INTRODUCTION

The proportion of organ recipients with diabetes mellitus at the time of transplantation varies widely and depends on the primary disease necessitating transplantation (Table 1).\textsuperscript{1,2} For example, diabetes is the most common cause of renal failure requiring transplantation, whereas peripheral blood stem cell transplantation is usually performed in individuals with diseases unrelated to preexisting diabetes mellitus. Approximately 2% to 50% of transplant recipients develop posttransplantation diabetes mellitus (PTDM) (Table 2);\textsuperscript{3,6–14} this percentage largely depends on the type of transplant and the definition of diabetes mellitus and PTDM.

There is a general consensus that the definition for diagnoses of abnormalities of blood glucose concentrations after transplantation should be the same as the current American Diabetes Association (ADA) definitions of diabetes mellitus, impaired glucose tolerance, and impaired fasting glucose (Table 3).\textsuperscript{7} Because there is no clear definition for PTDM, this term has been used to describe patients with recognized preexisting diabetes mellitus, previously unrecognized diabetes mellitus, and new-onset diabetes after transplantation. For the purposes of this review, PTDM describes patients who develop new-onset diabetes after transplantation. However, data reported herein are derived from sources using different definitions of PTDM. Whereas the management of hyperglycemia associated with new-onset diabetes after transplantation and preexisting diabetes are managed similarly, the former does not necessarily require interval screening for complications.

Studies have shown that preexisting diabetes mellitus is associated with adverse outcomes in recipients of heart and kidney transplantsations.\textsuperscript{1,15} In pancreas transplantation, although the purpose is to cure diabetes, there is potential risk for allograft failure leading to continuing type 1 diabetes. Diabetes may also persist or develop after pancreas transplantation in the presence of functioning allograft, possibly due to insulin resistance associated with increased weight and high-dose glucocorticoid use.\textsuperscript{6} PTDM is associated with complications, including risk for infection, cardiovascular events, graft failure, and death (Table 4).\textsuperscript{1,3,6–10,13,15–18} In one study, as many as 50% of patients with PTDM developed kidney graft failure within 4 years as opposed to 18% of patients without diabetes.\textsuperscript{19} Overall, the incidence of new-onset diabetes after transplantation appears to be declining.\textsuperscript{1,19} In addition, the associated long-term poor outcomes are also decreasing.\textsuperscript{1,9}

PRETRANSPLANT ASSESSMENT

• What should be included in the pretransplant assessment?

A careful assessment of the patient before transplantation can reduce the risk of new-onset diabetes after transplantation.\textsuperscript{7} The patient’s glycemic status should be assessed before transplantation by measuring fasting plasma glucose concentrations; this will help differentiate between a preexisting abnormality in glucose control and new-onset diabetes after transplantation.\textsuperscript{20} Patients should also be screened for risk factors for diabetes, including obesity, ethnicity predisposed to developing diabetes (eg, African American, Native American), family history of diabetes, infections (eg, hepatitis C), and use of high-dose glucocorticoids or certain immunosuppressive agents (eg, tacrolimus) (Table 5).\textsuperscript{8,10,13,19} Based on the presence or absence of risk factors, immunosuppressive therapy can be individualized. Previous history of type 2 diabetes, impaired fasting glucose, and impaired glucose tolerance should be elucidated, since patients with these metabolic abnormalities are at much higher risk of worsening hyperglycemia after transplantation with use of high-dose glucocorticoids. Patients undergoing transplantation may have received a blood transfusion and may have bleeding or hemolysis for various reasons. In this case, fructosamine may be a more reliable marker of previous glycemic control, since hemoglobin A\textsubscript{1c} values will be distorted by an altered lifespan of red blood cells.
In a systematic review, Montori et al. found that immunosuppression, specifically with high-dose glucocorticoids, cyclosporine, and/or tacrolimus, was strongly associated with the development of PTDM. These findings have been confirmed by subsequent studies. What role do specific immunosuppressive agents play in the development of PTDM?

**GLUCOCORTICOIDS**

**Increased Appetite and Weight Gain**

Excess glucocorticoid intake is associated with truncal obesity and an apparent removal of fat from the periphery (limbs). It was previously believed that treatment with corticosteroids was associated with an increase in appetite and dose-dependent weight gain; however, data on this issue are sparse. In a small group of healthy volunteers, use of short-term (7 days) systemic glucocorticoids was associated with increased food consumption. Other studies have shown that glucocorticoid use is associated with weight gain, although weight gain was not necessarily more than what was seen in placebo-treated patients in double-blind randomized trials. As demonstrated by a retrospective review of medical charts of patients who underwent renal transplantation, amount of weight gain depends on presteroid body mass index, with patients with a lower body mass index prior to steroid administration experiencing more weight gain. However, similar weight gain was observed in a comparable population not on glucocorticoids.

**Insulin Resistance and Effects on Adipocytes and Fat Metabolism**

Seminal studies have shown that glucocorticoids induce both hepatic and extrahepatic insulin resistance in humans (Figure). Animal studies have shown that glucocorticoids induce insulin resistance irrespective of hyperglycemia. Glucose intolerance and insulin resistance develop quickly upon intake of glucocorticoids. Glucose tolerance becomes impaired even with a single dose of dexamethasone, and within 2 days of dexamethasone use, marked insulin resistance ensues. Glucocorticoids increase fasting and postprandial free fatty acid concentrations and are associated with increased lipid oxidation and reduced glucose oxidation.

**Islet Function in Relation to Glucocorticoid Intake**

Glucocorticoid use is associated with increased fasting and postprandial insulin and glucagon concentrations. If compensatory insulin release is adequate for the prevailing glucose concentration, hyperglycemia does not develop because higher insulin adequately

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**Table 1. Proportion of Patients with Diabetes Mellitus Before Transplantation**

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Patients with Diabetes Before Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>22%</td>
</tr>
<tr>
<td>Kidney</td>
<td>~25%–30%</td>
</tr>
<tr>
<td>Lung</td>
<td>30%</td>
</tr>
<tr>
<td>Liver</td>
<td>~14%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>~7%</td>
</tr>
</tbody>
</table>

Data from references 1–5.

*Percentage primarily in patients with cystic fibrosis.

**Table 2. Proportion of Patients with Diabetes Mellitus After Transplantation**

<table>
<thead>
<tr>
<th>Type of Transplant</th>
<th>Patients with Diabetes After Transplantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>15%–40%</td>
</tr>
<tr>
<td>Kidney</td>
<td>2%–50%</td>
</tr>
<tr>
<td>Lung</td>
<td>20%–30%</td>
</tr>
<tr>
<td>Liver</td>
<td>7%–30%</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Data from references 3, 6–14.

**Table 3. Definitions**

Normal fasting plasma glucose (FPG): < 100 mg/dL
Normal glucose tolerance: 2-hr postload glucose < 140 mg/dL
Impaired fasting glucose: 100–125 mg/dL
Impaired glucose tolerance: 2-hr postload glucose 140–199 mg/dL
Diabetes mellitus: FPG ≥ 126 mg/dL or symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL or 2-hr postload glucose ≥ 200 mg/dL during an oral glucose tolerance test

NOTE: Fasting is defined as no caloric intake for at least 8 hr.
*The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.
† In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.
‡ Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
suppresses glucose production and stimulates glucose utilization.\textsuperscript{39,90,32,33,36–38} Obesity reduces appropriate insulin secretory response to insulin resistance induced by glucocorticoids.\textsuperscript{39}

**CALCINEURIN INHIBITORS**

The general consensus is that calcineurin inhibitors adversely affect glucose metabolism, presumably via destruction/impairment of pancreatic beta cell function.\textsuperscript{40–44} The development of PTDM is more strongly associated with tacrolimus as compared with cyclosporine.\textsuperscript{10,45} Tacrolimus use is associated with impaired beta cell function, as evidenced by decreased pancreatic insulin content, defects in mRNA transcription, and destruction of beta cells.\textsuperscript{40–43} Insulin gene expression is reduced in islets exposed to cyclosporine A.\textsuperscript{46} Of note, tacrolimus and cyclosporine A have not been consistently shown to induce insulin resistance.

**MAMMALIAN TARGET OF RAPAMYCIN INHIBITOR (mTOR)**

The mTOR pathway is critical for beta cell growth and proliferation and can be affected by nutrients (eg, glucose, amino acids) and some medications for diabetes.\textsuperscript{47,48} Studies have shown a relationship between sirolimus and the development of diabetes;\textsuperscript{49,50} however, most studies do not account for concomitant use of agents such as cyclosporine A and tacrolimus. Sirolimus impairs in vivo proliferation of beta cells.\textsuperscript{51} Inhibition of mTOR can increase or decrease insulin resistance, based on nutritional status.\textsuperscript{52} Studies have indicated increased basal and stimulated insulin concentrations in vivo and insulin content in vitro and a reduction in apoptosis with sirolimus,\textsuperscript{53} but the effects of sirolimus on insulin secretion and glucose metabolism are unclear at present.

**OTHER IMMUNOSUPPRESSIVE AGENTS**

Mycophenolate mofetil has been shown to induce islet cell apoptosis\textsuperscript{54} and prevent pancreatic ductal neogenesis, which are thought to be the precursors for islet cell neogenesis.\textsuperscript{55} However, switching from calcineurin inhibitors to mycophenolate-based therapy may improve glucose concentrations in patients with diabetes.\textsuperscript{56} Thus, it is unclear if mycophenolate mofetil per se is associated with an increased risk of developing diabetes. It is also unknown if azathioprine is associated with an increased risk of diabetes mellitus.

**INPATIENT MANAGEMENT OF HYPERGLYCEMIA AFTER TRANSPLANTATION**

An international expert panel has published guidelines for the detection and treatment of PTDM.\textsuperscript{7} Even in patients without diabetes mellitus, postoperative hyperglycemia is common, a result of surgical stress and illness-related increases in counterregulatory hormones. Studies have shown an association between hyperglycemia and poor clinical outcomes and death in hospitalized patients.\textsuperscript{57,58} However, benefits of tight glycemic control in hospitalized patients have not been unequivocally demonstrated.\textsuperscript{59,60}

- **How is hyperglycemia managed in the hospital after transplantation?**

Glycemic goals for inpatients should be based on the American Association of Clinical Endocrinologists/ American Diabetes Association consensus statement\textsuperscript{61} between 140 and 180 mg/dL for intensive care unit (ICU) patients and less than 140 mg/dL (premeal) in conjunction with random blood glucose levels of less
than 180 mg/dL for patients in the general inpatient setting. Generally, all glucose levels, including postprandial values, should be below 180 mg/dL. Transplant recipients who develop hyperglycemia in the hospital typically require insulin therapy for glucose management. A multidisciplinary team approach to diabetes care of the transplant patient should be implemented, with physicians, nurse practitioners/physician assistants, dietitians and nutritionists, and diabetes nurse educators managing transplant patients throughout their hospitalization, providing recommendations for dismissal therapy, and arranging outpatient follow-up.

INTENSIVE CARE UNIT MANAGEMENT

In the ICU, hyperglycemia at glucose levels greater than 180 mg/dL is managed by a nurse- or provider-initiated protocol using intravenous (IV) regular insulin. Rapid-acting insulin analogs may be administered intravenously under proper medical supervision while monitoring glucose and potassium levels. Transplant recipients usually require moderate to high doses of IV insulin. With insulin infusion protocols, rates of infusion correspond with measured glucose levels, and most protocols take into consideration glucose trends within the prior few hours. A sample insulin infusion protocol is outlined in Table 6. Patients should be routinely monitored (ideally hourly) to determine if the protocol is effectively managing glucose levels, if glucose concentrations are in the target range, and to check for episodes of hypoglycemia.

MANAGEMENT AFTER INTENSIVE CARE

Upon transfer to the general inpatient setting (generally within 12–24 hr after transplantation), IV insulin infusion remains the best option for the management of hyperglycemia, as patients are on very high-dose glucocorticoids. However, unlike the ICU setting, the insulin infusion is often not a nurse-driven protocol but rather the infusion must be ordered by a clinician in most institutions. In the step-down unit, patient response should be reevaluated after 2 to 4 hours on the insulin protocol, and modifications to the standard insulin infusion protocol may be required. Many patients with type 2 diabetes require more aggressive titration of insulin due to insulin resistance, and patients with type 1 diabetes may have variations in insulin sensitivity, necessitating modification of the standard insulin protocol.

• How should patients be transitioned from IV to subcutaneous insulin?

   Basal/bolus insulin (a long-acting insulin analog plus a rapid-acting insulin analog) and split mix insulin (neutral protamine Hagedorn [NPH] plus a rapid-acting insulin analog) are most commonly used to transition from IV to subcutaneous therapy. When transitioning from IV to subcutaneous basal insulin analog, the 24-hour insulin need should be estimated from the rate of infusion of insulin during the previous 3 to 4 hours. A patient on a stable dose of IV insulin typically can be transitioned to a similar but somewhat reduced (60%–80%) total dose of subcutaneous insulin. If the patient has not received any nutrition while on IV insulin, this dose is considered the basal rate. If transitioning to a multiple daily injection program, approximately 80% of the basal dose is given as a bolus of a long-acting insulin analog as a single daily dose or as 2 divided doses 12 hours apart. IV insulin should be discontinued approximately 4 hours after the first subcutaneous dose is administered. A rapid-acting insulin analog is then added prior to meals as the patient starts consuming nutrition. If the serum glucose level is greater than 180 mg/dL at the time of bolus insulin injections, a correction scale of rapid-acting insulin is added to the bolus doses. However, sliding scale insulin therapy is not appropriate as monotherapy for hyperglycemia in most instances. In our institution, a large proportion of transplant recipients require insulin therapy for carbohydrate management.

   Figure. Mechanism of hyperglycemia induced by immunosuppressive agents.
Posttransplantation Diabetes Mellitus

patients are managed with NPH insulin once or twice daily, with or without a rapid- or short-acting insulin analog. The basal/bolus program is more flexible with variable eating times in the hospital; however, studies have not shown the basal/bolus regimen to be superior to the split mix regimen in the inpatient setting.

- **Are there special considerations in treating transplant recipients with hyperglycemia?**

  Use of high-dose glucocorticoids in the posttransplant setting often necessitates substantially high prandial insulin coverage. Rather than 1:1 prandial to basal proportions, many patients often require ratios of 3:1 or more. Likewise, when using NPH, the morning NPH dose is often much higher than the usual two thirds of the total NPH dose for the day. In clinical practice, glucocorticoids have been noted to have a compounded effect on glucose concentrations throughout the day (ie, it is not uncommon for morning fasting glucose levels to be at goal or at the lowest values of the day, whereas bedtime values are generally the highest values of the day).

  Patients who develop graft-versus-host disease of the gut after peripheral blood stem cell transplantation pose a particular challenge due to poor nutritional intake, nausea, vomiting, malabsorption, and abdominal discomfort. A basal/bolus program is often a more suitable approach for these patients, as the rapid-acting insulin analog can be administered after the meal after ensuring that the patient was able to retain the food.

  After transplantation, successful management of hyperglycemia requires a team approach that involves the patient, especially if insulin is required after discharge from the hospital. Coordinating follow-up in the outpatient setting facilitates transition from the hospital and reduces patient anxiety, especially in the setting of new organ transplantation and a new diagnosis of diabetes mellitus. Follow-up with the transplant diabetes nurse educator within 1 to 2 days after discharge from the hospital should be arranged in addition to phone contact every 2 to 4 days to review glucose measurements and to adjust insulin as glucocorticoid doses are tapered. Additionally, follow-up with the transplant endocrinology team should be arranged within 1 month after discharge to review the insulin program, insulin dose adjustment, and recommended follow-up plan. A well-structured plan is essential for reducing doses of insulin while tapering glucocorticoids. If an insulin reduction plan is not in place, hypoglycemia can occur. Glucocorticoids have different effects on glycemic control based on the type, dose, and duration of administration and potency of the specific glucocorticoid

### Table 6. Sample Insulin Infusion Protocol*

<table>
<thead>
<tr>
<th>Serum Glucose Level, mg/dL</th>
<th>Insulin Infusion Rate, U/hr</th>
<th>Serum Glucose Level, mg/dL</th>
<th>Insulin Infusion Rate, U/hr</th>
<th>Serum Glucose Level, mg/dL</th>
<th>Insulin Infusion Rate, U/hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 400</td>
<td>18</td>
<td>&gt; 400</td>
<td>25</td>
<td>&gt; 400</td>
<td>30</td>
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<tr>
<td>351–400</td>
<td>16</td>
<td>351–400</td>
<td>22</td>
<td>351–400</td>
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<td>301–350</td>
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<td>18</td>
<td>251–300</td>
<td>21</td>
</tr>
<tr>
<td>201–250</td>
<td>10</td>
<td>201–250</td>
<td>15</td>
<td>201–250</td>
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<td>176–200</td>
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<td>176–200</td>
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<td>15</td>
</tr>
<tr>
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<td>151–175</td>
<td>9</td>
<td>151–175</td>
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<tr>
<td>121–150</td>
<td>4</td>
<td>121–150</td>
<td>7</td>
<td>121–150</td>
<td>9</td>
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<td>6</td>
</tr>
<tr>
<td>80–100</td>
<td>1</td>
<td>80–100</td>
<td>2</td>
<td>80–100</td>
<td>3</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>Off</td>
<td>&lt; 80</td>
<td>Off</td>
<td>&lt; 80</td>
<td>Off</td>
</tr>
</tbody>
</table>

*When glucose level is < 80 mg/dL, stop insulin infusion and initiate 50 mL/hr of 10% dextrose infusion. Check glucose every 30 minutes until glucose level is ≥ 80 mg/dL. Discontinue 10% dextrose infusion. Resume insulin infusion, always in column 1. If glucose level is < 60 mg/dL, initiate treatment of hypoglycemia protocol. Restart insulin infusion in column 1 when glucose level is ≥ 80 mg/dL.

†Start in this column; restart in this column when insulin infusion has to be discontinued for glucose level ≥ 80 mg/dL.

‡Patient has not reached glucose level range of 80–100 mg/dL within 2 hr of using column 1 and glucose level has decreased by < 50 mg/dL over preceding 1 hr.

§Patient has not reached glucose level range of 80–100 mg/dL within 2 hr of using column 2 and glucose level has decreased by < 50 mg/dL over preceding 1 hr.
used (Table 7). There are theoretical reasons for these differences in glycemic effects, possibly related to patient variation in sensitivity to glucocorticoids. Additionally, differences in albumin-binding and corticosteroid-binding globulin (specifically with prednisone) concentrations; 11β-hydroxysteroid dehydrogenase type 1 and 2 activity; polymorphism, affinity, and concentration of glucocorticoid receptor-α and glucocorticoid receptor-β; and coexisting conditions (e.g., cancer, sepsis) may also play a role. Therefore, insulin dose reduction depends on the type of glucocorticoid and speed of tapering doses. For example, when discontinuing dexamethasone, the patient will continue the same insulin dose as while on dexamethasone for 1 day after discontinuation. The next day, the insulin dose should be reduced and subsequently the patient resumes their original insulin dose. On the other hand, patients discontinuing hydrocortisone can resume their usual insulin dose the day after the morning supraphysiologic dose of hydrocortisone is given.

### OUTPATIENT MANAGEMENT OF POSTTRANSPLANTATION DIABETES MELLITUS

Generally, patients with PTDM should be managed similarly to patients with type 2 diabetes. As demonstrated by the Diabetes Control and Complications Trial, which evaluated patients with type 1 diabetes, and the United Kingdom Prospective Diabetes Study, which included patients with type 2 diabetes, better glycemic control reduces the risk of microvascular complications. Epidemiologic studies have also suggested that better glycemic control reduces cardiovascular events and death. There have been no trials to date on glycemic control in patients with diabetes after transplantation. Mohan et al reported that simultaneous pancreas and kidney transplantation in patients with type 1 diabetes is superior to kidney transplantation only.

- What are the appropriate steps to management of PTDM in the outpatient setting?

After discharge from the hospital, screening for new-onset diabetes after transplantation by measuring fasting glucose levels should be performed every week for the first month, then at 3, 6, and 12 months, and annually thereafter. The 2003 international consensus guidelines recommend a stepwise approach to therapy: (1) lifestyle modification, (2) monotherapy with an oral agent, (3) oral agent combination therapy to maximum effective dose of agent in each class, (4) insulin and oral agents, and (5) insulin monotherapy adjusted to achieve target glucose goals. Treatment should be aggressively titrated to achieve a goal of hemoglobin A1c level below 7.0%, advancing to the next step in therapy after 2 to 4 months if this target is not achieved.

### LIFESTYLE MODIFICATION

Because the amount of carbohydrates eaten varies from day to day due to unreliable eating schedules, transplant patients are taught carbohydrate counting. Dosing of rapid-acting insulin analogs can be based on the amount of carbohydrate intake. This is especially relevant after solid organ transplantation and in patients with graft-versus-host disease after peripheral blood stem cell transplantation. As previously mentioned, it may be necessary to administer a rapid-acting insulin analog at the end of a meal, so that consumed carbohydrates may be covered by appropriate doses of insulin. This reduces the risk of insulin-meal mismatch and postprandial hyperglycemia and hypoglycemia.

Meeting with a dietician as part of routine outpatient follow-up can reinforce instructions received as an inpatient and provide ongoing education for the patient with PTDM. The ADA recommendations for medical nutrition therapy (reducing total calories, limiting fat, and reducing dietary cholesterol) and exercise (at least 150 min/wk of moderate-intensity exercise) often need to be modified based on the general well-being of the patient after transplantation. Patients are encouraged to start a routine exercise regimen when their surgical wound heals and when the initial immunosuppressive therapy protocol is complete, which is generally 3 weeks from the date of transplantation. Exercise initiated early after transplantation improves the capacity for physical endurance. Particularly for cardiac transplantation recipients, patients should begin

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**Table 7. Equivalent Doses of Glucocorticoids**

<table>
<thead>
<tr>
<th>Equivalent Dose, mg</th>
<th>Plasma Half-Life, min</th>
<th>Biologic Half-Life, hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td>20.0</td>
<td>90</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25.0</td>
<td>80–118</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5.0</td>
<td>60</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5.0</td>
<td>115–200</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4.0</td>
<td>30</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4.0</td>
<td>180</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.5</td>
<td>200</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6</td>
<td>300</td>
</tr>
</tbody>
</table>

Sulfonylurea monotherapy is generally ineffective. Hypoglycemia is a well-known risk associated with sulfonylureas. Sulfonylureas are predominantly cleared by hepatic or renal mechanisms. Posttransplant abnormalities in these functions can result in decreased clearance, thereby potentiating the risk of hypoglycemia. If the patient has a poor appetite or erratic oral intake, this risk can be exacerbated. Additionally, there is a theoretical risk of declining beta cell function associated with sulfonylureas when used concomitantly with glucocorticoids, with some sulfonylureas potentially being less toxic to beta cells than others.

In one study, use of a meglitinide for new-onset diabetes after renal transplantation was effective for improving blood glucose concentrations and lowering hemoglobin A1c to less than 7%. Despite the fact that meglitinides are metabolized by cytochrome P450 isoenzymes, CYP3A4, and CYP2C8, there was no significant effect on cyclosporine A, tacrolimus, or sirolimus blood concentrations or doses.

**Metformin**

Metformin is not often used for PTDM due to concerns for lactic acidosis; however, the incidence of lactic acidosis appears to be low. On the other hand, metformin does not cause weight gain, decreases hepatic gluconeogenesis, reduces insulin resistance, and helps with lipid lowering. In a study by Cantin et al involving rat heterotopic heart transplantation models treated with metformin, diabetes-induced transplant coronary artery disease decreased in the large vessels; however, metformin did not prevent progression of transplant coronary artery disease in the smaller vessels at 60 days. In posttransplant patients, metformin should generally not be initiated until 6 to 12 months following organ transplantation. In addition, metformin should be discontinued prior to the administration of IV contrast and before major surgery.

**Thiazolidinediones**

Pioglitazone is metabolized by the P450 enzymes CYP3A4 and 2C8 and does not significantly impact renal function and concentrations or dose of tacrolimus. Rosiglitazone is metabolized by the P450-2C8 pathway and not by CYP3A4. Rosiglitazone has no significant interaction with cyclosporine or tacrolimus and does not cause renal or hepatic dysfunction. Rosiglitazone appears to be an effective adjunct to both insulin and sulfonylurea for treatment of PTDM; however, more studies are needed to confirm this finding.

Risks associated with thiazolidinediones (TZDs), including weight gain, fluid retention, heart failure, and osteoporosis, remain concerns in the posttransplant setting.

**ORAL AGENTS**

**Sulfonylureas and Meglitinides**

Sulfonylureas and meglitinides stimulate insulin secretion and thereby lower glucose levels, but they have different receptor binding sites. A recent retrospective study of patients who underwent renal transplantation suggests that sulfonylureas may be a safe and effective treatment option for new diabetes after transplantation. However, anecdotal evidence suggests that sulfonylurea monotherapy is generally ineffective.

**ANTIREJECTION REGIMEN**

PTDM can be prevented or at least better managed with regimens without or with low doses of glucocorticoids and tacrolimus. Woodle et al performed the first randomized, double-blind, placebo-controlled trial comparing early corticosteroid withdrawal with tacrolimus/mycophenolate mofetil induction therapy at 7 days posttransplant with chronic low-dose corticosteroid therapy over a 5-year period. Although corticosteroid withdrawal correlated with an increase in biopsy-confirmed acute rejection, long-term allograft survival and function were similar when compared with low-dose corticosteroids. Moreover, corticosteroid withdrawal is associated with lower cardiovascular risk factors, diabetes requiring insulin, and weight gain.

- What are the effects of oral therapy in the posttransplant setting?
setting, where weight gain and osteoporosis are often seen.90 TZDs do not achieve therapeutic effect for several weeks and therefore do not immediately impact glycemic control.

**INSULIN**

Insulin is the most common antidiabetic therapy for PTDM, especially early after transplantation when the glucocorticoid doses are substantial. NPH insulin once or twice daily is sufficient for a subgroup of patients. When the patient’s glycemic pattern and insulin dose requirements imply that the insulin reserve is minimal, NPH plus a rapid-acting insulin analog or a multiple daily insulin plan (basal/bolus regimen) can be initiated. The basal/bolus regimen is more flexible with regard to timing and content of meals. However, it costs more than NPH with or without regular insulin.

- What are important considerations in posttransplant follow-up?

**FOLLOW-UP**

As previously mentioned, a multidisciplinary approach to long-term management of PTDM is important for ensuring high-quality diabetes care. The patient should be seen by the diabetes educator within 1 to 3 days of discharge from the hospital to ease the transition and reinforce diabetes education. A follow-up appointment should be scheduled with a physician within 1 to 2 weeks after discharge to establish a plan of care for the upcoming months. In the initial posttransplant stages, it is essential to have close contact with the patient to aid in insulin dose adjustment and ongoing education, with an ultimate goal for patients to self-adjust their own insulin doses. Follow-up is typically scheduled at 3- and 6-month intervals, particularly the first year following transplant. Additionally, frequent telephone consultation should be maintained by a diabetes educator to reinforce insulin self-adjustment guidelines. The frequency of contact is often decided by the diabetes educator and the patient. Metering frequency is also determined collaboratively between the treatment team and individual patient, giving consideration for therapeutic program and individual patient needs.

**CONCLUSION**

Diabetes mellitus afflicts a substantial proportion of patients who have undergone transplantation. The risks of PTDM increase with the use of high-dose glucocorticoids, tacrolimus, and cyclosporine. In addition, genetic predisposition, age, obesity, and infection with hepatitis C increase this risk. No randomized trials have demonstrated benefits of glycemic control or specific antidiabetic therapies in patients with PTDM. Patients often require large prandial doses of insulin while receiving large doses of glucocorticoids. Renal and hepatic dysfunction and simultaneous use of antirejection agents limit the type and doses of drugs used for diabetes management. Insulin remains the mainstay of therapy, although oral agents are increasingly being used. Glycemic goals depend on the clinical situation, although fasting and premeal glucose concentrations generally should be between 100 to 140 mg/dL but certainly less than 180 mg/dL.

**BOARD REVIEW QUESTIONS**

Test your knowledge of this topic. Go to www.turner-white.com and select Endocrinology from the drop-down menu of specialties.

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