CASE REPORT

New-onset diabetes after renal transplantation: A case series as seen in a Nigerian kidney transplant population

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Abstract

New-onset diabetes after transplantation (NODAT) is an important metabolic complication of transplantation because of its associated morbidity and mortality. Risk factors for NODAT include those known to cause diabetes mellitus in non-transplant patients as well as transplant-specific factors. This study was aimed at illustrating the presentation and management of NODAT in three kidney transplant recipients in our center and reviewing the literature. To our knowledge, this is the first report from Nigeria. Two of the patients were males of ages 60 and 36 years, respectively, while the third was a female aged 25 years. They were all receiving prednisolone, two were on tacrolimus, and one was on cyclosporine as part of their immunosuppressive regimens. They developed NODAT at varying times post transplant, ranging from 3 months to 6 years. Two patients were managed with oral hypoglycemic agents and one with insulin. One patient died of hemorrhagic stroke. We conclude that NODAT occurred in our kidney transplant recipients and recommend that physicians should have a high index of suspicion in order to make an early diagnosis and institute appropriate management to reduce morbidity and mortality.

Key words: New-onset diabetes, Nigerians, renal transplant

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Introduction

Patient and allograft survivals after kidney transplants have improved over the last half century, leaving aside other complications such as malignancies, opportunistic infections, cardiovascular disease, and metabolic complications as important barriers to disease-free survival.[1]

New-onset diabetes after transplantation (NODAT), also called post-transplant diabetes mellitus, is an important complication because of its associated morbidity and mortality.[2]

Many risk factors have been identified for the development of NODAT such as immunosuppressive medications, family history of diabetes, and black race.[3] Unfortunately, there is paucity of data on NODAT from indigenous black African populations. We present three illustrative case series seen in our center and review the literature.

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Case Summaries

Case 1

A 60-year-old civil servant who had living related kidney transplant 6 years prior to presentation. The donor was his son. He was hepatitis C positive with no evidence of active liver disease prior to kidney transplantation; liver enzymes were normal, no detectable viremia by

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quantitative polymerase chain reaction (PCR), and liver histology was normal. His tissue typing was; HLA CLASS I A9 (23), A19 (29), B78, B70, BW6, CW2, CLASS II DR3, DR6 (13), DR51, DR52, DQ1, DQ4. His post-transplant immunosuppressive medications include prednisolone started on 20 mg and tapered to 5 mg daily starting from third month post transplant, tacrolimus 2 mg twice daily, and sirolimus 2 mg daily. His primary renal disease was hypertensive nephropathy. He had no family history of diabetes mellitus. He had no history of cigarette smoking or alcohol ingestion. He had no immediate post-transplant complications and maintained normal graft function until the current presentation. He presented 6 years after transplant with an acute diarrheal illness of 2 days' duration. The diarrhea was watery, non-bloody, and non-mucoid with a frequency of 5–6 times daily but no associated fever. He had no history of osmotic symptoms suggestive of diabetes mellitus. He was found to be volume depleted with a blood pressure 70/40 mmHg. Investigations revealed mild azotemia, which resolved on rehydration, and an elevated random blood sugar of 24 mmol/L.

A diagnosis of NODAT was made and he was started initially on insulin because of intercurrent illness, and was later switched to gliclazide (diamicron) 80 mg daily with good glycemic control. His last fasting blood glucose was 6.2 mmol/L.

Case 2

A 36-year-old school teacher who had kidney transplantation done in our center. His primary renal disease was chronic glomerulonephritis. He had no history of cigarette smoking or alcohol ingestion. He had a family history of hypertension (father) and diabetes mellitus (mother) but no family history of kidney disease. His height was 1.67 m, weight 68 kg, and BMI 24 kg/m^2. His serology for HBsAg, HCV-Ab, and retroviral screen were all negative. His donor was his 26-year-old brother. At induction, he was given intravenous methylprednisolone 500 mg and this was repeated on the second and third day. Oral Cyclosporine was also given at induction. Maintenance immunosuppression included cyclosporine, azathioprine, and prednisolone 20 mg daily from Day 3, which was tapered from the third month. He maintained a good allograft function and by the fifth day, his creatinine had normalized to 84 μmol/L. He was discharged by the eleventh day post-op with a creatinine of 92 μmol/L and blood pressure of 120/70 mmHg. He remained stable on follow-up and by the third month post transplant he presented with a 3 days' history of excessive thirst and water intake and excessive micturition. No history of fever, dysuria, or loin pain. Urgent random blood sugar was 20 mmol/L, fasting blood sugar 20.1 mmol/L, and lipid profile was normal. Diagnosis of NODAT was made and he was counseled on the nature of the disease, dietary advice was given, and he was started on metformin and later glibenclamide. His blood sugar was controlled successfully and allograft function remained excellent. Eight months later, he was brought to the emergency room by his relatives with 1-day history of sudden collapse and loss of consciousness. Urgent brain CT revealed extensive intracerebral hemorrhage. He was managed as a case of hemorrhagic cerebrovascular disease, but he expired within 24 hours of admission.

Case 3

A 25-year-old civil servant who had living related kidney transplant in India one year prior to presentation. Her primary renal disease was unknown. She was not a known diabetic. Her donor was her brother. Immediate post-transplant course was unremarkable. HLA typing was not reported. Her immunosuppressant protocol include prednisolone 7.5 mg daily, Tacrolimus 4 mg twice daily, and mycophenolate mofetil 500 mg twice daily.

She was noted to have developed progressively rising blood sugar on routine follow-up without significant osmotic symptoms. There was no significant improvement on dietary modification and oral hypoglycemics. She was switched to mixtard insulin with good glycemic control at a dose of 24 units in the morning and 10 units in the evening. She maintained good graft function on outpatient follow-up with serum creatinine about 80 μmol/L. She was admitted with features of urosepsis and acute allograft dysfunction. Her creatinine on admission was 425 μmol/L. Full blood count revealed anemia with a hemoglobin of 7.5 g/dL, leukocytosis with white cell count of 27 × 10^9/L, and differential showing neutrophils of 89%. Platelets were normal. Her random blood sugar on admission was 9.1 mmol/L. Renal allograft ultrasound revealed mildly enlarged kidneys with bipolar diameter of 13 cm, increased echogenicity, but preserved cortico–medullary differentiation.

She was treated with intravenous ceftriaxone and a 3-day course of methylprednisolone, and tacrolimus was temporarily withheld. She was continued on mixtard insulin with blood sugar monitoring.

Urine culture yielded *Enterococcus fecalis* sensitive to levofloxacin and ciprofloxacin. She improved and was discharged on oral levofloxacin and maintenance immunosuppressants with improved allograft function, to continue follow-up on outpatient basis. Her serum creatinine at discharge was 177 μmol/L.

Discussion

Renal transplantation is becoming increasingly available in Nigeria after the first successful kidney transplant in a private hospital in 2000.[4]

Two years after that, two government hospitals started renal transplant programs.[5,6] With the increase in overall life

expectancy of post-renal transplant recipients, the likelihood of long-term transplant-related complications now present a major challenge to the quality of life of these patients.[1] Studies have shown that cardiovascular diseases, infections, and metabolic conditions like diabetes mellitus constitute the main long-term complications of post-renal transplant drug management.[1,2] The factors implicated in the development of new-onset diabetes after renal transplant include older age of the patient, post-prandial hyperglycemia, immunosuppressive drugs (steroids, calcineurin inhibitors), and mammalian target of rapamycin inhibitors, obesity, presence of hepatitis C viral infection, and unhealthy lifestyle.[3,7] Although the relationship of type 2 diabetes and hepatitis C virus (HCV) in the general population has been described,[8] an association between NODAT and HCV has been found in both kidney and liver transplant patients.[7,8] Although pathophysiological mechanism of HCV-induced NODAT is not quite clear, HCV induced autoimmune or direct b-cell damage, development of insulin resistance, hemochromatosis, and fibrosis are recognized as factors responsible for the NODAT development.[9,10] The traditional risk factors for developing diabetes mellitus as in the general population, if present in renal transplant patients, can also significantly increase the chances of diabetes mellitus.

All the three cases described in this report demonstrated significant use of immunomodulating agents like prednisolone, which could partly explain the new-onset transplant-associated diabetes mellitus. The diagnosis of diabetes mellitus in these patients met the current WHO criteria.[11] Only one of the patients had a significant family history of diabetes mellitus, which probably increased the risk of NODAT. The exact mechanism of diabetes in renal transplant patients is not known. Controversies exist as to the relative contribution of therapy in the development of diabetes in renal transplant patients. One recent study that compared the risk of developing NODAT in persons receiving tacrolimus versus those on cyclosporine observed increased tendency towards diabetes among those on tacrolimus.[12] If the observations from this study are true, it may be possible that the use of tacrolimus in addition to the presence of hepatitis C viral infection in Case 1 predisposed the patient to developing diabetes mellitus. However, it is widely acceptable that use of drugs like prednisolone and methylprednisolone, especially over prolonged periods, substantially increase the risk of renal transplant-related diabetes mellitus.[13]

With advances in renal transplantation and increase in availability of transplant in our setting, it is anticipated that many patients would develop metabolic problems, especially diabetes. A comprehensive evaluation of these patients for possible risk factors for the development of diabetes must be undertaken before the transplant and periodically during the course of post-transplant follow-up and therapy. Screening for abnormalities of glucose metabolism should be routine in patients before and after renal transplantation; immunosuppression should be modified according to the risk of new-onset diabetes mellitus and the likelihood of acute rejection. In this way, the devastating effects of diabetes would be minimized in our renal transplant patients.

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