Approach to the patient: Early post-renal transplant hyperglycemia

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Abstract

Context: Though post-transplant diabetes mellitus (PTDM, occurring >45 days after transplantation) and its complications are well-described, early post-renal transplant hyperglycemia (EPTH) (<45 days) similarly puts kidney transplant recipients at risk of infections, re-hospitalizations, graft failure and is not emphasized much in the literature. Proactive screening and management of EPTH is required given these consequences.

Evidence acquisition: A PubMed search was conducted for "early post-renal transplant hyperglycemia", "immediate post-transplant hyperglycemia", "post-renal transplant diabetes", "renal transplant", "diabetes" and combinations of these terms.

Evidence synthesis: EPTH is associated with significant complications including acute graft failure, re-hospitalizations, cardiovascular events, PTDM and infections.

Conclusion: Patients with diabetes experience better glycemic control in end-stage renal disease (ESRD), with resurgence of hyperglycemia after kidney transplant. Both patients with and without known diabetes are at risk of EPTH. Risk factors include elevated pre-transplant fasting glucose, diabetes, glucocorticoids, chronic infections, and post-transplant infections. We find that EPTH increases risk of re-hospitalizations from infections (CMV, possibly COVID-19), acute graft rejections, cardiovascular events and PTDM. It is essential, hence, to provide diabetes education to patients prior to discharge. Insulin remains the standard of care while inpatient. Close follow up after discharge is recommended for insulin adjustment. Some agents like dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists have shown promise. The tenuous kidney function in the early period post-transplant and lack of data limits the use of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. There is a need for studies assessing non-insulin agents for EPTH to decrease risk of hypoglycemia associated with insulin and long-term complications of EPTH.

Keywords: hyperglycemia, renal, transplant, early, immediate, transient

Learning objectives

Upon completion of this learning activity, participants should be able to

- Identify early post-renal transplant hyperglycemia (EPTH).
- Describe the underlying pathophysiology of, and risk factors for, EPTH.
- Demonstrate acute and long-term complications stemming from EPTH.
- Identify strategies to appropriately monitor and manage a patient with EPTH.

Target audience: This activity should be of interest to endocrinology providers, transplant surgeons and all health-care professionals who care for post-renal transplant patients.

I. Introduction

Hyperglycemia is frequently observed after kidney transplantation, and is a risk factor for increased readmission, infection, and acute graft rejection rates. However, hyperglycemia within the first 45 days after transplant (which we will refer to as early post-renal transplant hyperglycemia or EPTH) has not been given as much attention as the later period, perhaps because of less clarity in its definition and clinical implications. Conceivably, the term EPTH might also refer to other organ transplants in the future, but since there are unique pathophysiologic mechanisms and specific immunosuppressive treatment timelines in kidney transplantation, our review is focused on this organ currently.

The nomenclature for hyperglycemia or diabetes after transplantation had led to confusion in the literature such that an International Consensus meeting was held in Vienna in 2013 to discuss challenges surrounding diabetes after renal transplantation where the term post-transplant diabetes mellitus (PTDM) was proposed (1). PTDM includes newly diagnosed diabetes approximately >45 days after transplant, irrespective of whether it was present but undetected prior to the transplant or not. However, EPTH (stated as up to 45 days after transplant in the meeting) was excluded from the term PTDM. Prior to PTDM, the term new-onset diabetes after transplant (NODAT) was used and included patients without known pre-transplant diabetes who had a new diagnosis of diabetes any time after transplant (2). The term NODAT had fallen out of favor because it implied exclusion of patients with diabetes prior to transplant but included patients who might have had unrecognized diabetes prior to transplant. The term transplant-associated hyperglycemia has also been infrequently used to include patients with hyperglycemia at any point after transplant (3) (**figure 1**). Most published studies and guidelines focus on PTDM/NODAT as these are known risk factors for post-transplant complications such as infections, readmissions, graft failure and cardiovascular events (4-8). However, early post-transplant hyperglycemia is important to highlight. For our article, we define hyperglycemia as any episode of fasting glucose (FG) >/=140mg/dL in the inpatient setting or FG >/=126mg/dL in the outpatient setting or random glucose (RG) >/=200mg/dL or requirement of insulin at any time after surgery. In the inpatient setting immediately after transplant, RG >/=200mg/dL and requirement of insulin is more commonly used as a measure of hyperglycemia.

Amongst patients who have undergone renal transplant, diabetes remains the most frequent clinical condition listed, making up to 30% of patients in 2018 (9). Many patients with pre-existing diabetes experience better glycemic control while in end-stage renal disease (ESRD) state, with a resurgence of hyperglycemia after kidney transplant. Maintaining adequate glucose control after transplant in these patients is necessary to prevent recurrent diabetic nephropathy and transplant failure in the long term (10). Even in patients without known pre-transplant diabetes, monitoring for hyperglycemia post-transplant is important. EPTH occurs in 75-92% of patients within the first week (11-13). In a retrospective study conducted by Chakkera et al of 424 patients who underwent renal transplant, 100% of patients with and 87% without pre-transplant diabetes had evidence of inpatient hyperglycemia (RG ≥200 mg/dl or physician-instituted insulin therapy) which was sustained throughout hospitalization (72 hours of hospital stay) (11). EPTH is a risk factor for readmissions, infections and can affect morbidity and mortality in the transplant patient. We hereby present data on the recognition, pathophysiology, adverse effects, and management of EPTH.

II. Patient Cases

Case 1

A 64-year-old male with ESRD secondary to diabetes presented to our institution for kidney transplant. He had been on oral diabetes medications for a few years, and then was transitioned to basal-bolus insulin. He was started on hemodialysis in 2013, after which his insulin requirement decreased until he was able to completely stop using insulin in 2017. In 2020, he received a deceased donor kidney. He received methylprednisolone on the day of surgery, and on post-operative day (POD) 1, followed by prednisone 60 mg twice a day on POD 2, tapering until the dose was down to 7.5 mg on POD 56 onward. Tacrolimus was also initiated during admission. The inpatient endocrine consult team was notified immediately after transplant.

He developed hyperglycemia on POD 1 and was given insulin lispro based on correction scale, given his lean habitus, lack of appetite, and low insulin requirement. He was discharged on insulin glargine U100 10 units in the morning, and an insulin lispro correction scale with meals. He was seen by an endocrinologist at the renal transplant clinic two days after discharge when scheduled insulin lispro 2 units with meals was added. At the next clinic visit after four days, insulin was further up titrated. At 2 weeks after transplantation, the patient contracted COVID19, was readmitted, and was kept on home doses of insulin. After discharge, he continued to be followed by the endocrinology team closely and was eventually transitioned to an oral agent (glimepiride 2 mg daily) approximately 8 weeks after transplant.

Case 2

A 56-year-old male with autosomal dominant polycystic kidney disease (ADPKD) and stage 5 chronic kidney disease (CKD) presented to our institute for kidney transplant. He had no prior history of diabetes and there was no pre-transplant hemoglobin A1C on file. He underwent living donor kidney transplant in February 2020. Immunosuppression was initiated with tacrolimus, glucocorticoid, and mycophenolate mofetil. He developed hyperglycemia while inpatient. He was started on scheduled Neutral Protamine Hagedorn (NPH) insulin 10 units with breakfast along with insulin glulisine correction scale with meals. Prior to discharge on POD2, he was seen by a registered dietician, pharmacist, and diabetes educator to educate about new insulin use and signs of hypoglycemia. Two days after discharge, he was seen by the endocrinology team and his NPH insulin was decreased to 8 units. Correctional insulin was discontinued given tapering dose of glucocorticoids and lower blood glucose values. In follow up visit one week later, he reported increased appetite and higher glucose levels, so NPH insulin was increased and scheduled insulin glulisine with dinner was added. One month later, prednisone was titrated down to 7.5 mg daily at which time insulin was stopped and he was transitioned to alogliptin 25 mg daily with good blood glucose control.

Case 1 demonstrates the return of hyperglycemia in a patient with known diabetes after transplant, while Case 2 shows the onset of hyperglycemia requiring treatment in a patient without prior known diagnosis of diabetes.

III. Pathophysiology of post-renal transplant hyperglycemia

Post-renal transplant hyperglycemia is a result of insulin resistance and relative insulin deficiency, like type 2 diabetes or glucocorticoid-induced diabetes. However, several specific considerations need to be highlighted. Endogenous insulin enters the bloodstream via the portal vein and is mainly cleared by the liver, with the kidney playing a secondary role. Exogenous insulin, on the other hand, bypasses first-pass hepatic excretion, and is cleared proportionately more by the kidneys (14). Therefore, renal function directly affects the metabolism of injected insulin for treatment of diabetes leading to increased insulin susceptibility and predisposition to hypoglycemia. As renal disease progresses, insulin requirement decreases due to decreased clearance by the kidney. In addition, uremia from renal failure causes nausea and loss of appetite, thus reducing hepatic glycogen stores, causing fasting hypoglycemia. Accumulation of uremic toxins also impairs degradation of insulin in the liver prolonging the half-life of endogenous insulin (15). Approximately 20% of gluconeogenesis occurs in the kidneys, which is further decreased in renal dysfunction (14). It is, thus, not uncommon for patients with type 2 diabetes, who previously needed several oral antidiabetic agents and/or insulin, to no longer need these while awaiting kidney transplantation. After successful kidney transplant, insulin clearance improves remarkably which unmasks the preexisting glucose intolerance. Appetite improves due to resolution of uremia, and with addition of oral glucocorticoids. This results in repletion of hepatic glycogen stores, glycogenolysis and renal gluconeogenesis resumption, adding to hyperglycemia (16, 17). The use of oral glucocorticoids as post-transplant immunosuppression increases insulin resistance at the skeletal muscle and adipose tissue level, contributing to hyperglycemia (18-20). Other immunosuppressants, such as cyclosporine and tacrolimus, are reported to decrease insulin secretion, although this has been recently challenged as further discussed in section IVb. Surgical stress and post-transplant infections can further increase the risk of EPTH.

In case 1, the patient ceased to have exogenous insulin requirement prior to transplant. He developed hyperglycemia post-operatively requiring insulin which sustained throughout his hospitalization as well on discharge. This demonstrates the known phenomenon of reduced to nil insulin requirement during ESRD and resurgence of hyperglycemia after renal transplant. In case 2, there was no exogenous insulin requirement prior to transplant but he still developed hyperglycemia post-operatively. The possible reasons for this are discussed below.

IV. Risk factors for early post-renal transplant hyperglycemia (table 1)

a. Impaired pre-transplant glycemic control

The level of fasting glucose pre-transplant is the strongest risk factor for EPTH. In a retrospective study by Cosio et al (12) in 490 kidney transplant recipients with pre-transplant FG<126mg/dL, it was observed that increased FG levels prior to transplantation were related to higher glucose levels one-week post-transplant (FG >/=126 mg/dL or requiring insulin/oral antidiabetic agents). The risk of post-renal transplant hyperglycemia also increased as the fasting pre-transplant glucose levels increased. Sheu et al (21) included patients with pre-existing diabetes in their retrospective analysis and found that this population was at higher risk of developing hyperglycemia in the early post-transplant period compared to those without pre-existing diabetes. Pre-existing diabetes was also associated with increased rejection rates, possibly due to increased ischemic-reperfusion injury.

Prior to development of overt diabetes, there is loss of beta cell function and mass which causes elevated fasting glucose (38). Based on cross-sectional studies, normoglycemia can be maintained

until ~50% of beta cell mass is lost (39). In patients with impaired fasting glucose (IFG) prior to transplant, there is underlying loss of >50% beta cell mass which predisposes them to hyperglycemic effects of glucocorticoids. There might also be underlying insulin resistance in these patients which is unmasked with the use of glucocorticoids intra- and post-transplant predisposing to EPTH.

b. Immunosuppression regimen (table 2)

Oral glucocorticoids are an integral part of post-transplant immunosuppression and act as one of the biggest risk factors for early hyperglycemia. Suggested mechanisms include increased insulin resistance in skeletal muscle and adipose tissue and hepatic gluconeogenesis (18-20). The incidence of hyperglycemia increases with both the dose and duration of glucocorticoid therapy, although a plateau effect might be seen at a certain dose of glucocorticoids after which there is no worsening hyperglycemia. High dose glucocorticoids are commonly prescribed with induction and to treat rejection or graft-versus-host disease in the early post-transplant period. Unfortunately, dose reduction in glucocorticoids can also increase the risk for graft rejection. Consensus is that immunosuppression regimens should have the best outcome for patient and graft survival, irrespective of risk for hyperglycemia (1).

Other immunosuppressants could also contribute to hyperglycemia, including the calcineurin inhibitors (tacrolimus more than cyclosporine) and inhibitors of the mammalian target of rapamycin (mTOR), such as sirolimus and everolimus. Calcineurin inhibitors (CNIs) are reported to reduce insulin secretion, increase islet cell destruction, and exacerbate insulin resistance (22-25). CNIs inhibit calcineurin-dependent gene transcription that leads to dose-dependent reductions in insulin mRNA, cellular insulin content, and glucose-stimulated insulin secretion in β-cell lines and rodent islets (26). In human adipocytes, both cyclosporine and tacrolimus inhibit glucose uptake independent of insulin signaling by removing GLUT4 from the cell surface through an increased rate of endocytosis (29). Tacrolimus has been associated with a higher risk of PTDM as compared to cyclosporine, but this trend is unclear in the early post-transplant period. The hyperglycemic effects of these medications are observable as early as 2 months after initiation of immunosuppression (27). Sirolimus disrupts insulin action through multiple effects on the insulin signal transduction pathway and can reduce beta cell function and islet mass although its use has decreased recently because of adverse effects (23). However, another line of evidence suggests that insulin secretion may be maintained in the presence of tacrolimus, as demonstrated in a study comparing pancreas-kidney and kidney-alone transplant recipients to islet cell recipients (29). While beta cell secretory capacity was reduced in islet transplant recipients, it was normal in the other two groups while they were on the same tacrolimus-based immunosuppression. This was attributed to islet recipients having lower engrafted beta-cell mass. None of the groups showed increased insulin resistance suggesting that tacrolimus might not markedly contribute. This was also noticed in a study using mTOR inhibitors such as sirolimus (30).

Notably, the kidney-alone transplant recipients in the study by Rickels et al (29) did not have diabetes prior to transplant and the average BMI of all the participants was 20-25 kg/m^2. This suggests that CNIs and mTOR inhibitors, by themselves, might not contribute as much to impaired post-transplant glycemic control as pre-transplant risk factors and post-transplant weight gain. Modern lower dose tacrolimus and sirolimus regimens seem to have lesser effect on insulin secretion and resistance (29, 30). Further studies would be necessary to state this conclusively.

Mycophenolate mofetil, azathioprine and the new agent belatacept have not been shown to have a large impact on insulin action or glucose metabolism and do not appear to have a major role in early hyperglycemia (27, 40, 41).

c. Surgical stress, nutrition, physical activity, post-operative pain, and infections

Surgery and post-operative pain are known to increase risk of hyperglycemia by triggering cytokines and stress hormones. Surgical stress has a deleterious effect on pancreatic β-cell function due to release of catabolic hormones causing inhibition of insulin secretion resulting in hyperglycemia (29). This hyperglycemia is usually transient and resolves after discharge. In addition, especially in the first few weeks after surgery, patients' appetite increases compared to when they were in end-stage kidney disease. High dose glucocorticoids also increase appetite, and post-operative recovery limits the amount of exercise that can be done.

The immunosuppressed state post-transplant increases the risk of infections. Severe infection or sepsis can precipitate hyperglycemia even in patients with normal glucose tolerance (30, 40). Pre-existing chronic infections such as chronic hepatitis C or cytomegalovirus can also increase risk of post-transplant hyperglycemia (41).

Early hyperglycemia was also seen to be associated with increasing age, obesity, and elevated triglyceride levels (12, 31-33).

For Case 1, his major risk factors for development of EPTH included pre-existing diabetes (probably his biggest risk factor), surgical stress, post-operative pain, high dose glucocorticoids, possibly tacrolimus use and COVID infection.

For Case 2, while he did not have known pre-existing diabetes, the absence of screening prior to transplant restricts us in saying that he did not have diabetes. His other risk factors included surgical stress, post-operative pain, glucocorticoid, and possible tacrolimus use.

V. Complications of early post-renal transplant hyperglycemia: re-hospitalizations, infections, graft survival and cardiovascular risk (table 3)

Inpatient hyperglycemia, in general, is known to be associated with adverse patient outcomes, higher mortality and greater costs (60-62).

a. Infections and re-hospitalizations

Hyperglycemia in the immediate period after renal transplant has been associated with increased risk of re-hospitalization for infections while being on the same immunosuppressive regimen as patients without hyperglycemia (42). This can be explained by the complex deleterious effects of hyperglycemia on the immune system including changes in leukocyte function, cytokine response, altered microvascular response, and the pro-inflammatory state caused by hyperglycemia leading to oxidative stress (63). In a study done by Thomas et al (10), all patients with poor post-operative glycemic control (mean glucose levels >200 mg/dL) in the first 100 hours after transplant developed infections. Studies have reported a higher incidence of CMV infection, which is one of the most common post-renal transplant infections, in patients with EPTH (43, 44).

The recent SARS-Cov-2 (COVID-19) pandemic deserves mentioning. Kidney transplant recipients may be at high-risk of severe COVID-19 infection due to long-term immunosuppression, residual CKD and other comorbidities, in particular diabetes and hypertension, which are now recognized as significant factors that influence outcomes in patients with COVID-19 infection (63). A study done in the epicenter of the pandemic (Bronx, New York) suggested a prevalence of 23.4% (including asymptomatic patients) of COVID-19 infection in renal transplant recipients (45). Kidney transplant recipients infected with COVID-19 have been seen to have a higher rate of graft rejection and death in a few reports (46, 47). However, in a case report of a patient who contracted COVID-19 and was maintained on conventional-dose immunosuppression during inpatient treatment, it was proposed that the immunosuppressed state could have protected the patient from the cytokine storm and severe immune injury (48). There is not enough data to suggest a modified hyperglycemia management approach for kidney transplant recipients admitted for COVID-19. Following guidelines, these patients are managed with insulin, like other patients with inpatient hyperglycemia as specified further in VII b.

Case 1 was managed for COVID-19 at home without oxygen requirement or further treatment specific for COVID-19. He continued to require 12 units of glargine in the morning with mealtime lispro increased to 6 units (from 4 units) along with correctional scale. He did not develop diabetic ketoacidosis and was seen in clinic 2 weeks after detection of COVID19. We now know that, per COVID-19 treatment guidelines laid out by the National Institute of Health (NIH), anti-SARS-CoV-2 monoclonal antibodies would be indicated to treat non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression, such as transplant recipients on immunosuppression (64). Monoclonal antibodies have been shown to reduce the risk of severe disease requiring hospitalization (65). A transplant specialist should also be consulted prior to adjusting immunosuppressive regimen and clinicians should pay careful attention to drug-drug interactions and potential toxicities when treating these patients.

b. Renal graft dysfunction and acute graft rejection

Acute rejection is believed to be initiated in the early post-operative period by antigen presentation, possibly in response to allograft inflammation and injury. Early hyperglycemia has been associated with acute graft rejection, which was defined as biopsy-proven or clinical rejection occurring within 20 days of transplantation (10, 44, 49). This was shown in a retrospective study done by Thomas et al in 2001 (50) wherein 58% of patients (n=50) with poor perioperative glycemic control (mean glucose levels >/=200 mg/dL) developed acute rejection. High glucose levels in the immediate period after surgery potentiate ischemic injury and can predispose to acute graft rejection (66-68). These patients have increased rates of return to dialysis after transplant which was found to be related to blood glucose control during transplant admission (51). This suggests that hyperglycemia immediately after transplant may represent a modifiable risk factor for donor graft failure.

While the exact mechanism has not been elucidated, it can be hypothesized that the inflammatory response associated with hyperglycemia contributes to rejection. Hyperglycemia has deleterious effects on the endothelium by attenuation of endothelium-dependent vasodilation resulting in vasoconstriction potentially causing ischemic injury to graft (69). The generation of lactate and reactive oxygen species is augmented by hyperglycemia which could lead to re-perfusion injury (70). The inflammatory response to ischemia/reperfusion and rejection is also exaggerated by hyperglycemia worsening the rejection episode (71).

Wyzgal et al observed that early hyperglycemia was associated with acute graft rejection, worse renal graft function and higher proteinuria (44). It is important to note that there was still a high incidence of acute rejection (37%) in patients who had immediate hyperglycemia but did not end up developing PTDM in the follow up period. In a study done by Schiel et al (52), the prevalence of acute transplant rejections was 16.3% in patients with diabetes and 7.1% in patients without diabetes, although this was not clinically significant (p=0.11). In multivariate analysis though, the most important parameter associated with the incidence of transplant rejections was high FG at 6-8 weeks, which was significant (*P*=0.009). All other parameters included (body mass index, time since transplantation, diabetes duration, immunosuppressive therapy, HbA1c and HLA mismatch) revealed no associations.

c. Cardiovascular complications and mortality

Renal transplant recipients have an increased risk of premature death, with cardiovascular disease (CVD), malignancy and infectious disease being the predominant causes of mortality (53). Diabetes as a risk factor for increased cardiovascular risk is now widely accepted. Multiple studies have now shown hyperglycemia and fluctuating glucose levels to be an independent risk factor for cardiovascular risk (72, 73). This could be attributable to the endothelial dysfunction, caused by hyperglycemia through oxidative stress, which is the first step to atherogenesis. Acute hyperglycemia attenuates endothelium-mediated vasodilation and reduces myocardial perfusion causing increased cardiovascular risk (74).

High FG levels (>/=100 mg/dl) at one month (as well as at 4 and 12 months) post-transplant have been significantly related to cardiovascular events such as myocardial infarction, cerebrovascular accidents, and peripheral vascular disease (6). These relationships were independent of other cardiovascular risk factors including older age, pre-transplant cardiovascular events, male gender and dyslipidemia. In a prospective study done by Valderhaug et al (56) of 1,410 patients without known diabetes who underwent renal transplant, it was shown that post-transplant hyperglycemia (defined as 2-hour serum glucose after oral glucose tolerance test >/=140 mg/dL) at 10 weeks was associated with an approximately two-fold increased risk of death from CV disease, malignancy and infectious disease as compared to patients with normoglycemia. However, data regarding effect of hyperglycemia occurring within 45 days of transplant on cardiovascular risk is scant.

d. Post-transplant diabetes mellitus (PTDM)

In patients without pre-existing diabetes prior to transplant, not everyone who develops early hyperglycemia will progress to PTDM. Of those who do, development of fasting hyperglycemia during the first week post-transplant has been shown to be the strongest predictor of PTDM at one year (6, 12). Multiple retrospective studies in patients with PTDM have reported a high frequency of early hyperglycemia as compared to those that did not develop PTDM (18, 57, 75). Early initiation of basal insulin to achieve glycemic control after kidney transplant may reduce risk of developing PTDM (13). Wyzgal et al (44) demonstrated, in their prospective 3-year study, that 75% of the people with hyperglycemia during first week of renal transplantation developed diabetes mellitus in the follow-up period of 3 years.

It is well documented that PTDM is associated with poor graft outcomes, increased infections, cardiovascular disease, and recurrent hospitalizations following renal transplants (4-8). Thus, an increased risk of PTDM in this population calls for a need for early intervention.

Table 3 attempts to consolidate and summarize the available evidence regarding complications of EPTH. Further studies are needed to predict long-term effects of EPTH on morbidity and mortality. The authors recommend studies looking at long-term cardiovascular effects of EPTH. It would also be beneficial to study the rates of COVID-19 infection in the patients undergoing renal transplant during the pandemic (2020-21) and whether patients with EPTH were more predisposed to contracting the infection.

VII. Clinical considerations and management

Most of the recommendations published on hyperglycemia management after renal transplant are focused on PTDM occurring months or years after surgery and not in the early postoperative period. Management is currently done on an institutional basis and requires coordinated interdisciplinary care while inpatient and on discharge.

a. Inpatient diabetes education

Patients with pre-existing diabetes may have experienced a decrease in diabetes medication requirement, including insulin, in the setting of ESRD or might have been controlled on diet alone prior to transplant. After kidney transplantation, there is a resurgence of hyperglycemia as explained above. Even for patients without a pre-transplant diagnosis of diabetes, most patients develop hyperglycemia while in the hospital (11). Therefore, a significant percentage of patients will need education or re-education on checking capillary blood glucose via self-monitoring of blood glucose (SMBG) or a continuous glucose monitor (CGM). Though nutrition and exercise are also integral components of diabetes management, patients have poor appetite and have limited physical activity during this early post-operative period.

At our institute, patients are often discharged 2 days after renal transplantation, unless with complications such as in our case 1. Most patients with hyperglycemia are discharged on insulin. To facilitate this, the inpatient endocrine consult team is notified after surgery, and the diabetes educators initiate insulin and glucose meter teaching. We have found that many patients are too tired or overwhelmed after surgery, so we have started the insulin and glucose meter teaching prior to transplantation for patients not currently on insulin as they approach the top of the transplant list. So far, we have initiated this for patients on the list for deceased kidney donation since there is time to schedule the training. We are evaluating the feasibility of doing this in a timely manner for live donor recipients but the time from evaluation to surgery in this scenario is a bit tighter.

While case 1 had diabetes prior to transplant and was well educated about insulin use, case 2 had no prior experience with insulin administration and side effects. Diabetes education must be personalized based on patient's experiences and a brief visit with a diabetes educator and a pharmacist is warranted after transplant prior to discharge home.

b. Inpatient hyperglycemia management

In the post-transplant hospitalized setting, insulin remains the standard of care for hyperglycemia along with avoidance of all non-insulin anti-diabetic agents in accordance with the American Diabetes Association (ADA) standards of care (76). The anti-inflammatory and antioxidant effects of insulin have contributed to the recommendation of its use for correction of post-surgical stress-induced hyperglycemia (77). Optimization of glycemic control is difficult with non-insulin agents and is limited by side-effects. Renal transplant patients are more sensitive to glucose variability and may

suffer from hypoglycemia, which is also a well-recognized risk factor for complications and could be associated with renal failure in the post-transplant patient (78). Glycemic variability (both hyper- and hypoglycemia) has been shown to be also a risk factor for falls in hospitalized patients (79).

Immediately after transplantation, some institutes might manage their patients in the ICU and treat hyperglycemia aggressively with intravenous insulin while other institutes might manage patients on the regular nursing floor with subcutaneous insulin. A randomized controlled study of kidney transplant recipients designed to assess the impact of tighter glycemic control during the post-transplant hospitalization period (blood glucose 70–110 vs <180 mg/dL) showed that the intensive group experienced not only more hypoglycemia but also more rejection episodes, although the latter was not statistically significant (80). The ADA recommends a target glucose range of 80 to 180 mg/dL in the perioperative period (81). For critically ill patients, the American Association of Clinical Endocrinology (AACE) and the ADA recommend starting an intravenous insulin infusion and frequent glucose monitoring for patients with blood glucose (BG) ≥ 180 mg/dl, targeting a BG of 140–180 mg/dl, with lower targets of 110–140 mg/dl in selected patients (82). For non-critically ill patients, the Endocrine Society and AACE/ADA guidelines recommended a target pre-meal BG of <140 mg/dl and random BG < 180 mg/dl, with subcutaneous basal-bolus regimen preferred (83). Control of hyperglycemia assists in wound healing, decreases the risk of infection, and reduces osmotic diuresis which is essential as post-transplant diuresis is a risk factor for volume depletion and hemodynamic instability. Given the hyperglycemia exacerbation caused by glucocorticoids, insulin is used during the inpatient period after transplant, and most are discharged on insulin as well.

c. Glucose monitoring and glycemic goals

In the early post-transplant period and few weeks after discharge, frequent point-of-care glucose testing is important to determine glycemic status since hemoglobin A1C measures about 3 months of glycemic control and will not be useful in this setting. Post-challenge 2-hour serum glucose measured early after renal transplantation has been found to be superior to fasting glucose to detect hyperglycemia even after adjustments for confounding risk factors (56).

Current ADA targets are recommended, using a patient-centered approach, with a goal pre-meal blood glucose of 80–130 mg/dl and post-prandial blood glucose of <180 mg/dl (84). In transplant recipients with advanced micro- and macro-vascular complications and/or high hypoglycemic risk, a less stringent pre-meal goal of 110–140 mg/dl is acceptable to avoid hypoglycemia.

d. Insulin regimen at discharge

The current recommendation is insulin therapy on discharge for patients with EPTH, with the introduction of oral hypoglycemic agents (OHAs) as tolerated out-patient on an individualized basis (1). The insulin treatment regimen required at the time of discharge is highly variable and does not readily lend itself to a fixed insulin per kilogram dose, in part, because of the variability in kidney function, glucocorticoid and other immunosuppressant doses used, severity of obesity, and other factors which drive insulin resistance in this group. Drug-drug interactions, glucocorticoid dosing changes, and oral intake can influence further regimen choice and dosage.

Discharge algorithms in transplant have not been well studied; however, it is reasonable to consider basal/bolus insulin therapy if the total daily dose required at discharge is >/=0.25 units/kg (on stable glucocorticoids) (85). Basal insulin with a correctional insulin scale or an oral agent can be considered for those on <0.25 units/kg/day insulin, minimal nutritional intake, and stable glucocorticoid dosing.

Studies suggest that regimens that include basal insulin significantly reduce the risk for PTDM at one year, presumably via insulin-mediated protection of β cells (13). Twelve months after transplantation, all patients in the treatment group (with basal insulin) were insulin-independent, whereas 28% controls (on short acting insulin) required anti-diabetic agents. The groups did not differ for insulin sensitivity, but the treatment group showed better β-cell function throughout the 1-year follow-up, as measured by the insulinogenic index (IGI).

e. Non-insulin agents (table 4)

Though insulin is the usual for management post-renal transplant, consideration has been given to non-insulin agents for managing EPTH. Traditional oral agents, such as metformin and sulfonylureas require dose adjustment for renal function (which varies in the initial post-transplant period) and have significant side effects including gastrointestinal upset and hypoglycemia, respectively. Most studies done for non-insulin agents initiate these agents years after transplant and in patients that develop PTDM.

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) may be a relatively safe and effective treatment for kidney transplant recipients. The benefit of GLP-1 RA extends beyond glycemic control to weight loss and improved cardiovascular risk. Multiple recent trials have shown that therapy with GLP-1 RA 3-5 years after transplant has no adverse effect on the kidney allograft outcomes, has a similar side effect profile to the general population, and has no significant impact on tacrolimus dosing (86-88). Importantly, these agents facilitated significant insulin dose reduction allowing for less hypoglycemic events.

In pre-clinical models, dipeptidyl peptidase-4 (DPP-4) inhibitors have demonstrated efficacy in preserving beta cell function under stress (89). Thus, the use of DPP-4 inhibitors could offset the possible calcineurin inhibitor induced toxic effect on beta cells and improve insulin resistance. Linagliptin is a DPP-4 inhibitor that does not have the side effects associated with insulin or metformin use and does not require dose adjustment with reduced renal function as is commonly seen in the early post-transplant setting (90). A small comparative study of 28 patients showed that the use of linagliptin plus insulin provided better glycemic control with a lower insulin dose and less severe hypoglycemia in comparison to insulin alone in patients with hyperglycemia immediately after renal transplantation (from POD 0 to POD 5) (91). Another study compared intensive surveillance and early commencement (as early as 2 days after transplant) of oral therapy with linagliptin to conventional treatment in a historical cohort of patients with post-transplant immunosuppression. Patients who were treated with linagliptin had better HOMA-IR (homeostatic model assessment for insulin resistance) and HOMA-B (homeostatic model assessment of beta cell function) scores along with better blood glucose at every time point after a glucose load (92). Vildagliptin has been shown to improve B-cell function in PTDM (93) and sitagliptin has been shown to improve Hemoglobin A1C in kidney transplant recipients (94).

The use of sodium-glucose cotransporter 2 (SGLT2) inhibitors in post-renal transplant patients is limited by the risk of renal graft dysfunction and urinary tract infections (UTI). Canagliflozin was studied in patients who underwent renal transplant with prior history of diabetes or if they developed PTDM and results were favorable in causing reduction in body weight, blood pressure, Hemoglobin A1C and requirement of other hypoglycemic agents without any hypoglycemic episodes or significant adverse effects including UTIs and diabetic ketoacidosis (95). However, the initiation of canagliflozin in these patients was, on average, 0.2-13.2 years after transplantation and not exclusively in the early post-transplant period.

While insulin is an appropriate agent to control hyperglycemia in the early post-transplant period, the timing of initiation of agents other than insulin requires further investigation for safety and efficacy. Case 1 had stable renal function 8 weeks after transplant and, since he had diabetes prior to transplant, was aware of hypoglycemic symptoms to be alerted by. For this reason, he was transitioned to glimepiride, a sulfonylurea. Case 2 was transitioned to an oral agent (alogliptin, a DPP-4 inhibitor) about 6 weeks after transplant.

f. Lifestyle modifications

Lifestyle modification including dietitian referral, exercise program, and weight loss benefits kidney transplant recipients with impaired glucose tolerance and should be implemented on discharge. Intensive lifestyle modifications and a diet rich in omega-3 and omega-9 fatty acids showed promising benefits in kidney transplant recipients (96). Exercise aimed at building of muscle mass and reduction of fat, as opposed to weight loss, has been postulated to be beneficial in the renal transplant population (97).

Table 5 summarizes our recommendations for management of EPTH.

VIII. Conclusion:

Patients with pre-existing diabetes experience better glycemic control while in end-stage renal disease (ESRD) state, with a resurgence of hyperglycemia after kidney. Renal insulin clearance decreases significantly in ESRD while renal transplant increases insulin clearance paving the path for resurgence of hyperglycemia. Early post-renal transplant hyperglycemia (EPTH) occurring within 45 days of renal transplant puts recipients at increased risk for re-hospitalization due to infections such as CMV, acute graft rejection within 20 days of transplant, increases rate of return to dialysis, cardiovascular events, and post-transplant diabetes mellitus (PTDM). Both patients with and without known diabetes prior to transplant can develop EPTH. It is important to identify risk factors for EPTH including elevated fasting glucose levels prior to transplant, pre-existing diabetes, glucocorticoid use, surgical stress, post-operative pain, pre-existing chronic infections such as chronic hepatitis C or CMV and post-transplant infections. Screening patients without a known diagnosis of diabetes prior to renal transplant, utilizing tools such as oral glucose tolerance test, will help recognize patients with impaired fasting glucose and impaired glucose tolerance. Early recognition and management strategies include providing education to patients prior to discharge, frequent self-monitoring of blood glucose after discharge and close follow-up with an endocrinology provider and pharmacist. Current ADA targets are recommended, using a patient-centered approach, with a goal pre-meal blood glucose of 80–130 mg/dl and post-prandial blood glucose of <180 mg/dl. Insulin is the current standard for management, however, non-insulin agents like DPP-4 inhibitors (particularly linagliptin) have shown some promise in the early post-transplant setting. Other agents such as GLP-1 RA and SGLT-2 inhibitors might also be effective, however, studies are lacking. There is a need for further studies looking at safety profiles and efficacy of injectable and oral non-insulin agents in the early post-renal transplant setting to decrease risk of hypoglycemia associated with insulin and reduce long term complications stemming from EPTH.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Table 1: Risk factors for EPTH and supporting evidence

Risk factor	Pathophysiology	Reference studies
Impaired pre-transplant glycemic control	Loss of beta cell function and mass predisposing to hyperglycemic effects of glucocorticoids, underlying insulin resistance	12, 21
Glucocorticoids	Increased insulin resistance at skeletal muscle and liver, hepatic gluconeogenesis	1, 18-20
Calcineurin inhibitors, mTOR inhibitors	Possible impaired insulin secretion, insulin resistance	22-30
Surgical stress, post-operative pain, increased appetite	Increased cytokines and stress hormones	31
Pre- and Post-transplant infections (Chronic hepatitis C, CMV)	Increased cytokines and stress hormones	32-34
Increasing age, obesity, and elevated triglyceride levels	Developing insulin resistance, relative insulin deficiency	12, 35-37

Table 2: Commonly used immunosuppressants which cause hyperglycemia and mechanism

Agent	***Proposed Mechanisms of Hyperglycemia***
Glucocorticoids (19-21)	Increased insulin resistance at the level of skeletal muscle and liver Increased hepatic gluconeogenesis
Calcineurin Inhibitors (22-25)	Dose-dependent β-cell toxicity which reduces insulin secretion Exacerbate insulin resistance
Tacrolimus	Removal of GLUT4 transporter from cell surface
Cyclosporine	Tacrolimus associated with more PTDM than cyclosporine
mTor Inhibitors (26)	Impairment of insulin signaling pathway
Sirolimus	Possibly reduces beta cell function
Everolimus	Possibly reduces islet mass

Table 3: Complications of EPTH and supporting evidence

Complications	Pathophysiology	Reference studies
Infections/Re-hospitalization	Hyperglycemia affects the immune system by causing changes in leukocyte function, cytokine response, microvascular response and results in a pro-inflammatory state causing oxidative stress	42, 10, 43, 44
COVID-19 infection		45-48
Acute graft rejection, return to dialysis	Hyperglycemia causes attenuation of endothelium-dependent vasodilation causing ischemic injury to graft. The generation of lactate and reactive oxygen species is augmented by hyperglycemia which could lead to re-perfusion injury.	10, 44, 49-52
Increased cardiovascular risk	Hyperglycemia causes endothelial dysfunction through oxidative stress, which is the first step to atherogenesis. Attenuation of endothelium-mediated vasodilation also reduces myocardial perfusion.	6, 53-56
Post-transplant diabetes mellitus	Hyperglycemia might be due to underlying insulin resistance and relative insulin deficiency which can progress to DM if not controlled well.	6, 12, 13, 18, 44, 57, 58

Table 4: Non-insulin agents that could be used for management of EPTH

Non-insulin agent	Considerations for use in EPTH	Reference studies	Comments
Metformin	○ Avoid with tenuous renal function ○ Gastrointestinal upset ○ Can rarely cause lactic acidosis in impaired renal function		Not favored in EPTH
Sulfonylurea	○ Require dose adjustment with renal function which varies in the early post-transplant period ○ High risk of hypoglycemia ○ Weight gain		Not favored in EPTH
Glucagon-like peptide-1 receptor agonists (GLP-1 RA)	○ Potential risk of acute kidney injury with higher dose ○ Cardiovascular benefit ○ Weight loss	86-88	Need further studies for use in EPTH
Dipeptidyl peptidase-4 (DPP-4) inhibitors	○ Better HOMA-IR (homeostatic model assessment for insulin resistance) and HOMA-B (homeostatic model assessment of beta cell function) as compared to insulin ○ Linagliptin does not require renal dose adjustment	89-94	Favorable studies, need randomized controlled trials to compare glycemic control for EPTH
Sodium-glucose cotransporter-2 (SGLT2) inhibitors	○ Avoidance with tenuous kidney function ○ Potential for causing dehydration ○ Genitourinary infections ○ Weight loss	96	Need further studies for use in EPTH

	○ Blood pressure control ○ Increased risk of volume depletion and ketoacidosis perioperatively ○ Canagliflozin showed glycemic improvement at 6 months post-transplant without significant adverse effects		
Thiazolidinediones	○ Potential for fluid retention ○ Slow onset of action in improving hyperglycemia ○ Weight gain ○ Increased risk for heart failure		Not favored

Table 5: Recommendations for inpatient and discharge management of hyperglycemia after renal transplant

Inpatient	Diabetes education even prior to transplant with reinforcement of information afterwards Medication reconciliation and ensuring insurance coverage is critical for successful discharge Blood glucose target is 140-180 mg/dL while inpatient o Lower target 70-110 mg/dL increases hypoglycemia without improving outcome Therapy of choice is insulin o Non-insulin therapy side effect profile can be significant o Risk of unpredictable hypoglycemia with certain oral agents o Basal/bolus recommended if total daily dose ≥0.25 units/kg o Basal with correctional scale or oral for those <0.25 units/kg/day or minimal nutrition
Early Outpatient	BG target 80-130 mg/dL pre-meal and <180 mg/dL post-prandial o In patients with DM complications or high-risk hypoglycemia, can target pre-meal 110-140 mg/dL For insulin therapy o Quick follow up with endocrinology post-discharge for titration o If glucocorticoids are being weaned, no specific titration of insulin proven to be more efficacious and is done at discretion of physician o If bolus requirements are low can consider non-insulin therapy to replace For non-insulin therapy o GLP-1 RA is safe and effective with benefits of weight loss and reduced cardiovascular risk o DPP-4 inhibitor linagliptin, vildagliptin and sitagliptin have all been studied and safe and effective in reducing hyperglycemia o SGLT2 inhibitors have been avoided due to concern for UTI and graft

	dysfunction For lifestyle recommendations ○ Weight loss should not be emphasized but rather improvement in muscle mass and reduction in fat mass

Figure 1: Terminologies used for post-renal transplant hyperglycemia and timing