New-Onset Diabetes Mellitus in the Kidney Recipient: Diagnosis and Management Strategies

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Advancing care has markedly improved survival after kidney transplantation, leaving patients susceptible to the effects of chronic transplant-associated morbidities. New-onset diabetes mellitus (NODM) is common in kidney recipients, threatening health and longevity by predisposing to microvascular and cardiovascular disease and by reducing graft survival. A strong rationale therefore exists for the aggressive treatment of NODM in kidney recipients to limit these complications. Screening for diabetes should be systematic and should span the pre- and posttransplantation periods. Once NODM is diagnosed in the kidney transplant patient, a comprehensive plan of therapy should be used to achieve treatment targets. As in the general population, treatment includes lifestyle modification and drug therapy as needed, but transplant-specific factors add complexity to the care of kidney recipients. Among these, minimizing immunosuppression-related toxicity without compromising graft outcomes is of paramount importance. Preexisting allograft functional impairment and the potential for significant interactions with immunosuppressive agents mandate that the expanding armamentarium of hypoglycemic agents be used with care. A team-oriented treatment approach that capitalizes on the collective expertise of transplant physicians, diabetologists, nurse-educators, and dieticians will optimize both glycemic control and the overall health of hyperglycemic kidney recipients.

Clin J Am Soc Nephrol 3: S38–S48, 2008. doi: 10.2215/CJN.02650707

Immunosuppression advances have dramatically improved kidney transplant outcomes (1). Chronic transplant-associated morbidities have consequently assumed greater importance in determining posttransplantation life expectancy and quality of life. We previously proposed the term "transplant-associated hyperglycemia" (TAH) to encompass abnormal glucose homeostasis developing for the first time after transplantation, including new-onset diabetes mellitus (NODM), impaired fasting glucose (IFG), and impaired glucose tolerance (IGT; Table 1). TAH is a common comorbidity that has been associated with graft failure and cardiovascular risk in kidney recipients (2,3). Furthermore, diabetes-related microvascular complications may develop within the lifetime of recipients who have NODM. Effective management of hyperglycemia is therefore fundamental to optimizing posttransplantation care. We and others (4,5) have reviewed the state of knowledge regarding the epidemiology, pathogenesis, and health implications of TAH. This review more specifically focuses on current approaches to hyperglycemia detection and the use of expanding therapeutic options for achieving NODM treatment goals in kidney recipients.

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Rationale for Treating NODM

Epidemiologic (6,7) and general population analyses have established that diabetes promotes cardiovascular disease and microvascular complications, including retinopathy and neuropathy (8–10). In the absence of contradictory evidence, it is presumed that these risks are shared by kidney recipients with NODM. This is underscored by transplant recipient studies associating NODM with inferior graft and patient survival (3,11,12), largely attributable to cardiovascular and infectious complications (2,3). Although controlled intervention trials are lacking in kidney recipients, general population studies demonstrate that aggressive treatment of hyperglycemia reduces diabetic microvascular complications (8–10,13) and may decrease cardiovascular events (14). These data collectively validate the notion that treatment of NODM in kidney recipients is an important goal.

Pathogenesis of TAH

A detailed understanding of TAH pathogenesis underlies effective intervention and has been extensively reviewed (4,5). Briefly, hyperglycemia results from imbalance between insulin production and target tissue insulin demand (15). In the transplant setting, this disparity may occur as a result of insulin resistance, increased insulin metabolism, or diminished insulin secretion (Figure 1). Preexisting TAH risk factors that antedate the transplant may be nonmodifiable (*e.g.*, advancing age, male gender, nonwhite ethnicity) or modifiable (*e.g.*, obesity, hepatitis C virus [HCV] infection) (3,15,16). These characteristics

ISSN: 1555-9041/–0038

Table 1. Definitions of hyperglycemia in kidney recipients[a]

Blood Glucose Measurement	Terminology
FPG (mg/dl)	Normal
<100	IFG
100 to 125	NODM
>126	
2-h plasma glucose after OGTT (mg/dl)	
<140	Normal
140 to 199	IGT
>200	NODM

[a]Adapted from American Diabetes Association criteria. FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NODM, new-onset diabetes mellitus; OGTT, oral glucose tolerance test.

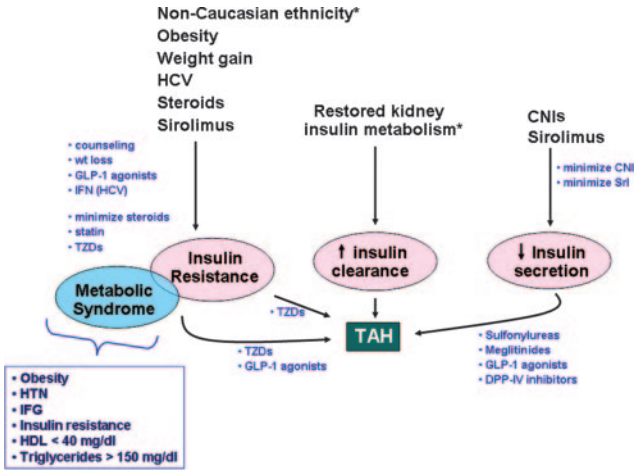

Figure 1. Illustration of the pathogenic mechanisms that lead to transplant-associated hyperglycemia (TAH) in kidney recipients. Bulleted blue text represents potential therapeutic interventions depicted at sites where their effects may be optimally mediated. *Nonmodifiable risk factors for TAH. CNIs, calcineurin inhibitors; DPP-IV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; HTN, hypertension; IFG, impaired fasting glucose; Srl, sirolimus; TZDs, thiazolidinediones.

reflect either inherited or acquired defects in insulin sensitivity and β cell function that contribute to hyperglycemia (Table 2). In addition, whereas normal kidneys contribute significantly to insulin degradation, decreased insulin requirements are observed as kidney disease progresses (17); restoration of insulin metabolism is unmasked by a functioning allograft and is likely an important, nonmodifiable factor that increases posttransplantation insulin requirements. TAH is most prevalent in the first few posttransplantation months (17), reflecting superimposition of transplant-specific factors (*e.g.*, weight gain, diabetogenic immunosuppressive therapies) on the baseline metabolic milieu of predisposed individuals (3,18). These transplant-specific factors, as well as the modifiable preexisting risk factors, are potential targets for treatment or prevention of hyperglycemia (4), complementing pharmacologic approaches to increasing insulin delivery and decreasing demand.

Metabolic Syndrome and TAH

The metabolic syndrome comprises a constellation of modifiable cardiovascular risk factors that cluster together sharing systemic insulin resistance as a root cause (19). Metabolic syndrome predisposes to systemic inflammation and cardiovascular disease (20,21), and its components (hyperglycemia, hypertension, dyslipidemia, and central obesity) are risk factors for progressive kidney disease (22–25).

After kidney transplantation, metabolic syndrome prevalence increases in conjunction with weight gain (26,27) and together with obesity has been associated with NODM, as well as inferior patient and graft outcomes (28,29). We therefore recommend that screening for diabetes and the metabolic syndrome be conducted in concert. Moreover, the pivotal pathogenic role of insulin resistance in metabolic syndrome should guide lifestyle intervention and promote investigation of pharmacotherapies that enhance insulin sensitivity and weight loss in transplant recipients.

Detection and Management of Diabetes in the Transplant Setting

Epidemiologic studies indicate that approximately 6% of candidates awaiting kidney transplantation develop diabetes annually (18). This prevalence increases two- to three-fold in the first posttransplantation year and returns to baseline rate thereafter (3,18). A recent prospective study (30) that investigated TAH in kidney recipients demonstrated that almost 30% of patients developed NODM or IFG within the first 6 mo after transplantation. This high risk for early posttransplantation hyperglycemia mandates vigilant screening during this period; however, cumulatively, the occurrence of diabetes is great even beyond this window. This knowledge obligates a methodical approach to diabetes screening and management that begins with a patient's initial pretransplantation visit, continuing

Table 2. Risk factors for TAH[a]

Preexisting	Transplant Specific
Nonmodifiable	
age	restored graft insulin metabolism
gender	
race/ethnicity	
family history	
Potentially modifiable	
obesity	weight gain
physical inactivity	glucocorticoids
hepatitis C	CNIs
	sirolimus

[a]CNIs, calcineurin inhibitors; TAH, transplant-associated hyperglycemia.

through the immediate postoperative period into the long term (Table 3).

Pretransplantation Screening

As detailed elsewhere (16), diabetes screening comprising risk factor assessment and measurement of fasting plasma glucose (FPG) and glucose tolerance should commence during pretransplantation evaluation. A thorough medical and family history to assess NODM risk is required and may influence decisions regarding when and how to perform screening tests. FPG should be tested at initial evaluation and regularly thereafter. We concur with recommendations that a 2-h oral glucose tolerance test (OGTT) be performed for patients who are on the waiting list and have normal FPG levels (16), for several reasons: (*1*) to detect individuals with isolated postprandial hyperglycemia, (*2*) to identify otherwise normoglycemic patients who have preexisting diabetes that is masked by diminished insulin metabolism associated with kidney dysfunction, and (*3*) higher 2-h glucose values are predictive of posttransplantation NODM (31) and may also reflect cardiovascular risk more accurately than FPG measurements (32). Although optimal timing and frequency of pretransplantation OGTT testing is undefined, the annual 6% diabetes incidence suggests that testing every 1 to 2 yr is acceptable. Positive screening tests should be confirmed, and patients with diabetes should be treated. IFG and IGT are prediabetic states, and their identification provides an opportunity to counsel patients and to initiate appropriate lifestyle changes (33).

Finally, screening and management of two additional risk factors for NODM in kidney recipients should be commenced during pretransplantation evaluation. First, because metabolic syndrome is common in patients with chronic kidney disease (34), screening for its components should be performed (19) to permit intervention as appropriate. Second, for HCV-infected candidates, the pretransplantation setting provides an opportunity to attempt viral clearance with interferon therapy. Successful elimination of HCV before transplantation may reduce posttransplantation NODM risk (35,36).

Immediate Posttransplantation Setting

Hyperglycemia is common immediately after transplantation, typically related to surgical stress and high glucocorticoid dosing (2). This frequently resolves as glucocorticoids are tapered, but persistent hyperglycemia 1 wk after transplantation is predictive of long-term glucose dysregulation (2). Handheld glucose meter monitoring should be performed multiple times daily to survey fasting and 2-h glucose concentrations until glucocorticoid dosages are <20 mg/d prednisone or equivalent and recipients have demonstrated euglycemia while eating a full diet. American Diabetes Association glycemic targets for hospitalized noncritical patients include premeal values of 90 to 130 mg/dl and postprandial values <180 mg/dl, based on association of hyperglycemia beyond this range with increased nosocomial infection rates (37).

The initial treatment approach (Table 3) involves ensuring that the diet is diabetic-appropriate. Avoidance of unnecessary

Table 3. Screening and treatment of TAH[a]

Parameter	Before Transplantation	Perioperatively	After Discharge
Screening	75 g OGTT every 1 to 2 yr	Multiple daily blood glucose assessments	Weekly FPG for first month after transplantation
	Test for metabolic syndrome components every year		FPG every 4 wk thereafter until 6 mo after transplantation
	HCV testing		FPG every 8 wk between 6 and 12 mo after transplantation
			FPG at least annually after the first posttransplantation year
			75 g OGTT at 3 to 6 mo
			Annual OGTT after first year
Treatment[b]		Limit intravenous/oral glucose intake	Medical nutrition therapy
		Insulin	Daily moderate exercise
		Consider meglitinides	Weight loss
			Minimize CNI/steroids
			Insulin/oral hypoglycemic agents as needed
			TZDs
			meglitinides
			exenatide
			Lipid management

[a]TZD, thiazolidinediones.
[b]Glycemic goals are those of American Diabetes Association (35): FPG 90 to 130 mg/dl; 2-h postprandial glucose <180 mg/dl; glycosylated hemoglobin (HbA_{1c}) < 7%.

infusion of glucose-containing fluids is recommended, although this has to be balanced against the risk of administering alternative solutions such as normal saline that may exacerbate hypertension and volume overload. A full, solid diet should be limited to 130 to 180 g of carbohydrate and 1800 to 2000 total kcal/d for most (38), and concentrated sweets should be eliminated. Despite the plethora of agents now available for treating hyperglycemia, exogenous insulin remains the treatment mainstay immediately after transplantation. If very high insulin requirements are apparent, then we have a low threshold for starting an insulin infusion because it may limit postoperative morbidity and because timely glycemic control can be difficult to achieve with subcutaneous insulin (37,39,40). Otherwise, an insulin "sliding scale" can be used whereby rapid-acting insulin is dosed every 6 h according to the glucose level. Total insulin requirements estimated from the cumulative 24-h insulin dosage required can be subsequently administered in a standing regimen divided between rapid-acting insulin given with meals and long-acting basal insulin. Typically, one third to one half of total is given as basal insulin, but decisions are individualized taking into account the dynamic changes in glucose homeostasis that occur early after transplantation. If 24-h insulin requirements are <15 to 20 U, then conversion to an insulin secretagogue (sulfonylurea or meglitinide) can be considered. Nonsecretagogue oral hypoglycemic agents are rarely started at this early time point. Education regarding diet, glucose monitoring, and insulin administration should be initiated as early as possible if postdischarge hyperglycemia seems likely. Because optimal posttransplantation glycemic control is often complex and long-term management frequently required, collaboration with the diabetology service is strongly advisable.

Long-Term Posttransplantation Detection and Management

Periodic diabetes screening is a routine facet of posttransplantation care for patients who are not hyperglycemic at discharge, although the intensity of surveillance declines with time (Table 3). International consensus guidelines have proposed screening patients weekly for the first month after transplantation, then every 3 mo thereafter (16). In light of the high risk for NODM within the first 3 to 6 mo after transplantation (2,3,18,30), we recommend more aggressive screening: FPG measurement weekly for the first posttransplantation month, at least monthly until month 6, at least bimonthly between months 6 to 12, and annually thereafter. We again favor routine use of the OGTT after transplantation. This recommendation is supported by a recent observational study in which OGTT was found to be more sensitive than FPG for diagnosing either NODM or IGT (41). Initial OGTT testing should be performed at 3 to 6 mo after transplantation and annually thereafter. If NODM is suggested and confirmed by repeat testing, then treatment should be started to target American Diabetes Association–defined goals for diabetes: FPG 90 to 130 mg/dl, 2-h postprandial glucose <180 mg/dl, and glycosylated hemoglobin (HbA_{1c}) <7% (37). Long-term NODM management is multidimensional and may involve (*1*) lifestyle intervention, (*2*) immunosuppression modification, and (*3*) effective use of diabetes therapies.

Lifestyle Intervention. Medical nutrition therapy describes the overall nutritional approach to preventing and managing diabetes and has been recently reviewed (38). Two medical nutrition therapy goals that contribute specifically to glycemic management are (*1*) to moderate overall carbohydrate intake, thereby lowering dietary glycemic burden, and (*2*) to increase insulin sensitivity by promoting moderate weight loss in overweight individuals (38). Studies have demonstrated a 1 to 2% decrease in HbA_{1c} with medical nutrition therapy implementation (42,43).

The principle dietary carbohydrate modification objective is to reduce overall carbohydrate intake to 130 to 180 g/d. A secondary goal is the favoring of carbohydrates with a lower glycemic index that may further facilitate glucose control (44,45). Calorie reduction is recommended in overweight (body mass index 25 to ≤30 kg/m^2) or obese (body mass index ≥30 kg/m^2) patients to promote weight loss. Subsequent weight maintenance is challenging, and many patients return to baseline weight. Thirty minutes of daily low-intensity exercise, such as walking, facilitates weight loss and promotes insulin sensitivity and should be specifically prescribed as a concrete intervention (33,38). Medical nutrition therapy education is specialized and time consuming, and referral to an experienced dietician is recommended (38). We advocate medical nutrition therapy for all recipients who are at risk for NODM to promote benefit to glucose regulation, hyperlipidemia (46), and hypertension (47,48).

Immunosuppression Modification. Several immunosuppressants, including glucocorticoids, calcineurin inhibitors (CNIs) cyclosporine and tacrolimus, and sirolimus are potentially diabetogenic (reviewed in reference [4]). Immunosuppression modification to prevent or mitigate NODM can take the form of minimization, withdrawal, or conversion from one drug or regimen to another, less diabetogenic one.

Glucocorticoids. Glucocorticoids typically either are tapered rapidly to a dosage that is unlikely to affect glucose homeostasis (49) or are discontinued altogether. Emerging data suggest that although early steroid withdrawal may be safe from an immunosuppression standpoint in the short to midterm, it may not affect long-term glucose metabolism; however, final publication of clinical trials in this area is awaited.

CNIs. CNIs, especially tacrolimus at present, form the backbone of most maintenance immunosuppressive regimens. Initial efficacy studies that compared cyclosporine and tacrolimus in kidney recipients demonstrated higher NODM risk with tacrolimus therapy (50,51). These findings were recently confirmed by the Diabetes Incidence after Renal Transplantation (DIRECT) trial, a randomized, prospective study in which the composite of NODM and IFG within the first 6 mo after transplantation was the primary safety end point analyzed (30). In that study, which used sequential OGTT, abnormal glucose homeostasis developed within 6 mo after transplant in 26% and 33.6% of cyclosporine- and tacrolimus-treated patients, respectively, with no difference in efficacy between the two drugs. NODM was more often transient among cyclosporine-treated recipients, with only 8.9% of patients requiring diabetes therapy at 6 mo after transplantation, compared with 16.8% among

the tacrolimus-treated cohort. Study limitations include a lack of standardization of steroid dosage and open-label design. That the majority of the patients were white additionally limits applicability to other populations, from either an efficacy or adverse events stand point. The reduced diabetogenicity associated with cyclosporine does, however, raise the possibility that conversion to this CNI in tacrolimus-treated patients with NODM could successfully eliminate hyperglycemia. Although supported by small series and anecdotes, this approach is not yet validated in large trials. This practice has to be balanced further against the superior lipid, BP, and kidney function profile observed with tacrolimus as compared with cyclosporine (52).

Minimization and Withdrawal Regimens. As far as minimization regimens are concerned, use of mycophenolate mofetil as an adjunctive agent spares tacrolimus exposure and may reduce the incidence of hyperglycemia (53–55). Efforts to spare CNI exposure with sirolimus, in contrast, have been associated with decreased insulin sensitivity and pancreatic β cell function, resulting in exacerbated glucose intolerance (56). Although avoidance of toxic therapies represents the holy grail of immunosuppression management, we do not advocate withdrawal of CNIs from maintenance regimens, on the basis of increased risk for graft dysfunction and immunologic injury. In summary, an optimal maintenance regimen should balance risk for rejection as well as long-term cardiovascular disease *versus* the potential for permanent hyperglycemia.

Antiviral Therapies. Virus infections have been associated with diabetes in the general population (57). HCV infection is a well-established diabetes risk factor. Pretransplantation administration of interferon may successfully clear viremia and reduce the risk for development of NODM after transplantation (35,36). Similarly, a recent study suggested that asymptomatic cytomegalovirus infection may impair insulin release and provoke diabetes. The impact of either a prophylactic or preemptive antiviral approach remains to be ascertained (58).

Pharmacologic Therapies. Drug treatment options for TAH are expanding, although safety and efficacy data for most agents are limited in transplant populations. Other than insulin, most have at least theoretical potential to interact with immunosuppressants through either shared metabolic pathways or effects on gastric motility. We therefore recommend careful monitoring of FPG and potential adverse effects in the first weeks after initiation of any noninsulin agents. Generally, combination therapy with agents from different classes is more effective than monotherapy. An exception is the sulfonylureas and meglitinides, which act through a related mechanism and are not used together (Table 4).

Insulin. Modern insulin regimens use once-daily long-acting agents such as glargine or detemir to provide basal glycemic control and rapid-acting insulin analogues such as aspart, lispro, and glulisine to provide postprandial control (59). Newer insulins are favored over their older counterparts because of greater ease in achieving glycemic targets with less hypoglycemic potential. Adequacy of basal insulin dosing is demonstrated by FPG measurements, and prandial control is indicated by glucose excursion from just before eating to 90 to 120 min after a meal. Highly portable insulin pens facilitate administration, and some patients may be candidates for insulin pump therapy, providing even greater flexibility. Because the kidney plays an important role in insulin metabolism (60,61), perturbations in allograft function may necessitate changes in insulin dosage. Insulin is not known to interact significantly with currently used immunosuppression. Despite the complexity of its use, insulin should be initiated sooner rather than later if judgment suggests that other agents will be inadequate.

Sulfonylureas. Sulfonylureas directly stimulate insulin secretion and lower both fasting and postprandial glucose concentrations. Second-generation sulfonylureas (*e.g.*, glipizide, glyburide, glimepiride) have largely replaced the original agents. Glipizide is favored when kidney function is impaired, because it is almost entirely metabolized by the liver (62). Glipizide is a reasonable option for NODM if hyperglycemia is not severe and can be introduced at a low dosage and up-titrated every 3 to 4 wk as needed. Because the principal adverse effect of sulfonylureas is hypoglycemia, they should be used with caution, especially with deteriorating allograft function.

Meglitinides. The meglitinides repaglinide and nateglinide are insulin secretagogues with a rapid onset and short duration of action. They can be taken immediately before meals and may have less hypoglycemic potential than sulfonylureas (63). Repaglinide lowers fasting and postprandial glucose and has been demonstrated to be safe and efficacious in kidney recipients with NODM (64). Our personal experience is that repaglinide is useful in treating modest postprandial hyperglycemia. Both repaglinide and nateglinide are hepatically metabolized and can be used with any level of kidney function (package inserts of Prandin [Novo Nordisk Inc., Princeton, NJ; 65] and Starlix [Novartis Pharmaceuticals, East Hanover, NJ; 66]).

Thiazolidinediones. Thiazolidinediones (TZDs) promote peripheral insulin sensitivity and are widely used for type 2 diabetes treatment (67). TZDs may exert favorable glucose-independent effects on vascular health (68–70), and one, pioglitazone, has displayed modest efficacy in the prevention of cardiovascular events in a population with diabetes (71). The initial TZD marketed and subsequently withdrawn in the United States, troglitazone, raised concerns in the transplant population because it altered cyclosporine metabolism and rarely caused severe liver injury (72,73). The currently available TZDs rosiglitazone and pioglitazone are not associated with significant liver injury, have no apparent significant interaction with CNIs, and seem to be safe and effective for treating NODM in organ recipients (74–77).

TZDs promote fluid retention and are contraindicated in patients with heart failure or refractory edema. TZDs are metabolized *via* the liver, and dosing adjustment is not required for kidney allograft dysfunction (package inserts for Avandia [GlaxoSmithKline, Philadelphia, PA; 78] and Actos [Takeda Pharmaceuticals, Lincolnshire, IL; 79]). Although a recent meta-analysis suggested that rosiglitazone may promote cardiovascular events (80), inherent weaknesses in design make this study difficult to interpret (81). This finding is further not

Table 4. Noninsulin drug therapy for NODM[a]

Class	Principle Mechanism of Action	Example	Effect on HbA_{1c}	Adverse Effects	Metabolism/ Elimination	Altered Dosing in CKD
Sulfonylureas	Insulin secretagogue	Glipizide Glyburide Glimepiride	−1.0 to −2.0%	Hypoglycemia	Major: Hepatic	No
Meglitinides	Insulin secretagogue	Repaglinide Nateglinide	−0.6%	Hypoglycemia	Major: CYP2C8 and 3A4	CrCl >40 ml/min: No CrCl <40 ml/min: Gradual introduction
Biguanides	Decrease hepatic glucose production	Metformin	−1.0 to −1.7%	Nausea Lactic acidosis (extremely rare)	Major: Renal tubular secretion	Avoid with more severe levels of kidney dysfunction
TZD	Increase insulin sensitivity	Pioglitazone Rosiglitazone	−1.0 to −1.9%	Weight gain Fluid retention	Major: CYP2C8 Minor: CYP3A4	No
α-Glucosidase inhibitors	Decrease intestinal glucose absorption	Acarbose	−0.3 to −0.6%	Nausea Flatulence	Major: Fecal Minor: Renal	Not recommended if creatinine >2 mg/dl
GLP-1 receptor agonists	Stimulates glucose mediated insulin secretion Inhibits glucagon Induces weight loss due to delayed gastric emptying and appetite suppression	Exenatide	−0.4 to −0.8%	Nausea, other gastrointestinal	Major: Renal	Not recommended if CrCl ≤30 ml/min
DPP-IV inhibitors	Increases GLP-1	Sitagliptin	−0.5%	Minimal	Major: Renal Minor: CYP3A4, 2C8	Dosage reduction

[a]CKD, chronic kidney disease; CrCl, creatinine clearance; DPP-IV, dipeptidyl peptidase-IV; GLP-1, glucagon-like peptide-1.

supported by a prospective clinical trial in a prediabetic population (82). For now, pioglitazone is preferred on the basis of once-daily dosing frequency, a more favorable lipid effect (83,84), and a large, published clinical trial suggesting modest potential cardiovascular benefits (71).

Agents that Promote Glucagon-Like Peptide-1 Receptor Activation. Glucagon-like peptide-1 (GLP-1) is a natural hormone that facilitates postprandial nutrient disposal. GLP-1 stimulates pancreatic β cell insulin secretion in a glucose-dependent manner and has minimal hypoglycemic potential. GLP-1 also slows gastric emptying and suppresses appetite (85). GLP-1 is degraded by dipeptidyl peptidase-IV (DPP-IV) (86) and has a very short half-life; therefore, synthetic GLP-1 receptor agonists that are resistant to DPP-IV and small molecule DPP-IV inhibitors have been designed to promote GLP-1 receptor activation (85).

Exenatide is the only GLP-1 receptor agonist currently available for clinical use. It is used as a twice-daily premeal injection and has demonstrated the beneficial effects of native GLP-1 (87). It has been shown to blunt postprandial glucose excursions and durably lowers HbA_{1c} in patients with diabetes (88–90). Another striking benefit of exenatide is substantial weight loss attributed to appetite suppression, averaging 4 to 5 kg during 18 mo of treatment in one trial (91,92). No reports describing use of this agent in transplant recipients has yet emerged. Anecdotally, several of our own patients have and continue to be successfully treated with it. Because exenatide is renally metabolized, it should not be used if creatinine clearance is <30 ml/min (Eli-Lilly package insert). Given the effect of exenatide on gastric emptying and weight loss, immunosuppressive dosing may require adjustment and should be carefully monitored. The most common adverse effect of exenatide is nausea, which is usually transient (88–90).

The DPP-IV inhibitor sitagliptin has recently been approved for clinical use in the United States. When taken as a once-daily pill, it effectively raises blood concentrations of endogenous active GLP-1 (93), lowers fasting and postprandial blood glucose concentrations, and decreases HbA_{1c} by 0.6 to 0.8% when used as monotherapy (94) or when added to metformin or a TZD (Januvia package insert [Merck and Co. Inc., Whitehouse Station, NJ; 95]) (93). Advantages over exenatide include ease of administration and a milder adverse effect profile, although sitagliptin does not promote weight loss. Dosage reduction is required for kidney dysfunction, and few data are available concerning potential drug interactions. Because available clinical information is limited, we recommend careful monitoring of kidney recipients and their immunosuppression dosing requirements if sitagliptin is used. Vildagliptin, a second DPP-IV inhibitor with similar properties (96,97), may become available in the near future.

Biguanides. Metformin is the only biguanide available in the United States. It reduces hepatic glucose production and is effective in the general type 2 diabetes population for both control of hyperglycemia and weight loss or stabilization (10,33). Metformin is largely cleared by renal tubular secretion, and exposure increases in the setting of renal insufficiency (Metformin package insert). Because metformin has extremely rarely been associated with lactic acidosis (98,99), we recommend avoiding its use in kidney recipients with more severe degrees of kidney dysfunction.

Conclusions

Optimizing glycemic control in kidney recipients with NODM is an important goal in long-term posttransplantation care. General population studies provide strong evidence that improved glucose regulation decreases the risk for microvascular disease and, potentially, cardiovascular disease. The demonstrated association between NODM and adverse recipient outcomes suggests that treatment of hyperglycemia may enhance patient and graft survival; therefore, screening for glucose dysregulation should be systematic and should be implemented in all phases of the transplant process, commencing at evaluation. Efforts should be made to diminish the impact of transplantation on glucose homeostasis by limiting posttransplantation weight gain and minimizing exposure to diabetogenic immunosuppression while simultaneously preserving efficacy. Lifestyle intervention should promote dietary carbohydrate moderation and exercise in all recipients and weight loss in those who are overweight. An expanding battery of pharmacologic agents can be used to reach glycemic targets. Many of these agents require dosage adjustment for kidney dysfunction, and several have potential to alter immunosuppressant pharmacokinetics, underscoring the need for caution. Finally, NODM is often present as a component of the metabolic syndrome, and metabolic syndrome screening and treatment are an integral part of NODM care. A multifaceted and team-oriented approach to treatment that capitalizes on the skills of physicians, nurse-educators, and nutritionists will have the greatest chance of successfully and safely diagnosing and treating NODM, thereby optimizing the health of affected recipients.

Acknowledgments

Preparation of this manuscript was supported by a National Institutes of Health K12 (RR017625-03) Career Development Award (to M.F.C.).

Disclosures

R.D.B. receives grant support from Novartis and Roche and has consulted for Novartis, Roche, Merck, and CSL Behring.

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