Transplant-Associated Hyperglycemia: A New Look at an Old Problem

Michael F. Crutchlow* and Roy D. Bloom†

*Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, and the Institute for Diabetes, Obesity and Metabolism, and †Renal Electrolyte and Hypertension Division, Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

New-onset diabetes has long been recognized as a common complication of kidney transplantation, promoting cardiovascular disease, death, and graft failure. Studies in recent years have begun to highlight the very high posttransplantation prevalence of the prediabetic states of impaired fasting glucose and impaired glucose tolerance and the significant repercussions of these states on cardiovascular health. Therefore, the overall burden of transplant-associated hyperglycemia (TAH), which encompasses new-onset diabetes and the prediabetic states, is far greater than previously appreciated. The kidney transplant population is predisposed to insulin resistance and to additional insults of hypertension and hyperlipidemia that, together with hyperglycemia, compose the metabolic syndrome and promote atherosclerosis. When recipients with an underlying, frequently nonmodifiable predisposition to glucose dysregulation encounter transplant-specific, often modifiable, diabetogenic exposures, TAH manifests. Aggressive screening will effectively detect TAH, whereas risk factor modification, lifestyle intervention, and, when appropriate, drug therapy may decrease its impact. Topics of future investigation should include the use of emerging diabetes therapies and avenues for the prevention and reversal of TAH.

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Address correspondence to: Dr. Roy D. Bloom, Renal Electrolyte and Hypertension Division, University of Pennsylvania, 700 Clinical Research Building, 412 Curie Boulevard, Philadelphia, PA 19104. Phone: 215-662-4643; Fax: 215-349-5703; E-mail: rdbloom@mail.med.upenn.edu

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reconsidering and revising this definition is likely to become increasingly apparent as ADA criteria for hyperglycemic states becomes routinely incorporated into clinical transplant practice (3). To this end, we recommend that hyperglycemia after transplantation be diagnosed according to definitions described by current ADA criteria. Patients with fasting plasma glucose (FPG) of ≥126 mg/dl are defined as having diabetes; those with values between 100 and 125 mg/dl are defined as having IFG. If a 2-h, 75-g oral glucose tolerance test is used, then a 2-h plasma glucose level between 140 and 200 mg/dl diagnoses IGT, whereas a 2-h value >200 mg/dl represents overt diabetes. We favor ADA standards over World Health Organization criteria because IFG is more stringently defined, consistent with the recognition that CVD risk accrues even at these lower values (7,8).

Prevalence of Hyperglycemia after Kidney Transplantation

Numerous investigations have examined NODM prevalence in kidney recipients. A meta-analysis of 19 observational studies and controlled trials that use varying detection methods in diverse study populations reported NODM rates in the first posttransplantation year ranging from 2 to 50% (12). The largest epidemiologic studies examined NODM incidence, using data for Medicare beneficiaries from the US Renal Data System (USRDS) who were followed from 1994 to 1998 (11) or from 1996 to 2000 (10), respectively. Because similar methods (13) and overlapping data sets were used, results were comparable. The first of these studies additionally examined rates of new diabetes in patients who were on the waiting list for a transplant and found a 6% annual baseline incidence. Both studies demonstrated an augmented NODM incidence (14 to 16%) in the first posttransplantation year, declining thereafter to an annual incidence of 4 to 6%, similar to the pretransplantation baseline rate (10,11). The cumulative incidence of NODM was 24% at 3 yr after transplantation (10). These complementary studies indicate that NODM is particularly accelerated in the first few posttransplantation months, reflecting acute superimposition of transplant-associated factors on underlying baseline risk.

Two single-center studies used more contemporary and direct methods to detect posttransplantation hyperglycemia. Using current ADA FPG criteria, Cosio et al. (8) reported that NODM was present in 13% of 500 kidney recipients at 1 yr after transplantation. The other study prospectively assessed changes in oral glucose tolerance in living-donor kidney recipients (14). Using this relatively sensitive method, these investigators found that 24% of previously euglycemic patients met World Health Organization criteria for overt diabetes (2-h glucose ≥200 mg/dl) at 1 yr after transplantation (Figure 1). Besides corroborating the NODM incidence reported in the USRDS registry analyses, the two single-center investigations assessed the prevalence of prediabetic hyperglycemia after transplantation and observed that IFG or IGT was present in 33 to 46% of patients at 1 yr after transplantation (8,14). Prediabetic hyperglycemia in one of the studies presented a significant risk to subsequent recipient survival (8). This is consistent with general population data, where prediabetic hyperglycemic states, in part through the close link with the metabolic syndrome (MS), has been well characterized to predict future progression to overt diabetes (15–19), as well as to CVD (4–7).

MS after Kidney Transplantation

MS describes a constellation of modifiable CVD risk factors (Figure 2) that cluster together and share, as a root cause, obesity, physical inactivity, and systemic insulin resistance (20). The presence of MS heralds a multifaceted and deadly threat to kidney recipients in that it predisposes to NODM, kidney dysfunction, systemic inflammation, and CVD (21,22). Besides the well-described renal manifestations of hypertension and hyperglycemia, other components of MS have been identified as risk factors for kidney dysfunction, including dyslipidemia and central obesity (23–26).

MS is a concept in evolution in kidney transplantation, and the number of publications, although growing, is sparse. The prevalence of MS increases in the first years after kidney transplantation in concert with progressive weight gain and bur-
geoning obesity (27,28). Both obesity and posttransplantation weight gain have been linked to graft dysfunction and loss (27,28), although the underlying mechanisms are not yet elucidated. At least two additional, retrospective studies have associated MS with NODM, as well as inferior patient and graft outcomes (29,30).

It follows that identification of MS in transplant recipients will be central to optimizing posttransplantation care. Although intervention to correct individual components of MS will be beneficial, recognition of the central pathogenic role of insulin resistance should guide aggressive lifestyle intervention and stimulate clinical investigation of pharmacologic efforts to promote insulin sensitivity and weight loss in the transplant population.

Impact of TAH on Mortality and Graft Loss

NODM and CVD

The risk for CVD in patients with ESRD is estimated to be 10 to 30 times higher than in the general population (31). This is likely a consequence of both shared risk factors for CVD and kidney disease, such as hypertension and diabetes, as well as an independent effect of the uremic state itself (31,32). Kidney transplantation is associated with diminished risk for CVD compared with continued dialysis (33). This may be due, in part, to selection of healthier patients but also likely reflects beneficial physiologic effects of transplantation itself (32,34). Despite this, CVD is the most common cause of death among kidney recipients (10). In line with general population data, the presence of preexisting diabetes represents a major and even magnified independent risk factor for CVD in kidney recipients (10,35,36).

It is now widely recognized that NODM confers a higher likelihood of death than is seen in recipients without diabetes (10,37,38). This risk escalates with time after transplantation to the extent that, toward the end of the first posttransplantation decade, it approaches the magnitude that is observed in patients with preexisting diabetes (37). Part of the excess mortality in recipients with NODM may be attributed to infectious complications (10). Several studies have emerged linking NODM to increased CVD risk (8,39,40). Posttransplantation follow-up in these studies has ranged between 3 and 5 yr. One USRDS registry analysis demonstrated that both preexisting diabetes (hazard ratio 1.13; \( P = 0.05 \)) and NODM (hazard ratio 1.60; \( P < 0.0001 \)) were independent risk factors for myocardial infarction within the first 36 mo after transplantation (39). Although atherogenesis that is attributable to hyperglycemia would be expected to develop over a much longer time frame (41), most kidney recipients without diabetes have had other CVD risk factors for many years. Hyperglycemia may alter the quantity or the quality of established atherosclerosis over a short time frame to promote vascular events. However, it is possible that hyperglycemia per se is not directly responsible for increased CVD that is seen in patients with NODM. Rather, NODM may represent a surrogate of inflammatory burden that occurs in a dysregulated posttransplantation metabolic milieu. This notion is supported by a contemporary study in which cardiovascular mortality was prospectively examined in 357 recipients without pretransplantation diabetes (40). The relative risk of NODM for CVD was more than halved after adjustment for other cardiac risk factors and inflammatory markers such as low HDL and C-reactive protein.

Prediabetic Hyperglycemia and CVD

Despite widening the parameters for detecting patients who are at risk for CVD, current ADA guidelines still do not indicate the absolute level of hyperglycemia at which this occurs. Instead, they identify thresholds at which risk for diabetic microvascular complications, particularly retinopathy, appears (42,43). Two large, prospective, general population cohort studies (44,45) observed a direct relationship between increasing glycosylated hemoglobin (HbA1c) in the prediabetic range (<7%) and CVD risk. In one of these studies, risk more than doubled for every 1% increase above a HbA1c threshold of 4.6% (44). Other large studies that were performed in non–kidney disease populations of different ethnicities (9) established substantial independent CVD risk with IGT (5,6). Finally, increased FPG in the nondiabetic range (86 to 110 mg/dl) has been shown to increase long-term CVD mortality by up to 40% (7).

Together, these studies confirm that prediabetic hyperglycemia presents a major CVD risk to the general population.

Among kidney recipients, one recent study demonstrated an association between increased CVD risk and prediabetic hyperglycemia at 1 yr after transplantation (8). With average follow-up of >3 yr, 12% of patients had a major vascular event. Risk, specifically for cardiac events, escalated with incremental elevations in FPG >90 mg/dl and was progressively higher in patients with IFG and NODM (Figure 3). Although investigations to validate this observation are warranted, these findings are bolstered by their consistency with general population data, and they have major implications for cardiovascular health in kidney recipients, in whom the prevalence of IFG/IGT is extremely high (8,14).

TAH and Graft Loss

Unrelated to the obvious link to death with a functioning kidney, NODM has been recognized to be an independent contributor to premature graft loss in kidney recipients (10). Proposed mechanisms by which this may occur have been

![Figure 3. Association of TAH and cardiovascular events. The proportion of 351 patients who remained free from cardiovascular events in long-term follow-up after kidney transplantation is demonstrated, stratified by glycemic status at 1 yr after transplantation: Normal fasting blood glucose (Normal-FBS), impaired fasting glucose (IFG), and NODM. Adapted from reference (8).](Image 356x139 to 512x224)
described elsewhere but include (1) the eventual development of diabetic nephropathy; (2) the association of insulin resistance/diabetes with MS, impaired vascular health, and hypertension; (3) chronic underimmunosuppression that results from efforts to mitigate diabetogenic toxicity of available antirejection therapies; and (4) the use of higher dosages of diabetogenic immunotherapies in the setting of graft dysfunction associated with rejection (e.g., methylprednisolone pulse therapy) (2).

Pathogenesis of TAH

Hyperglycemia results from imbalance between pancreatic $\beta$ cell insulin production and insulin that is required by target tissues to regulate effectively fasting glucose production and postprandial glucose disposal (46). Baseline risks that predispose individuals to NODM include advanced age, obesity, male gender, nonwhite race, and a family history of diabetes (10,46,47) (Table 1). These traditionally nonmodifiable characteristics reflect inherited and acquired defects in insulin sensitivity and $\beta$ cell function that contribute to glucose dysregulation. The high incidence of TAH in the months after transplantation reflect superimposition of new, transplant-specific factors on the baseline metabolic milieu of predisposed individuals (10,11). The best elucidated transplant-specific exposures include immunosuppressive agents such as glucocorticoids, calcineurin inhibitors (CNIs) and sirolimus, posttransplantation weight gain, and hepatitis C virus (HCV) infection.

Immunosuppression and TAH

**Glucocorticoids.** Glucocorticoids (GC) affect glucose metabolism by increasing hepatic glucose production and by reducing peripheral tissue insulin sensitivity (48–50). In the pre-CNI era, heavy reliance on GC immunosuppression resulted in high rates of NODM (51–53). Supraphysiologic GC dosages are still commonly used in early posttransplantation induction regimens but are thereafter typically either withdrawn or tapered into the physiologic range within weeks. Whether elimination of chronic low-dosage GC (5 mg/d prednisone or equivalent) improves glucose metabolism remains a subject of controversy in the setting of conflicting published data (54–57). Midveld et al. (58) used euglycemic, hyperinsulinemic clamp testing to assess the impact of prednisolone dosage reduction and withdrawal on insulin sensitivity. They found that, whereas dosage reduction in the supraphysiologic range (16 to 9 mg/d) resulted in a 24% improvement in insulin sensitivity, withdrawal of 5 mg/d had no effect. In recent years, the emergence of steroid avoidance and early withdrawal regimens has been enthusiastically embraced by many in the transplant community, on the basis of theoretical potential to limit GC-related complications. Multiple uncontrolled or retrospective investigations have suggested that early GC withdrawal does not jeopardize allograft or patient outcomes (59–62). However, one prospective study that incorporated protocol kidney biopsy at 1 yr after transplantation demonstrated increased fibrosis in the early GC withdrawal group (63). Moreover, preliminary data from a large, multicenter, randomized, double-blind, controlled trial that evaluated early steroid withdrawal suggest that it may not reduce NODM, dyslipidemia, hypertension, or posttransplantation weight gain (64). Overall, available studies suggest that, whereas early steroid withdrawal is safe in the short to mid term, it may not have an impact on long-term glucose metabolism. Final publication of prospective clinical trials that are under way will provide valuable information in this area. For a more extensive update on steroid withdrawal, readers are referred to an excellent recent review (65).

**CNIs.** The CNIs tacrolimus and cyclosporine (CsA) are strongly associated with development of TAH. Mechanistic clinical studies and a large body of preclinical literature demonstrate the critical role of calcineurin in $\beta$ cell growth and function (66). Besides its critical role in T cell activation, calcineurin is expressed in the $\beta$ cell, and CNIs have long been demonstrated to impair the function of cultured $\beta$ cells by impairing insulin gene expression (67–69). This strongly suggests that CNIs contribute to TAH by impairing insulin secretion. Multiple studies have demonstrated high NODM rates in patients who were treated with either CsA or tacrolimus (70–72). Initial efficacy studies that were designed to compare CsA and tacrolimus in kidney recipients demonstrated higher NODM risk with tacrolimus therapy (70,71,73). Subsequent studies of combination immunosuppression with tacrolimus and mycophenolate mofetil documented reduced rates of hyperglycemia when compared with the initial investigations, likely attributable to tacrolimus sparing with more potent adjunctive therapy (74,75). The relatively greater diabetogenicity of tacrolimus is also strongly supported by analysis of USRDS data, which indicated that tacrolimus was associated with a 48 to 66% increase in NODM risk by 2 to 3 yr after transplantation compared with CsA (10,11). Buttressing these studies are several reports that examined the impact of CNIs on glucose metabolism. These investigations indicated that CNIs depress glucose-stimulated insulin secretion within days of exposure (76), that lowering CNI trough concentrations can result in an increased insulin secretory response to glucose (77,78), and that tacrolimus seems to have a more marked effect on insulin secretion than CsA (79). Together, these studies confirm that CNIs promote TAH and implicate impaired insulin secretion as the cause.

<table>
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<th>Table 1. Risk factors for TAH*</th>
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<td>Nonmodifiable age</td>
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<td>family history</td>
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<tr>
<td>Potentially modifiable obesity</td>
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<td>physical inactivity</td>
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*TAH, transplant-associated hyperglycemia.
Sirolimus. The mammalian target of rapamycin is a widely expressed cellular kinase and is a critical mediator of cytokine-induced lymphocyte proliferation (80). Sirolimus is a potent immunosuppressant that inhibits mammalian target of rapamycin and also seems to be diabetogenic (81,82). This is supported by the fact that (1) in initial studies that compared CsA and sirolimus, NODM rates were not reduced in sirolimus-treated patients (83,84); (2) combination CsA and sirolimus has been associated with more NODM than CsA alone (82); and (3) decreases in insulin sensitivity, pancreatic β cell function, and overall glucose tolerance have been demonstrated, either after conversion from CsA to sirolimus or after tacrolimus elimination from a combined tacrolimus/sirolimus regimen (81). Sirolimus-induced hyperglycemia has been attributed to several mechanisms. First, it impairs insulin-mediated suppression of hepatic glucose production (85); second, sirolimus may cause ectopic triglyceride deposition, leading to insulin resistance (86,87); finally, sirolimus may exhibit direct β cell toxicity (88–90). Therefore, although sirolimus is an important therapeutic alternative to CNI, its use is unlikely to diminish the incidence of TAH.

Restoration of Renal Insulin Metabolism

Increased insulin metabolism with restoration of kidney function is a rarely cited but potentially important contributor to TAH. In health, the kidneys contribute significantly to insulin degradation. This effect is underscored by the marked renal arteriovenous decrease in insulin concentration (91,92) and the decreased insulin requirements that are observed clinically as kidney disease progresses in patients with diabetes (93). Therefore, restoration of insulin metabolism is unmasked by a functioning kidney allograft and is likely an important, nonmodifiable factor that increases posttransplantation insulin requirements.

Obesity and Weight Gain

Obesity increases markedly in the first 1 to 2 yr after transplantation because substantial weight gain is typical (28,94–96). Multiple factors contribute to posttransplantation weight gain, including the glucocorticoids and reversal of the uremic state, stimulating appetite and food intake (96). Posttransplantation weight gain likely augments both hepatic and peripheral insulin resistance, increasing insulin secretory demand for normal glucose regulation. Although achieving sustained weight loss is challenging, it is highly effective in enhancing insulin sensitivity (97) and improving glucose metabolism (15,17). It is, therefore, an important therapeutic goal in overweight patients.

HCV Infection

Epidemiologic data have demonstrated strong associations between HCV infection and hyperglycemia in the general population (98). Conversely, other studies have reported an increased rate of HCV infection among patients with type 2 diabetes (99–101). The pathogenic mechanisms that link HCV infection and hyperglycemia remain unclear. Potential mechanisms for viral effects on glucose homeostasis include increased insulin resistance as a result of a postreceptor signaling defect, diminished hepatic glucose uptake and glycogenesis, and a direct cytopathic effect of the virus on β cells in the pancreas (102–105). Growing evidence suggests that a predominant effect of the virus is the induction of insulin resistance, an effect that has been demonstrated in liver transplant recipients, even in those with mild hepatic injury (106).

HCV infection has also been linked to NODM in kidney recipients. In one study, HCV infection was associated with a 33% increase in the risk for NODM (10). Another investigation indicated that the NODM rate was higher among HCV-infected recipients than uninfected patients (40 versus 10%; adjusted odds ratio 5.6) (107). Most of this effect was due to an elevated risk for NODM among HCV-infected patients who were treated with tacrolimus. Whether this propensity to NODM represents exposure to concomitant diabetogenic insults of HCV and tacrolimus versus a more permissive effect of tacrolimus on HCV replication is unknown. Taken together, these studies demonstrate that HCV infection predisposes patients to NODM and that the choice of CNI may have important modifying effects on that risk.

Although IFN may improve glucose tolerance in HCV-infected patients without kidney disease (108), the use of this antiviral therapy is contraindicated after kidney transplantation because of unacceptable rejection risk. However, preliminary evidence suggests that induction of a pretransplantation sustained virologic response by treatment with IFN usually persists after transplantation and may be associated with a reduced incidence of NODM (109,110). Therefore, HCV infection may represent a modifiable risk factor for TAH.

Detection and Management of TAH

General population studies have demonstrated a positive dosage–response relationship between diabetic-range hyperglycemia and the risk of microvascular disease (111–113). Diabetic kidney transplant recipients are highly predisposed to CVD, and the cardiovascular benefits of strict glycemic control may therefore be magnified. Furthermore, improved life expectancy in many of these patients places them at risk for diabetic microvascular complications, including diabetic nephropathy within their transplanted kidney. For these reasons, effective detection and management of hyperglycemia before, during, and after transplantation are necessary.

Pretransplantation Setting

The process of managing and detecting TAH commences during the pretransplantation evaluation and has been described in detail elsewhere (47). During the evaluation process, a thorough medical and family history tailored to assess specifically risk for TAH—and NODM in particular—is required. In conjunction with this, FPG should be tested at the time of initial evaluation and regularly thereafter. Guidelines recommend a 2-h oral glucose tolerance test (OGTT) in patients with normal FPG levels (47). One rationale for this is based on a general population study that indicated that the OGTT is more predictive of CVD risk than FPG testing (4). In addition, a single study in kidney transplant candidates revealed that both fasting and 2-h glucose values on a pretransplantation OGTT were
potential indicators of NODM (14). Therefore, OGTT before transplantation allows identification of candidates who are at high risk for subsequent hyperglycemia-related complications and provides an opportunity both to counsel such patients and to recommend and proactively initiate appropriate lifestyle changes. Because patients may languish on the waiting list, optimal timing or frequency of OGTT testing is unknown. It further goes without saying that the pretransplantation evaluation should include screening for MS and all other cardiovascular risk factors as well. Finally, as alluded to previously, for HCV-infected patients kidney transplant candidates, the pretransplantation period may provide a window of opportunity to attempt to clear the virus with IFN therapy and reduce the risk for NODM after the transplant (109,110) (Table 2).

Immediate Posttransplantation Setting
Abnormal glucose homeostasis is frequently the rule, rather than exception, in the immediate postoperative period, most commonly related to high corticosteroid dosages in the induction therapy setting. One recent study demonstrated that 66% of recipients with no previous diabetes history were hyperglycemic in the first posttransplantation week (8). For patients who receive steroids postoperatively, monitoring with a glucose meter should be performed multiple times daily until dosages have been tapered at least to the equivalent of 20 mg/d prednisone and recipients have demonstrated euglycemia while eating a full, solid diet. ADA glycemic targets for hospitalized, noncritical patients, including premeal values of 90 to 130 mg/dl and postprandial values <180 mg/dl, are based on the association of increased nosocomial infection with hyperglycemia beyond this range (3). Education regarding home glucose monitoring and insulin administration should be initiated as early as possible when postdischarge hyperglycemia seems likely. Our personal practice is to involve the diabetology service in the care of hyperglycemic patients earlier rather than later, particularly when hyperglycemia is likely to be an ongoing issue.

Long-Term Posttransplantation Management
After discharge, frequent FPG measurement is recommended, weekly for the first posttransplantation month, quarterly thereafter until the end of the 12th month, and then on an annual basis (47). Both the ADA and a guidelines committee have recommended principal reliance on FPG measurements, with OGTT performed in patients with IFG (3,47). However, a contemporary observational study in 200 mostly white kidney recipients indicated that FPG was less sensitive than OGTT for diagnosing either NODM or IGT (114). On the basis of this investigation and in keeping with recent recommendations for liver transplant patients, we suggest that a 75-g, 2-h OGTT be performed at 3 to 6 mo after transplantation and annually thereafter in all kidney recipients without diabetes (115). Testing should be repeated in all patients who meet diabetic criteria, to confirm a diagnosis of NODM. NODM should be treated with medical nutrition therapy and, as required, drug therapy to target ADA-defined glycemic goals for patients with diabetes: FPG 90 to 130 mg/dl, 2-h postprandial glucose <180 mg/dl, and HbA1c <7% (3).

Modification of Immunosuppression
As described, several immunosuppressive agents are potentially diabetogenic, albeit to a varying degree. Selection of an appropriate immunosuppressive regimen should involve balancing the risk for rejection versus the potential for hyperglycemia in the kidney transplant recipient. One option, as described, is to taper and withdraw calcineurin inhibitors (CNIs) or corticosteroids in the pretransplantation period to reduce the risk of hyperglycemia. After transplantation, target glycemic goals should be defined and strict adherence to these goals should be maintained with frequent FPG measurement and, if necessary, with OGTT. If initial targets are not met with medical nutrition therapy, then drug therapy to achieve glycemic goals should be initiated. Finally, all risk factors for NODM should be considered and managed with appropriate lifestyle changes and medical therapy where possible. In this way, the risk of NODM can be minimized, and the patient can be maintained in a euglycemic state as long as possible after transplantation.

Table 2. Screening and management of TAH

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<tr>
<th>Screening</th>
<th>Management</th>
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<tr>
<td>Pretransplant</td>
<td>Glycemic goals for all non-ICU scenarios</td>
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<tr>
<td>75-g, 2-h OGTT</td>
<td>FPG 90 to 130 mg/dl</td>
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<tr>
<td></td>
<td>postprandial glucose &lt;180 mg/dl</td>
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<td></td>
<td>HbA1c &lt;7% (long term)</td>
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<td>Peritransplant, in-hospital</td>
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<td>multiple daily blood glucose assessments</td>
<td>insulin</td>
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<td>consider meglitinides</td>
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<td>Long term</td>
<td>medical nutrition therapy/weight loss</td>
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<td>weekly FPG ×4</td>
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<td>FPG every 3 mo thereafter</td>
<td>minimize CNI/steroids</td>
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<td>insulin and oral hypoglycemic agents as needed</td>
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<td></td>
<td>consider TZD, meglitinide, exenatide</td>
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<tr>
<td></td>
<td>ACEI/ARB</td>
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^ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CNI, calcineurin inhibitor; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; ICU, intensive care unit; OGTT, oral glucose tolerance test; TZD, thiazolidinedione
cemia. This frequently dictates that maintenance regimens be individualized on a case-by-case basis. Whenever possible, efforts to minimize overexposure to any one particular immunosuppressant are encouraged as a means of reducing potential for toxicity.

Pharmacologic Therapies
Remarkably little information exists in kidney transplantation regarding conventional glucose-lowering therapies, either oral hypoglycemic agents or traditional insulin regimens. Increasingly and appropriately, the management of pharmacologic therapies for TAH seems to be falling under the domain of diabetologists. Recent years have witnessed the emergence of novel therapies with NODM-treating potential. The first of these newer agents is the thiazolidinediones (TZDs), which promote peripheral insulin sensitivity (116), enhance pancreatic β cell function (16), exert favorable glucose-independent effects on vascular health (117,118), and have displayed modest efficacy in the prevention of cardiovascular events in a high-risk population with diabetes (119). TZDs therefore have potential to treat hyperglycemia effectively and reduce CVD risk after kidney transplantation. Before its withdrawal, the initial TZD that was marketed in the United States, rosiglitazone, was found to be an inducer of the cytochrome p450 isoenzyme CYP3A4 and thereby to lower CsA levels (120). However, administration of the currently available TZDs rosiglitazone and pioglitazone has been assessed in NODM, and both seem to be safe and effective. Although not formally investigated, they seem to have minimal effect on CNI dosing requirements (121–124). TZDs have fluid-retentive properties and need to be considered in the differential diagnosis of edema in the posttransplantation period.

The second novel class of drugs is the meglitinides (repaglinide and nateglinide). These agents promote insulin secretion and have lower hypoglycemic potential than sulfonylureas. One study demonstrated that repaglinide is efficacious and safe in treating NODM in kidney transplant recipients (125).

The final category of glucose-lowering therapies is those that promote activation of the glucagon-like peptide-1 receptor. The first of these agents, Exenatide, is a subcutaneous injection that lowers fasting and postprandial glucose and promotes weight loss through effects on appetite and gastric emptying (126). Although not yet studied in transplant patients, it seems to have great potential. Agents that prevent the degradation of glucagon-like peptide-1 have also been developed; Sitagliptin is one such drug that was recently approved for clinical use, although experience with this agent is minimal (127).

Diabetes Prevention Therapies
The identification of IFG and/or IGT provides an opportunity to use interventions with twin goals of diabetes prevention and restoration of euglycemia. Lifestyle modification through weight loss and exercise has been shown in three prospective clinical trials (15,17,128) to be highly effective for type 2 diabetes prevention and, where assessed, for restoration of euglycemia (15). Current ADA goals for lifestyle intervention include weight loss for overweight individuals and 30 min of daily, low-intensity exercise such as walking (3). Multiple prospective studies have also demonstrated the efficacy of drug intervention in IFG/IGT to prevent progression to overt diabetes using metformin (15), acarbose (19), and, most effectively, TZDs (16,18). However, the ADA does not recommend drug treatment for diabetes prevention, citing unclear cost-effectiveness (3). Although institution of a TZD to reduce CVD risk in patients with prediabetic TAH is appealing, the decision to do so must be considered experimental.

Statins and Lipid-Lowering Therapy
Because statins improve insulin sensitivity, they might be predicted to reduce TAH in kidney recipients. One retrospective analysis of 300 kidney transplant patients revealed that statin treatment was associated with a 70% reduction in the incidence of NODM (129). Although statin treatment for this specific indication needs to be validated, any patient with TAH, dyslipidemia, MS profile, or CVD history should be aggressively treated with lipid-lowering therapy, per current guidelines (130). It is important to appreciate that statin bioavailability is markedly elevated by CsA, an interaction that does not occur with tacrolimus (130). We therefore recommend that starting dosages of statins should be lower in transplant patients who receive CsA as compared with tacrolimus.

Renin-Angiotensin System Blockade
A recent meta-analysis of 10 large studies, five conducted with angiotensin-converting enzyme inhibitors and five with angiotensin receptor blockers, found that the use of renin-angiotensin system blockade was consistently associated with a reduction in the incidence of diabetes (131). This finding has not yet been validated in either transplant recipients or prospective trials in the general population (132). However, given the potential cardiac, BP-lowering, and renoprotective benefits of these two classes of drugs, we advocate an extremely low threshold for considering their use.

Conclusion
Diabetes after transplantation has remained one of the most durable and elusive complications encountered by clinicians who are involved in the care of kidney recipients. With improved immunologic outcomes, the adverse impact of abnormal glucose homeostasis on patient and graft survival has become increasingly magnified. Emerging information indicates that IFG and IGT, prediabetic states that are highly prevalent in kidney recipients, are as ominous as overt diabetes in terms of their CVD risk potential, likely by virtue of their relationship to insulin resistance and MS. The evidence mandates that we take a fresh look at this old problem. Broader definitions, such as TAH, that encompass traditional NODM as well as the prediabetic states are required, stringent diagnostic criteria need to be applied, and management guidelines need to be revised. The pathogenic mechanisms that link risk factors for TAH to graft dysfunction and death in kidney recipients are becoming clearer, providing a rational basis for selecting potential therapies (Figure 4). Future clinical investigation will
need to focus on the effectiveness of these TAH treatment and prevention strategies and the impact of these interventions on the hard clinical end points of graft survival, CVD, and recipient mortality. Only once awareness of the magnitude of TAH is sufficiently heightened and the options for intervention expand will long-term outcomes for kidney transplant recipients finally improve.

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Disclosures
None.

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Figure 4. Pathogenic mechanisms that link risk factors for TAH to an increased risk for graft dysfunction and death in kidney transplant recipients. Red text boxes indicate processes by which TAH leads to demise of graft and patient. Bulleted blue text represents potential therapeutic interventions depicted at sites at which their effects may be optimally mediated. ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; CNI, calcineurin inhibitor; HCV, hepatitis C virus; TZD, thiazolidinedione.


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