

New-onset diabetes after transplantation presenting with diabetic ketoacidosis: A rare but life-threatening complication

Abstract

New-onset diabetes after transplantation (NODAT) is a recognized metabolic complication following kidney transplantation, typically occurring within the first year post-transplant. While hyperglycemia is a common manifestation, presentation as diabetic ketoacidosis (DKA) is exceedingly rare. A 22-year-old male with a history of hypertension and hypothyroidism underwent living-related renal transplantation from his mother for end-stage renal disease. Pre-transplant metabolic evaluation revealed normal fasting insulin and C-peptide levels with mildly elevated insulin resistance indices. Post-operatively, the patient received triple-drug immunosuppression with tacrolimus, mycophenolate mofetil, and prednisolone, maintaining euglycemia during early recovery. On day 110 post-transplant, he presented with altered sensorium, anuria, and severe hyperglycemia (random blood glucose 1183 mg/dL), fulfilling criteria for diabetic ketoacidosis with high anion gap metabolic acidosis and ketonuria. Laboratory evaluation revealed mild allograft dysfunction (serum creatinine 2.53 mg/dL) and severe anemia (hemoglobin 6.5 g/dL). Intensive management with intravenous insulin infusion, aggressive fluid therapy, and immunosuppressive dose optimization led to complete metabolic recovery, successful graft preservation, and transition to subcutaneous insulin therapy. This case highlights the potential for tacrolimus-based immunosuppression to precipitate severe hyperglycemic crises such as DKA in transplant recipients, even in young patients without conventional diabetes risk factors. Early recognition, prompt multidisciplinary management, and regular glycemic monitoring are vital to prevent graft loss and mortality, particularly within the first six months following transplantation.

Keywords: new-onset diabetes after transplantation, diabetic ketoacidosis, tacrolimus, kidney transplantation, immunosuppression, pancreatic beta-cell dysfunction

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Abbreviations: ESRD, end-stage renal disease; CNIS, calcineurin inhibitors; NODAT, notably new-onset diabetes after transplantation; DKA, diabetic ketoacidosis

Introduction

Kidney transplantation remains the optimal treatment modality for patients with end-stage renal disease (ESRD), offering significantly superior long-term survival and quality of life compared to maintenance dialysis. However, despite substantial advances in surgical techniques and immunosuppressive protocols, long-term transplant success continues to be challenged by metabolic complications, most notably new-onset diabetes after transplantation (NODAT).^{1,2} The reported incidence of NODAT varies widely—from 7% to 30% of kidney transplant recipients—depending on the diagnostic criteria employed and duration of post-transplant follow up.^{1,3,4} The clinical significance of NODAT extends far beyond the diagnosis of hyperglycemia. NODAT is independently associated with marked increases in morbidity and mortality, including elevated risks of cardiovascular disease, infectious complications, and progressive allograft dysfunction.⁵⁻⁷ Several cohort studies have demonstrated higher all cause and cardiovascular mortality among transplant recipients who develop NODAT compared with those who remain non diabetic.^{5,8} The pathophysiology of NODAT is multifactorial, involving a complex interplay between traditional diabetes risk factors—such as obesity, family history, and increasing age—and transplant specific contributors related to immunosuppressive therapy.^{1,3} Among immunosuppressive agents, calcineurin inhibitors (CNIs) remain integral to standard post-transplant immunosuppression.

Although tacrolimus offers superior efficacy in preventing acute rejection compared to cyclosporine, it is associated with a substantially higher incidence of NODAT.^{2,3,9} The diabetogenic mechanisms of tacrolimus are multifaceted, encompassing direct pancreatic beta cell toxicity, impaired insulin gene transcription, and reduced insulin secretion.^{9,10} Furthermore, recent studies have identified hypomagnesemia as an independent risk factor for NODAT development among patients receiving tacrolimus, suggesting an additional metabolic vulnerability within this cohort.⁶ While hyperglycemia is a common manifestation, presentation with diabetic ketoacidosis (DKA) as the initial clinical event remains exceptionally rare. Only a few reports of tacrolimus induced DKA have been documented in solid organ transplant recipients, most occurring within the first few months after transplantation.^{10,11} When DKA develops in this setting, it poses grave risks to both patient survival and graft function.^{10,11} Here, we present the case of a young kidney transplant recipient who developed severe, life threatening DKA 110 days post transplantation. Despite normal pre transplant glycemic indices and early postoperative euglycemia, the patient experienced catastrophic metabolic decompensation. To our knowledge, this represents one of the few documented instances of tacrolimus associated DKA in a young recipient without conventional diabetes risk factors. This case underscores the unpredictable metabolic consequences of immunosuppression and highlights the importance of prolonged, vigilant glycemic surveillance beyond the immediate post-transplant period.

Case presentation

Patient information and history

A 22-year-old male with hypertension and primary hypothyroidism presented with end-stage renal disease of undetermined etiology and no prior history or family history of diabetes or other metabolic disorders. After comprehensive cardiovascular, infectious, and metabolic evaluation, he underwent living-related renal transplantation from his mother with a 3/6 HLA haplotype mismatch, which is typical for living-related donor procedures.

Pre-transplant metabolic assessment

Pre-operative metabolic profiling demonstrated normal fasting insulin and C peptide levels, indicating preserved baseline pancreatic beta-cell reserve. Calculation of HOMA-IR and HOMA β revealed mildly elevated indices, suggesting compensatory hyperinsulinemia in the setting of pre-existing insulin resistance, a phenotype increasingly recognized as a predictor of subsequent NODAT.

Transplant procedure and early post-operative course

Renal allograft implantation was uneventful, with immediate graft function in the operating room. The patient received induction methylprednisolone followed by maintenance tacrolimus (target trough 8–12 ng/mL), mycophenolate mofetil 1000 mg twice daily, and prednisolone 20 mg daily with a tapering schedule. On post-operative day 0, 6 units of subcutaneous insulin were administered for stress hyperglycemia, after which days 1–7 were characterized by euglycemia without further insulin, serum creatinine improvement to 1.58 mg/dL, and normal hemoglobin at discharge on day 8.

Intermediate complication: pure red cell aplasia

At post-operative day 60, the patient re-presented with severe symptomatic anemia (hemoglobin 4.5 g/dL), and bone marrow studies confirmed pure red cell aplasia, a recognized but uncommon complication in renal transplant recipients receiving immunosuppression and erythropoietin exposure. Management involved transfusion of two units of packed red blood cells, oral iron supplementation, and increasing prednisolone from 15 mg to 30 mg daily before tapering back to 15 mg, after which hemoglobin stabilized until the DKA event.

Acute presentation: diabetic ketoacidosis

On post-operative day 110, the patient presented with 24–48 hours of progressive oliguria culminating in anuria and profound alteration of consciousness. Examination showed marked dehydration, Glasgow Coma Scale score of 11/15 (E3V4M4), tachycardia, and tachypnea consistent with Kussmaul respiration in severe metabolic acidosis.

Laboratory evaluation at DKA onset

Point-of-care capillary glucose exceeded device limits (>600 mg/dL), and serum glucose measured 1183 mg/dL, among the highest values reported in tacrolimus-associated DKA. Investigations showed serum creatinine 2.53 mg/dL, hemoglobin 6.5 g/dL, strongly positive urinary ketones (3+), arterial pH <7.25 with low bicarbonate and an anion gap >12 mEq/L, confirming high anion gap metabolic acidosis and fulfilling diagnostic criteria for DKA with associated acute allograft dysfunction. Figure 1 (Total Insulin and Max RBS) demonstrates the extreme initial hyperglycemia and subsequent decline in random blood sugar over the hospitalization in relation to total daily insulin dose.

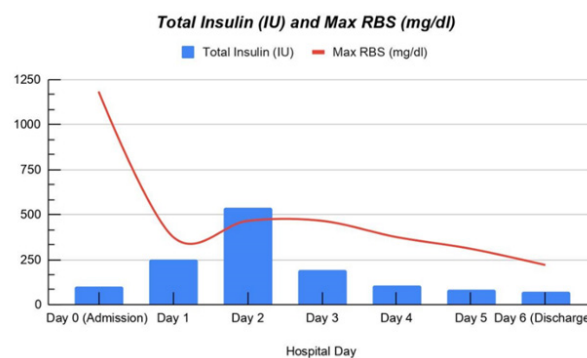


Figure 1 Temporal trend of glycaemic control and insulin requirements during the acute management of DKA.

The graph illustrates the relationship between Random Blood Sugar (RBS) levels and the total daily insulin dose administered over the first 6 days of admission. Note the rapid decline in RBS from an admission high of 1183 mg/dl and the resolution of ketonuria by Day 2, allowing for the tapering of insulin doses.

Intensive care management

The patient was transferred to the intensive care unit and commenced on continuous intravenous human soluble insulin following a high-dose sliding-scale protocol, receiving approximately 80 units in the first 10 hours then 40 units every subsequent 8 hours with titration based on hourly glucose monitoring. Aggressive but carefully titrated isotonic saline resuscitation, close electrolyte surveillance with targeted potassium, phosphate, and magnesium replacement, and a reduction of prednisolone to 10 mg daily were undertaken, while tacrolimus and mycophenolate doses were maintained under therapeutic drug monitoring.

Daily glycaemic course and renal response

By day 1, acidosis had substantially corrected, though 248 units of intravenous insulin were required with glucose 230–360 mg/dL and urinary ketones decreasing to 2+. On day 2, acidosis had fully resolved and ketones became negative, but insulin requirement peaked at 538 units as glucose gradually fell from 465 to 267 mg/dL; by day 3, intravenous insulin (168 units) was combined with 25 units of subcutaneous insulin, with stable ketone negativity. Complete transition to subcutaneous insulin was achieved by day 4 with declining total daily doses over days 5–6, paralleled by normalization of random blood glucose into the 90–220 mg/dL range and progressive improvement of serum creatinine toward baseline, as depicted in Figure 2 (Serum Creatinine vs Clinical Timepoint).

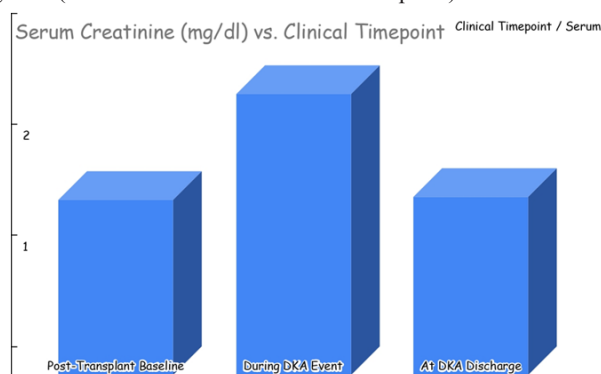


Figure 2 Impact of Diabetic Ketoacidosis (DKA) on renal allograft function.

Comparison of serum creatinine levels at three critical time points: post-transplant baseline (1.58 mg/dl), acute DKA presentation (2.53 mg/dl), and final discharge (1.6 mg/dl). The data demonstrates that the graft dysfunction observed at admission was acute and reversible following rehydration and metabolic correction.

Discharge and medication regimen

On hospital day 7 (post-operative day 117), the patient was discharged in stable condition with resolved DKA, normalized acid–base status, serum creatinine 1.6 mg/dL, hemoglobin 8.3 g/dL, fasting glucose 110–130 mg/dL, and negative urinary ketones. The discharge regimen comprised basal–bolus insulin (Human Actrapid 16 units before each meal and Human Lantus 30 units at bedtime), prednisolone 10 mg daily, tacrolimus with therapeutic-level monitoring, mycophenolate mofetil 1000 mg twice daily, antihypertensives, levothyroxine, and iron supplementation.

Long-term follow-up and overall outcome

During several months of subsequent follow-up, the patient has maintained excellent glycemic control with HbA1c below 7%, stable allograft function with serum creatinine 1.6–1.8 mg/dL, and gradual normalization of hemoglobin without recurrent hyperglycemic crises or severe hypoglycemia. Figure 3 (Clinical Timeline) summarizes the chronological sequence from transplantation through initial discharge, development of pure red cell aplasia, DKA admission, and final discharge, emphasizing the temporal association between intensified immunosuppression and metabolic decompensation.

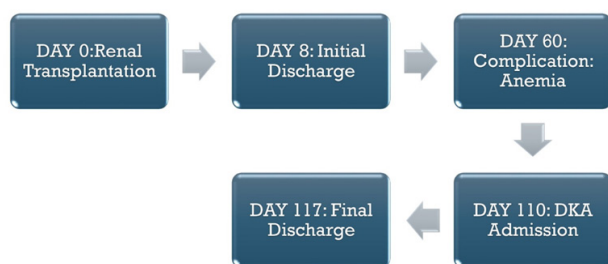


Figure 3 Timeline of clinical events from transplantation to the onset of NODAT.

A chronological overview of the patient’s course, highlighting the renal transplantation (Day 0), the treatment of Pure Red Cell Aplasia with increased corticosteroids (2 months post-op), and the subsequent presentation of DKA at 110 days post-operation.

Discussion

This case illustrates a rare presentation of tacrolimus-induced diabetic ketoacidosis (DKA) as the initial manifestation of new-onset diabetes after transplantation (NODAT) occurring at 110 days post-kidney transplantation in a 22-year-old without traditional diabetes risk factors. NODAT incidence varies widely from 7-30% within the first year post-transplant due to differences in diagnostic criteria, patient populations, immunosuppression protocols, and follow-up duration, with tacrolimus carrying higher diabetogenic risk than cyclosporine through mechanisms including calcineurin-NFAT pathway inhibition in pancreatic beta-cells, impaired insulin secretion, and mTOR pathway disruption leading to beta-cell dysfunction and apoptosis.^{1,2,3} Despite our patient’s young age and early post-operative euglycemia, pre-transplant insulin resistance (elevated HOMA-IR) represented a key modifiable risk factor increasingly recognized as predictive of NODAT, compounded by recent pure red cell aplasia requiring

escalated prednisolone dosing (30 mg daily)—a known precipitant of hyperglycemia in patients with borderline beta-cell reserve.⁴⁻⁶

DKA as NODAT’s presenting feature remains exceptionally uncommon, with fewer than 20 reported cases globally, typically within 3-6 months post-transplant and associated with 5-15% mortality risk from acute kidney injury, electrolyte derangements, and graft loss.^{10,11} Our patient’s extraordinarily severe presentation (serum glucose 1183 mg/dL) aligns with tacrolimus-associated DKA characteristics yet stands out for absent early hyperglycemia, extreme glucose elevation, and complete recovery with graft preservation through aggressive ICU management (peak insulin 538 units/day), underscoring the need for prolonged glycemic surveillance beyond the perioperative period, systematic pre-transplant HOMA-IR assessment, and prompt multidisciplinary intervention.^{3,9} Long-term, NODAT confers 65-95% higher mortality, doubled cardiovascular risk, and accelerated graft failure, emphasizing corticosteroid minimization, tacrolimus dose optimization, and consideration of conversion to cyclosporine in high-risk cases like this.^{7,8}

Conclusion

This case demonstrates that tacrolimus-associated diabetic ketoacidosis can manifest as a life-threatening complication of NODAT even in young kidney transplant recipients lacking traditional risk factors. Early recognition, aggressive multidisciplinary management with intensive insulin therapy, and judicious immunosuppression adjustment achieved complete metabolic recovery and allograft preservation. Systematic pre-transplant metabolic phenotyping, extended glycemic surveillance beyond the perioperative period, and proactive risk stratification remain essential to prevent such catastrophic events and optimize long-term transplant outcomes.

Acknowledgments

None.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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