ABSTRACT

Objective: Owing to advances in transplant science, increasing numbers of patients are receiving solid organ transplantation. New onset diabetes after transplantation (NODAT) frequently develops in transplant patients and requires acute and often ongoing management of hyperglycemia. The metabolic derangements of NODAT are similar to those of classic type 2 diabetes, and treatment has typically followed diabetes standards of care. Best practices for NODAT management remain to be developed.

Methods: The mechanistic suitability of incretins to treat NODAT pathogenesis has been hitherto underappreciated. This review details the specific mechanistic value of incretins in patients with immunosuppression-associated hyperglycemia.

Results: Corticosteroids have long been known to exert their effects on glucose metabolism by decreasing glucose utilization and enhancing hepatic gluconeogenesis. Corticosteroids also significantly and directly reduce insulin secretion, as do calcineurin inhibitors (CNIs), another commonly used group of immunosuppressive drugs that cause hyperglycemia and NODAT. The ability of incretins to counteract immunosuppressant-induced disruptions in insulin secretion suggest that the insulinotropic, glucagonostatic, and glucose-lowering actions of incretins are well suited to treat immunosuppressant-induced hyperglycemia in NODAT. Additional benefits of incretins include decreased glucagon levels and improved insulin resistance. In the case of glucagon-like peptide-1 (GLP-1) receptor agonists, weight loss is another benefit, countering the weight gain that is a common consequence of both hyperglycemia and transplantation. These benefits make incretins very attractive and deserving of more investigation.

Conclusion: Among diabetes treatment options, incretin therapies uniquely counteract immunosuppressant drugs’ interference with insulin secretion. We propose an incretin-based treatment paradigm for NODAT management.

Abbreviations:
CNI = calcineurin inhibitor; DPP-4 = dipeptidyl peptidase 4; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; HLA = human leukocyte antigen; NODAT = new onset diabetes after transplantation

NEW ONSET DIABETES AFTER TRANSPLANTATION (NODAT)

With advances in transplantation science, increasing numbers of patients are receiving solid organ transplants. According to the Organ Procurement and Transplantation Network (OPTN), more than 600,000 organ transplants have been performed in the United States through mid-2014. Posttransplantation complications are major contributors to patient morbidity and mortality. NODAT is associated with corticosteroid and calcineurin inhibitor (CNI) use and is a posttransplant complication that is a strong predictor of graft failure and long-term morbidity and mortality (1,2).

Reports of the incidence of NODAT 12 months after solid organ transplantation have varied widely and may be influenced by the organ transplanted; estimates are 20 to 50% kidney, 9 to 30% liver (40 to 60% if Hepatitis C infection is present), 28 to 30% heart, 6 to 45% lung, and 15%...
Chronic organ failure itself is often associated with gluconeogenesis, and diminished beta cell function (8-13). Stress hyperglycemia is characterized by insulin resistance, in genetically predisposed, normoglycemic individuals. A sustained stress response negotiates a near-term threat. A physiologic strategy to provide liberal circulating glucose while the body stress and inflammatory responses; it is a physiologic strategy used to identify type 2 diabetes in the general population along with several unique to transplant medications and transplant-related infections. Common to both include non-Caucasian ethnicity, age >45 years, family history of diabetes, obesity (insulin resistance), dyslipidemia, hypertension, pre-existing impaired fasting glucose or impaired glucose tolerance, hepatitis C infection, and male sex. Risk factors unique to the transplant setting include human leukocyte antigen (HLA) subtypes A30, B27, and B42; HLA DR mismatches; deceased donors; acute rejection; cytomegalo-virus infection; and male donors (7).

Best practices in the clinical management of NODAT are still being developed. This paper will discuss the specific value of incretins in patients with immunosuppression-associated hyperglycemia. We will propose an incretin-based treatment paradigm and describe the strong rationale for using incretins to manage, and perhaps forestall, NODAT.

Mechanisms of Dysglycemia by Immunosuppressive Drugs

Superimposed on the glucodysregulation associated with organ failure, transplantation introduces a new, dual metabolic insult: stress hyperglycemia due to the inherent physiologic stress of surgery and the transplant procedure and hyperglycemia induced by many commonly used immunosuppressive drugs. Corticosteroids are used for induction therapy, maintenance therapy, and treating organ rejection. Prednisone and methylprednisolone have each been shown to dose dependently induce hyperglycemia, increase insulin resistance and hepatic gluconeogenesis, inhibit insulin secretion, and potentiate the effects of glucoregulatory hormones such as glucagon and epinephrine (14,15). Incremental dose increases of 0.1 mg/kg prednisolone per day was shown to correlate with a 5% increased risk of NODAT and a 4% increased risk of impaired glucose tolerance in a study evaluating renal transplant patients (16). CNIs such as cyclosporine and tacrolimus and mammalian target of rapamycin (mTOR) inhibitors such as sirolimus have been shown to increase postprandial glucose elevations (17) and reduce beta cell insulin secretion (18-21). The choice of immunosuppressive drugs will impact the degree of insulin resistance, as well as impairment in insulin secretion leading to increased incidence of NODAT. Tacrolimus appears to have the most pronounced effect on glucose intolerance, followed by cyclosporine (6,19,22,23).

INCRETINS AND INCRETIN THERAPIES IN THE MANAGEMENT OF POSTTRANSPLANT HYPERGLYCEMIA

Incretins are hormones secreted by cells of the gastrointestinal tract that act as potent insulin secretagogues. In conjunction with glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1) is a primary controller of insulin secretion by beta cells following nutrient ingestion (24). In the therapeutic setting, GLP-1 receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors induce insulin secretion in a glucose-dependent manner; thus, reducing the risk of hypoglycemia. DPP-4 inhibitors act indirectly by blocking proteolytic cleavage of GLP-1 by DPP-4 (25). GLP-1 receptor agonists are structurally similar to endogenous GLP-1 but have been engineered to be resistant to DPP-4 degradation (24). In type 2 diabetic patients, circulating GLP-1 levels are increased 2- to 3-fold by DPP-4 inhibitors and 6- to 10-fold by GLP-1 receptor agonists (24). GLP-1 receptor agonists potently, and DPP-4 inhibitors modestly, exert effects via inhibition of glucagon secretion (26,27) and suppress hepatic glucose production.
Incretins have been approved for the treatment of type 2 diabetes: exenatide twice daily; liraglutide once daily; and, exenatide, albiglutide, and dulaglutide each given once weekly. Five oral DPP-4 inhibitors are commercially available for the treatment of type 2 diabetes: sitagliptin, saxagliptin, linagliptin, alogliptin, and outside the U.S., vildagliptin. The DPP-4 inhibitors have a favorable safety and tolerability profile; unlike GLP-1 receptor agonists, they rarely induce gastrointestinal side effects. DPP-4 inhibitors, however, do not demonstrate the weight loss benefit seen with GLP-1 receptor agonists.

**Therapeutic Benefits of Incretins**

GLP-1 receptor agonists effectively reduce HbA1c (Table 1), and are effective as monotherapy, as well as in combination regimens, and in patients who have been on long-standing insulin therapy (31). GLP-1 receptor agonists improve both first- and second-phase insulin secretion (32) and restore beta cell sensitivity to glucose (33). As a class, DPP-4 inhibitors induce relatively moderate reductions in HbA1c. Additionally, GLP-1- and DPP-4-targeted therapies have each been found to inhibit pancreatic beta cell apoptosis and stimulate the proliferation and differentiation of insulin-secreting beta cells (34,35).

A wide range of beneficial cardiovascular effects of incretins have been reported in preclinical and clinical studies and include reduced total and low-density lipoprotein cholesterol, apolipoprotein B, and triglyceride levels; increased high-density lipoprotein cholesterol; reduced high-sensitivity C-reactive protein; and lowered systolic and diastolic blood pressure (36-43). Translation of these endpoints into improved cardiovascular outcomes has not been consistently shown in outcomes studies, though most of these have been of short durations (only 1 or 2 years). A recent meta-analysis of Phase 3 trials with the DPP-4 inhibitors saxagliptin or linagliptin showed reductions in cardiovascular outcomes (44,45), whereas 2 recent prospective trials – the saxagliptin SAVOR-TIMI Study (46) and the alogliptin EXAMINE Study (47) – proved safety but did not show a significant reduction in cardiovascular outcomes. Longer term studies are underway.

**Incretin Safety**

Acute pancreatitis and pancreatic neoplasia have been raised as concerns for incretin-based therapy and are noted on the product labels of these drugs. These concerns initially arose in postmarketing data, as well as in small study of pancreata of brain-dead organ donors who were treated with incretin therapy (48). In early 2014, the U.S. Food and Drug Administration and European Medicines Agency independently reviewed available data and concluded that a causal association between incretin therapy and pancreatitis or pancreatic cancer cannot be made at this time, and ongoing investigation is necessary. Two recent large-scale studies were included in this analysis, each of which reported low rates that were similar in the drug and placebo groups (46,47). Similarly, a pooled analysis of 25 clinical trials from the sitagliptin database did not reveal an increased risk of pancreatitis or pancreatic cancer.

The SAVOR trial collected safety data for 16,884 person-years treatment with saxagliptin. In this study, a 27% increase in hospitalization for congestive heart failure in patients treated with saxagliptin was seen (46). No increase in new onset heart failure or worsening of existing heart failure was found upon reanalysis of alogliptin’s EXAMINE trial (47). A meta-analysis of 59 randomized controlled trials with various DPP-4 inhibitors evaluating data from 36,620 patients with diabetes for a minimal observation period of 24 weeks confirmed a 21% increase of heart failure events compared to placebo treatment. Importantly, however, the rate for DPP-4 inhibitor treatment was not higher than that with other blood glucose-lowering drugs (49). Further data is awaited from ongoing trials of cardiovascular safety of this class of drugs.

While DPP-4 inhibitors are safe to use with all degrees of renal impairment, GLP-1 agonists are actively being evaluated for safety and efficacy in moderate-severe renal impairment and in heart failure. There is minimal data on these agents in liver failure, but this is also an area of investigation.

**INCRETINS IN THE TRANSPLANT SETTING**

**Incretins Counteract Impaired Insulin Secretion by Immunosuppressive Agents**

The mechanisms of glucose-mediated insulin secretion are shown in Figure 1. Glucocorticoid-induced hyperglycemia is well understood and achieved by interference with both insulin secretion and insulin action and via multiple organ loci. In pancreatic beta cells, glucocorticoids exert direct proinflammatory (50) and insulinostatic actions. Glucocorticoid impairment of insulin secretion (51) is mediated, at least in part, by suppression of glucose transporter 2 expression (16,52). Cyclic adenosine monophosphate (cAMP) synthesis, protein kinase A activation, and calcium influx are pathways through which GLP-1 orchestrates exocytosis of insulin storage granules, pathways that are blocked by glucocorticoids. In animal beta cell models, glucocorticoids have been shown to induce beta cell apoptosis, including by transcription factors such as PDX-1 (pancreatic and duodenal homeobox 1). Notably, GLP-1 modulates PDX-1, and can rescue beta cells from glucocorticoid-induced cell death (50,53). The complex effect on glucocorticoids on beta cell function have recently been reviewed by Rafacho et al (54).

CNIs such as cyclosporine and tacrolimus block insulin release by impairing calcium- and cAMP-linked transport of insulin to secretory granules (55), as well as by decreasing insulin gene expression (20). The insulinostatic actions of CNIs have been shown to include the signal-
### Table 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>HbA1c-Lowering Capacity</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Metabolism/Elimination</th>
<th>Adjustment in Renal Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incretins</strong></td>
<td></td>
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<tr>
<td>GLP-1 agonists (exenatide, exenatide-QW, lixisend and dulaglutide)</td>
<td>Glucose-dependent insulin secretion, glucagon suppression, centrally induced satiety, decreased rate of gastric emptying</td>
<td>0.8-2%</td>
<td>Weight reduction, low risk of hypoglycemia, lowers blood pressure</td>
<td>Gastrointestinal side effects, possible risk of pancreatitis, potential for altered drug absorption, drug cost, case reports of renal impairment, subcutaneous administration, antibody production, putative link to certain cancers</td>
<td>Exenatide: Primarily renal</td>
<td>Dose adjustment for exenatide</td>
</tr>
<tr>
<td>DPP-4 inhibitors (sitagliptin, alogliptin, linagliptin, saxagliptin, vildagliptin)</td>
<td>Blocks enzymatic degradation of incretins (GLP-1, GIP)</td>
<td>0.5-0.8%</td>
<td>No weight gain, low risk of hypoglycemia, well-tolerated</td>
<td>Drug cost, possible risk of pancreatitis, putative link to certain cancers</td>
<td>Renal CYP2C8</td>
<td>Adjust dosages for renal insufficiency except linagliptin</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone)</td>
<td>Insulin sensitizer (primarily muscle/fat)</td>
<td>0.5-1.4%</td>
<td>No hypoglycemia</td>
<td>Weight gain, edema, increased congestive heart failure risk, drug cost, fracture risk in women, potential risk of bladder cancer</td>
<td>CYP2C8/CYP3A4</td>
<td>Nonspecific No renal dose adjustment</td>
</tr>
<tr>
<td>Biguanides (metformin)</td>
<td>Insulin sensitizing (primarily liver)</td>
<td>1.0-1.5%</td>
<td>Efficacy (micro- and macrovascular end points), no hypoglycemia, no weight gain, lower drug cost</td>
<td>Gastrointestinal side effects, risk of lactic acidosis in renal and liver impairment</td>
<td>Renal tubular secretion</td>
<td>Contraindicated for females with Cr &gt;1.4 and males Cr &gt;1.5</td>
</tr>
<tr>
<td>SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)</td>
<td>Decreases reabsorption of glucose from glomerular filtrate</td>
<td>0.5-1%</td>
<td>Efficacy, weight loss, decreased BP, decreased microalbuminuria</td>
<td>Increased risk of genitourinary infections and urinary tract infections, hypovolemia</td>
<td>Renal, hepatic</td>
<td>Canagliflozin and empagliflozin: not effective if eGFR &lt;45; Dapagliflozin: not effective if eGFR &lt;60 mL/min</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors (acarbose)</td>
<td>Decreases gastrointestinal carbohydrate absorption</td>
<td>0.5-0.8%</td>
<td>No hypoglycemia, weight neutral</td>
<td>Gastrointestinal side effects</td>
<td>Major: fecal</td>
<td>Minor: renal</td>
</tr>
<tr>
<td>Bromocriptine-QR</td>
<td>Improves AM surge dopamine in suprachiasmatic nucleus; reduces peripheral insulin resistance and sympathetic tone</td>
<td>0.5-1.0%</td>
<td>No hypoglycemia, weight neutral</td>
<td>Gastrointestinal side effects, hypotension</td>
<td>Major: bile, fecal</td>
<td>Minor: renal</td>
</tr>
<tr>
<td>Sulfonylureas (glipizide, glibenclamide, glipizide, tolbutamide, chlorpropamide, tolazamide)</td>
<td>Stimulation of insulin secretion</td>
<td>1.0-2.0%</td>
<td>Efficacy (microvascular end points), rapid effect, drug cost</td>
<td>Hypoglycemia, weight gain, accumulates in renal failure</td>
<td>Hepatic</td>
<td>Dose reduction or discontinuation</td>
</tr>
<tr>
<td>Meglitinides (repaglinide, nateglinide)</td>
<td>Stimulation of insulin secretion</td>
<td>0.5-0.1%</td>
<td>Reduces postprandial hyperglycemia, safer with advancing renal failure</td>
<td>Hypoglycemia, weight gain, drug cost, dose adjustment in renal failure</td>
<td>CYP2C8/3A4</td>
<td>Dose reduction in severe renal dysfunction</td>
</tr>
<tr>
<td>Insulin</td>
<td>Exogenous administration of primary glucose-storing hormone</td>
<td>&gt;2.0% (dose limited by hypoglycemia)</td>
<td>Efficacy (micro- and macrovascular end points), range of insulin types for individualization</td>
<td>Weight gain, hypoglycemia, putative link to certain cancers</td>
<td>Major: hepatic</td>
<td>Minor: renal</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; Cr = creatinine; CYP = cytochrome P450; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; HbA1c = glycated hemoglobin; QR = quick release; QW = once weekly; SGLT-2 = sodium-glucose cotransporter 2.
ing pathways through which activation of T lymphocytes is accomplished by calcineurin (22). The GLP-1 receptor agonist exendin-4 was shown to reverse CNI-induced beta cell death in animal cell models. In mouse cell models, GLP-1-overexpressing cells were able to overcome the deleterious effects of treatment with a cocktail of sirolimus, tacrolimus, and mycophenolate.

A cross-over study of healthy volunteers showed that treatment with exenatide effectively prevented glucose intolerance after high-dose daily prednisolone. Cotreatment of exenatide normalized postprandial glucose levels compared to prednisolone alone, decreased gastric emptying, and improved first- and second-phase glucose- and arginine-stimulated C-peptide secretion (56,57). In a patient with glucocorticoid-induced hyperglycemia due to Cushing disease, administration of GLP-1 restored physiologic plasma glucose levels (58). It is noteworthy that in a small study of healthy adults evaluating metformin and pioglitazone, neither of these antidiabetes agents were able to reverse hyperglycemia in response to dexamethasone-induced insulin resistance (59).

The ability of incretins to counteract immunosuppressant-induced disruptions in insulin secretion suggest that the insulinotropic, glucagonostatic, and glucose-lowering actions of incretins are ideally suited to treat immunosuppressant-induced hyperglycemia in NODAT. Indeed, recent case reports demonstrated the efficacy of exenatide in treating diabetes mellitus patients with worsening hyperglycemia after initiation of corticosteroid treatment for the management of rheumatoid arthritis, myasthenia gravis, or amyopathic dermatomyositis (16).

**Fig. 1.** Mechanisms of glucose-mediated insulin secretion. Glucose stimulates insulin secretion from the beta cells by triggering and amplifying pathways. The direct inhibition of these pathways by calmodulin inhibitors and corticosteroids can be overcome by elevated levels of incretins. AC = adenyl cyclase; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; GIP = glucose-dependent insulinotropic polypeptide; GK = glucokinase; GLP-1 = glucagon-like peptide-1; GLUT2 = glucose transporter 2; PKA = protein kinase A; TCA = tricarboxylic acid (Kreb’s) cycle.

**Reports to Date of Incretin Use in NODAT**

Studies to date of the use of DPP-4 inhibitors in NODAT demonstrate safety and efficacy in this patient population. A randomized, double-blind Phase 2 clinical trial in 509 stable kidney transplant recipients with newly diagnosed NODAT assessed treatment with vildagliptin versus lifestyle modification only. At 3 months, vildagliptin-treated patients had 2-hour plasma glucose values of 182.7 mg/dL and an HbA1c value of 6.1%; values for lifestyle modification only group had 231.2 mg/dL and 6.5%, respectively (both $P \leq .05$). Adverse events were generally mild (60).

In 48 stable renal transplant recipients with newly diagnosed impaired glucose tolerance who were at least 6 months from transplantation, HbA1c and 2-hour plasma glucose at 3 months was significantly reduced compared with baseline in response to vildagliptin; pioglitazone was also tested and demonstrated to safely decrease HbA1c and total daily insulin dose without significant changes in serum creatinine or mean tacrolimus dose (61,62). In 2014, Boerner and colleagues conducted a retrospective analysis of 22 renal transplant
recipients diagnosed with NODAT who were treated with sitagliptin and found it to be efficacious, while renal function and immunosuppressant levels remained stable. Transplant-specific adverse events were rare (63).

A retrospective study in 15 stable heart transplant patients with NODAT treated with vildagliptin therapy reported a mean HbA1c value of 7.4 ± 0.7% before vildagliptin therapy versus 6.8 ± 0.8% after 8 months of vildagliptin therapy (*P* = .002 vs. baseline). Significant reductions in mean blood glucose were found without negative effects on lipid profile or body weight (64).

Even fewer clinical studies are available to systematically evaluate the use of GLP-1 receptor agonists in NODAT. In 1 clinic, 8 patients (6 renal and 2 liver transplant) were treated with exenatide (5 mcg subcutaneously twice daily) while on immunosuppressant regimens (prednisone, tacrolimus, and mycophenolate mofetil). In all 8 patients, exenatide treatment decreased HbA1c levels by 0.7 to 1.8%. Among the 6 patients receiving insulin therapy, 3 discontinued insulin therapy completely; the remaining 3 were dose adjusted to 25 to 50% less insulin, and bolus insulin was discontinued (Ahmed, personal communication).

In a small group of patients, coadministration of liraglutide with tacrolimus improved postprandial glucose and engendered weight reduction without clinically altering trough tacrolimus concentrations in stable kidney transplant recipients with mild renal impairment (65).

In addition to HbA1c lowering, GLP-1 agonist therapy has shown a weight-loss benefit in the transplant population. In posttransplant patients with pre-existing diabetes or NODAT well controlled on insulin, add-on GLP-1 agonist therapy led to weight loss in 19 of 20 patients, with 14 patients losing at least 4.5 kg. There were no significant changes in immunosuppressant drug levels or serum creatinine (66).

While these reports have demonstrated the safety and efficacy of incretins in the transplant setting, none, to our knowledge, have posited the intrinsic value of incretin therapy in this patient population. Hitherto unrecognized by the medical community at large seems to be the distinct mechanistic rationale for an incretin-based approach to NODAT management. Impaired insulin secretion rather than impaired insulin sensitivity appears to be the principal pathophysiologic defect in NODAT. Incretin-targeting of insulin secretion directly counters the hypoinsulinemia and hyperglucagonemia conferred by stress hyperglycemia, glucocorticoids, and CNIs on beta cells. Incretins uniquely and directly redress these defects in beta cell insulin dysfunction present in NODAT.

**TREATMENT RECOMMENDATIONS FOR INCRETIN-BASED THERAPY FOR PERITRANSPLANTATION AND NODAT**

All patients should undergo screening as part of the transplant evaluation to identify patients with undiagnosed diabetes and those at increased risk for progression to NODAT. Screening for diabetes should be also incorporated into posttransplant care. Screening tests should follow ADA recommendations, with diagnostic criteria of fasting plasma glucose ≥126 mg/dL on more than 1 occasion, HbA1c ≥6.5% using a certified assay, or 2-hour glucose ≥ 200 mg/dL during an OGTT (67).

Best practices for the management of hyperglycemia in NODAT are of considerable interest but are still to be developed. There is currently no standard approach, and clinical study data within this patient population are relatively new (68-70). On the basis of this review, we recommend peri-transplantation incretin therapy. DPP-4 inhibitors and GLP-1 receptor agonists may be initiated in patients with prediabetes, previously undiagnosed diabetes, or those with known diabetes identified even before elective admission for transplant. In the hospital setting, incretin therapy should be considered when oral intake is reinitiated following transplantation. Transplant medications should be used as required by current protocols. As reviewed, studies to date in NODAT report the safe and effective use of GLP-1-based therapy (65) or DPP-4 inhibitors (61-63, Ahmed, personal communication) in combination with immunosuppressant therapies.

The chief benefits of an incretin-based regimen include improved glycemic variability and the potential for decreasing reliance on insulin. All commercially available DPP-4 inhibitors are approved for use in combination with insulin; no changes in existing in-hospital protocols, order-sets, or regimens for existing insulin therapy are needed. In patients receiving stress or immunosuppressive agents, the glucose-lowering effectiveness corresponds to 20 to 30 units of insulin for DPP-4 inhibitors and 40 to 60 units for GLP-1 receptor agonists (71). Sitagliptin has been demonstrated to be safe and effective for management of hyperglycemia in hospitalized medical and surgical patients (72). GLP-1 agonists have not been assessed in posttransplant patients, although studies in the critical care setting have been encouraging. Given the unique benefits of incretin therapy in the immediate post-transplant setting of high-dose immunosuppression, further investigation on their use immediately after transplantation is warranted.

The lower overall efficacy of DPP-4 inhibitors as compared to GLP-1 receptor agonists on lowering HbA1c levels is compensated by their ease of use and lack of serious side effects. In hospitalized patients new to incretin therapy, a DPP-4 inhibitor may be the incretin of choice, and a renal-adjusted dose may be advisable for posttransplant patients. In liver transplantation, incretin therapy might be withheld until proven to have an absence of biliary complications with attendant pancreatitis risk.

The GLP-1 receptor agonists liraglutide, exenatide, and albiglutide are each approved in combination with basal insulin, whereas dulaglutide has been approved with prandial but not basal insulin. We have had success with use of GLP-1 receptor agonists in combination with short-acting...
insulin analogues in the clinical setting. Liraglutide requires no significant renal-dose adjustment; exenatide should be avoided if creatinine clearance is <30 mL/min. A low incidence of gastrointestinal symptoms has been noted with the use of GLP-1 receptor agonists in a critical care setting (71). This may be attributed to the decreased caloric intake, relatively low-fat diets, and the tendency of critical patients to eat slower than the general type 2 diabetes population.

Transplant-related drugs may have their own potential for gastrointestinal side effects. Therefore, we correspondingly recommend that GLP-1 therapy be introduced only once the patient has accommodated the transplant-related drug regimen without gastrointestinal intolerance. Patients should be advised to stop eating at the first sense of satiety. Those patients who report gastrointestinal upset or nausea can be managed with metoclopramide or ondansetron (73) along with monitoring of immunosuppressive drug levels to avoid the risk of organ rejection due to inadequate absorption of these medications. In lung transplantation, true neural-induced gastroparesis may occur after surgery; GLP-1 receptor agonist therapy might be withheld until this risk has been ruled out.

On discharge from hospital, we recommend continuing incretin therapy, as well as any discharge insulin doses. If prescribed a DPP-4 inhibitor on discharge, switching to a GLP-1 receptor agonist on follow-up may be done for its greater efficacy among the incretins, as well as the higher likelihood of decreasing – or eliminating – insulin therapy. Use of bolus insulin is of particular concern, as bolus insulin accounts for 85% of the hypoglycemia found with basal/bolus insulin therapy (74).

We are comfortable with the principles of the American Association of Clinical Endocrinologists (AACE) comprehensive diabetes management algorithm (75). This guideline highlights the effectiveness of early integration of combination therapy. Incretins can be used in combination regimens or as monotherapy. Some data exists on the beneficial use of incretins with pioglitazone for the treatment of NODAT, but the risk of weight gain and volume retention must be considered, particularly if there is graft dysfunction in recipients of kidney, liver, or heart transplants (61). As outlined in the AACE Guideline, sulfonfonylureas and glinides should be avoided to reduce risk of hypoglycemia and weight gain. Sodium-glucose cotransporter 2 inhibitors have not yet been studied in transplant patients but may be a reasonable oral agent. The risk of genitourinary infections, often increased in the setting of immunosuppression, are a concern. Table 1 provides additional information on individualizing choice of therapy for NODAT.

CONCLUSION

Although widely accepted since their introduction a decade ago, incretins are one of the newer classes in the diabetes armamentarium, and more clinical studies of NODAT are needed. Indeed, there have been few investigations for any treatment approach in this special patient population. Nonetheless, there exists a strong rationale for an incretin-based approach to managing NODAT by virtue of their unique ability to counter the defects in insulin secretion imposed by immunosuppressant therapies. The ability to dose reduce insulin cotreatment, the weight loss benefit of GLP-1 receptor agonists, and the potential cardiovascular benefits of both classes of incretins make these agents particularly attractive among antidiabetic treatment options. We recommend incretins as first-line treatment or as part of combination regimens for patients with overt NODAT, impaired glucose tolerance in peritransplant patients, and in transplant patients with pre-existing diabetes prior to transplantation.

DISCLOSURE

S.S.S. has served on advisory boards for Takeda, Merck, AZ-BMS, Janssen, Lilly, and Salix and on speaker bureaus for Takeda, Merck, Janssen, BI-Lilly, Salix, Novo, GSK, Eisai, and Salix. A.S. and M.E.H. have no multiplicity of interest to disclose.

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