulin preparations and delivery devices, oral agents, or combinations thereof. 40 Metformin, because of the risk for lactic acidosis in patients with renal insufficiency, usually is contraindicated in this population. In patients with type 2 diabetes, there is accumulating evidence that early insulin admin-
istration may help preserve residual islet function in the presence of ongoing hyperglycemia; reliance on oral agents alone may not provide the best outcomes. Glucose self-monitoring is essential, with target fasting blood glucose levels of 80 to 120 mg/dL (4.4 to 6.7 mmol/L) and postprandial glucose levels less than 140 to 160 mg/dL (<7.8 to 8.9 mmol/L). Glycosylated hemoglobin (A1C) levels should be measured quarterly, with a minimum target of 7% or less as recommended by the ADA. The work group agreed that these standards are not widely applied in the posttransplantation setting, and their implementation may require greater resources to facilitate access to dietitians, diabetic educators, and endocrinologists. Finally, for some select kidney recipients with type 1 diabetes, PAK transplantation should be considered an option to enhance glycemic control.

Dietary awareness and intervention are important in patients with PTDM. The primary objective should be to prevent excess weight gain after transplantation while enhancing glycemic and lipid control. In patients with increased body mass index, even small amounts of weight loss can improve glucose control, blood pressure, and lipid levels and reduce the need for medications.

Hypertension and Renal Function

K/DOQI guidelines for monitoring renal function in patients with CKD also should be applicable to kidney transplant recipients with diabetes.11,94 Thus, there should be sequential monitoring of GFR over time, with quantitation of protein excretion. Preservation of GFR requires appropriate prophylaxis when intravenous contrast agents are to be administered. As transplants last longer, recurrent diabetic nephropathy is an increasingly frequent cause of graft loss. In patients with diabetic changes in an allograft, despite the paucity of strong supportive evidence, most would advocate aggressive blood pressure control, minimization of calcineurin inhibitors, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker use, and good glycemic control.95 Although well supported in other settings and reasonable in concept, no data exist regarding monitoring for microalbuminuria after kidney transplantation.96

Good blood pressure control preserves renal function and reduces cardiovascular risk, especially in transplant recipients with diabetes. As listed in Table 2, target blood pressure goals for patients with diabetes range from 130 to 135/80 mm Hg.40,94 New K/DOQI guidelines for blood pressure control in transplant recipients indicate no specific drug preferences.97 The bulk of evidence supporting use of angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers was generated in patients with diabetes without ESRD.95 However, there is some evidence that use of these agents in transplant recipients reduces albuminuria, which may be beneficial to the allograft.98 Thus, it was recommended that angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers be considered in transplant recipients with diabetes, even though their use requires close monitoring of hemoglobin, potassium, and creatinine levels. Risk for acute renal failure is low, and these agents may help preserve renal function and prevent vascular disease. Common practice favors the introduction or reintroduction of these agents within 2 to 4 weeks after transplantation in patients with stable renal function.

Minimizing the Impact of CVD

In the most recent National Cholesterol Education Program guidelines (Adult Treatment Panel III), diabetes is considered a coronary heart disease risk equivalent, justifying aggressive targeting for risk reduction initiatives.59 All potentially modifiable risk factors, including cigarette smoking, hypertension, and hyperlipidemia, should be addressed (Table 2). 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are very effective in reducing low-density lipoprotein cholesterol levels and have been documented to reduce CVD mortality in many clinical settings.99 Very high triglyceride levels (>500 mg/dL [>5.65 mmol/L]) require intervention; fibrates are the most commonly used agents. Glycemic control, particularly when insulin and thiazolidinediones are used, also improves hyperlipidemia. Because of potential drug-drug interactions between immunosuppressants and lipid-lowering agents, close monitoring of drug levels and hepatic enzymes is indicated.

Monitoring of fasting lipid levels should occur regularly during the first year after transplantation and at least annually thereafter. Despite the considerable attention given to noninvasive as-
Table 7. Issues for Future Research Initiatives as Defined by Individual Work Groups

<table>
<thead>
<tr>
<th>Pretransplantation issues</th>
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<tbody>
<tr>
<td>• Does aggressive pre-CKD glycemic control impact on outcomes in patients with diabetes on dialysis therapy and after transplantation? Are trials specific to dialysis and transplantation necessary to answer these questions?</td>
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<tr>
<td>• Does tight glycemic control after the onset of ESRD impact on long-term outcomes?</td>
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<table>
<thead>
<tr>
<th>Selection of therapeutic modality</th>
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<tr>
<td>• Organ procurement organizations should be subject to more uniform policies to ensure that all potentially usable pancreata are procured and allocated</td>
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<tr>
<td>• Should there be a single waiting list for whole pancreas and islet transplant candidates?</td>
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<tr>
<td>• Should patients with diabetes have earlier access to the waiting list because of their relatively worse prognosis on dialysis therapy?</td>
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<tr>
<td>• Is early beta cell replacement more effective than tight insulin control in preventing the development of diabetic nephropathy?</td>
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<table>
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<tr>
<th>PTDM</th>
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<tr>
<td>• What is the relationship between impaired glucose tolerance before transplantation and PTDM?</td>
</tr>
<tr>
<td>• Do risk factors and pathophysiological characteristics differ between early (first 6 months) and late (beyond 6 months) onset of PTDM?</td>
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<tr>
<td>• Do the diagnostic categories of impaired fasting glucose and impaired glucose tolerance impact on CVD risk after transplantation?</td>
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<tr>
<td>• Is pretransplantation dyslipidemia a risk factor for the development of PTDM?</td>
</tr>
<tr>
<td>• What is the pathogenetic relationship between hepatitis C and PTDM?</td>
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<tr>
<td>• What is the relative impact of different immunosuppressant agents on clinical outcomes after transplantation? For example, is less rejection a more desirable end point than less PTDM?</td>
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<tr>
<td>• What is the impact of weight reduction pretransplantation and posttransplantation in preventing and treating PTDM?</td>
</tr>
<tr>
<td>• In patients with PTDM, what are the effects of altering immunosuppression (eg, reducing the dose or discontinuing corticosteroids or calcineurin inhibitors, switching tacrolimus to cyclosporine)?</td>
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<tr>
<th>Improving outcomes for transplant recipients with diabetes</th>
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<tbody>
<tr>
<td>• To be of greater assistance in improving outcomes, registries should identify and segregate patients with type 1 and type 2 diabetes and PTDM.</td>
</tr>
<tr>
<td>• Does better glycemic control (measured by hemoglobin A1c levels) impact on outcomes after transplantation?</td>
</tr>
<tr>
<td>• In patients with preexisting diabetes, do immunosuppressant agents that alter insulin resistance/secretion affect outcomes after transplantation?</td>
</tr>
<tr>
<td>• What is the relative impact of nontraditional risk factors for CVD after transplantation (eg, infection, inflammation, dystrophic calcification, and homocysteine levels)?</td>
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<tr>
<td>• What are appropriate guidelines for cardiac screening after transplantation?</td>
</tr>
<tr>
<td>• What is the appropriate blood pressure target in transplant recipients with diabetes?</td>
</tr>
<tr>
<td>• Are there specific benefits of angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker therapy after transplantation in this population?</td>
</tr>
</tbody>
</table>

Assessment of coronary disease before transplantation (discussed previously), no data exist regarding need for posttransplantation monitoring. The work group favored daily administration of aspirin (81 to 325 mg), an intervention associated with minimal risk, to reduce risk for vascular events.100 Peripheral vascular disease causes significant morbidity in transplant recipients with diabetes and also should benefit from interventions that reduce overall CVD risk. Regular examination of feet by physicians, nurses, and patients is an important element of health maintenance in patients with diabetes. Any lesion should precipitate early consideration of antibiotic therapy, if indicated, along with vascular assessment and avoidance of weight bearing to prevent rapid progression in immunosuppressed patients with diabetes.

CONCLUSION

With more therapeutic options than ever before and unprecedented success rates, transplantation offers the best outcomes available to patients with diabetes and advanced CKD. Early referral to the transplant center is mandatory to allow effective implementation of these options and foster opportunities for preemptive transplantation. Beta cell replacement is an increasingly attractive option for patients with type 1 diabetes. Although preserving allograft function is always the foremost priority, care of patients with diabetes before and after transplantation...
also must address modifiable cardiovascular risk factors if outcomes are to improve. Although many unanswered questions remain as the basis for future research (Table 7), excellent guidelines already exist regarding the delivery of sophisticated care to patients with diabetes.

Among all work groups, considerable concern was expressed and summarized in the question, “Who’s paying attention?” Implementing optimal care for patients with diabetes and advanced CKD requires multidisciplinary involvement. Ideally, this would imply the existence of a team dedicated to addressing all cardiovascular risk factors and diabetic outcome variables, as well as ESRD management, surgical complications, and immunosuppression. At a minimum, patients with diabetes must be made aware of which aspects of care are being addressed by an individual practitioner and which are not. It is the responsibility of the transplant center not only to promote access to transplantation, but also to counsel transplant recipients with diabetes regarding optimal diabetic care after the operation. Only by increasing awareness of current developments in diabetes care, as more of us pay attention, can potential benefits become actual benefits.

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APPENDIX

National Kidney Foundation Task Force on Diabetes and Transplantation

Steering committee: Giacomo Basadonna, MD, PhD; Fernando G. Cosio, MD; Connie Davis, MD; Francis Delmonico, MD; Robert Gaston, MD; Bertram Kasikes, MD; Alan Leichtman, MD; Robert Straatta, MD.

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Work Group 2: Choosing Among Therapeutic Options for the Diabetic CKD Patient. Chairs: Giacomo Basadonna, MD, PhD; Alan Leichtman, MD. Participants: Stephen T. Bartlett, MD; Kenneth L. Brayman, MD, PhD; Ruth Campbell, MD; William Herman, MD; Alok K. Mandal, MD, PhD; Rajiv Saran, MD, PhD; Ron Shapiro, MD; Peter G. Stock, MD, PhD; David Sutherland, MD, PhD; J. Richard Thistlewaite, MD, PhD; Michael Thompson, MD.

Work Group 3: Minimizing PTDM. Chairs: Fernando G. Cosio, MD; Bertram Kasikes, MD. Participants: Hugh Aucinloss Jr, MD; William Bennett, MD; Edward H. Cole, MD; William Harmon, MD; Alan R. Hull, MD; Yogish Kudu, MD; Kevin C. Mange, MD; Arthur J. Matas, MD; Nancee VanderPluyf, RD; Pedro J. Vergne-Marini, MD; Alan Wilkinson, MD.

Work Group 4: Improving Outcomes for Diabetic Transplant Recipients. Chairs: Robert Gaston, MD; Robert Straatta, MD. Participants: Daniel Battle, MD; Roy D. Bloom, MD; George Burke, MD; Viken Douzdjian, MD; Francesca Egid, MD; Scott A. Gruber, MD, PhD; Mitchell L. Henry, MD; Ann Kalis, MD; Dixon B. Kaufman, MD, PhD; Jennifer Larsen, MD; Christopher L. Marsh, MD; Angela de Mattos, MD; Thomas Pearson, MD, PhD; Richard Perez, MD; John Pirsch, MD; Fritz Port, MD; Sudhakar Reddy, MD; Mark E. Williams, MD.