Case Report

New onset diabetes after transplantation: Not another acronym!

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Lesson

New onset diabetes after transplantation is the onset of diabetes in previously non-diabetic individuals extending beyond the first month post-transplantation.

Keywords

NODAT, diabetes, transplantation

Case presentation

A 49-year-old man with end-stage renal failure secondary to reflux nephropathy underwent elective primary renal transplantation. Pre-transplant creatinine was 857 µmol/L with an estimated glomerular filtration rate of 6 mL/min/1.73m², calculated using the abbreviated modification of diet in renal disease equation.1 His medical history consisted of gout, hypertension and gastro-oesophageal reflux disease. His medications were cilazapril 5 mg once daily and furosemide 160 mg once daily. He did not smoke, was married with two children and worked as a director of an insurance firm. Pre-transplant body mass index was 33.5 kg/m². He received a live donor graft from his wife with an uneventful surgical procedure. His initial immunosuppression consisted of cyclosporine, mycophenolate and prednisolone. He was managing well and reported increased energy. Pre-transplant fasting plasma glucose was 4.9 mmol/L, HbA1c 32 mmol/mol, BP 124/82 mmHg and total cholesterol:HDL cholesterol ratio was 4.3. Plasma glucose concentrations were monitored closely. As is standard practice in our unit, a plasma glucose was measured at 2 h post-lunch on day five following his transplant, with a value of 8.6 mmol/L. He attended the transplant clinic for daily clinical review and serum urea and electrolyte (including random plasma glucose) measurement during the first month post-transplant. At one month post-transplant, his creatinine was 157 µmol/L. At seven weeks post-transplantation, his creatinine was noted to be rising (Figure 1). Renal biopsy confirmed a grade 1A acute rejection, which was treated with pulsed intravenous methylprednisolone over three days with no improvement in serum creatinine concentrations. A further renal biopsy showed a grade 1B acute rejection, and given the failure to respond to glucocorticoids, a 10-day course of thymoglobulin was administered. Cyclosporin was discontinued and tacrolimus commenced. He was discharged on 20 mg of prednisolone once daily in the morning, 11 mg tacrolimus twice daily and mycophenolate 1 g twice daily. Renal function improved with creatinine returning to concentrations of 150 to 160 µmol/L.

He reported low energy, nausea, dry mouth, thirst and general malaise, which was attributed to the deterioration in renal function and the thymoglobulin component of his anti-rejection treatment regimen. At two weeks following discharge, he continued to complain of tiredness, thirst and general malaise. Fasting plasma glucose was 5.4 mmol/L and a random plasma glucose concentration of 11.6 mmol/L confirmed the diagnosis of new onset diabetes after transplantation (NODAT). He was provided with a glucometer, and referred to the diabetes service. Mean pre-meal capillary glucose concentrations over a four-day period are shown in Figure 2. He was commenced on metformin 500 mg twice daily and gliclazide 80 mg twice daily, increased over 48 h to 160 mg twice daily. As his steroid and tacrolimus doses were reduced, his gliclazide dose was cautiously reduced. Fasting plasma glucose concentrations have been below 6.0 mmol/L since commencing metformin and gliclazide (Figure 3). He has experienced only one hypoglycaemic episode which he recognised and treated appropriately. HbA1c at five months post-transplantation is 33 mmol/mol. He continues to require gliclazide (40 mg twice daily) alongside metformin, as on discontinuation of gliclazide he developed post-prandial hyperglycaemia (12–16 mmol/L).

Discussion

NODAT is the onset of diabetes in previously non-diabetic individuals following organ transplantation,
extending beyond the first month post-transplantation. It is common with the most recent estimates following renal transplantation of occurrence of up to 20% with highest incidence in the first 12 months following transplantation.2

Hyperglycaemia in the first month post-transplantation is referred to as transient hyperglycaemia and may resolve, however, it is a predictor of NODAT development at one year.3 Diagnosis of NODAT is based on the WHO/IDF glucose criteria.4 The use of HbA1c in this situation is discouraged as HbA1c almost certainly underestimates glycaemia in chronic renal failure and is often complicated by the concomitant presence of anaemia and iron deficiency.5

NODAT is associated with increased mortality, graft loss, cardiovascular events and infections.

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**Figure 1.** Serum creatinine concentration following transplantation. Creatinine starting to rise at seven weeks post-transplantation.

**Figure 2.** Mean pre-meal capillary glucose concentrations (mmol/L) over a four-day period. Note the normal fasting glucose concentrations with elevated capillary glucose concentrations throughout the remainder of the day. Dashed lines show the venous glucose WHO cut-offs for impaired fasting glucose (≥6.1 mmol/L), and diabetes (fasting glucose ≥7.0 mmol/L and random glucose ≥11.1 mmol/L).4

**Figure 3.** Fasting serum glucose concentration (mmol/L) since commencing on oral hypoglycaemic agents. Dashed lines show the venous glucose WHO cut-offs for impaired fasting glucose (≥6.1 mmol/L), and diabetes (fasting glucose ≥7.0 mmol/L and random glucose ≥11.1 mmol/L).4
The main cause of death following renal transplantation is cardiovascular disease. Death from cardiovascular disease is 6.4 times greater in transplant recipients aged 55 to 64 years without NODAT or pre-existing diabetes than in the non-transplant population and 20.8 times greater in transplant recipients with diabetes (both NODAT and pre-existing diabetes). Patients with NODAT develop microvascular complications more rapidly than type 2 diabetes mellitus (T2DM) patients without a transplant and should be screened regularly for complications. The increased mortality is independent of graft malfunction.

Classical risk factors for the development of T2DM are also implicated in the post-transplant population, however a number of transplant-specific risk factors also exist. Immunosuppressive medications contribute, with an increased incidence seen in patients receiving tacrolimus-based immunosuppression rather than cyclosporine. Genetic factors are also relevant, with a threefold increased risk seen in recipients with autosomal dominant polycystic kidney disease and an association demonstrated with the TCF7L2 polymorphism.

Episodes of acute rejection are more frequent in patients with NODAT and, as in our case, the acute rejection episode is usually reported to precede the development of NODAT. The prediction of patients who may develop NODAT is imprecise, however two risk scores have shown some utility.

Current screening guidelines for NODAT recommend a fasting plasma glucose measurement weekly for four weeks, proceeding to an oral glucose tolerance test (OGTT) if the value is between 6.1 and 6.9 mmol/L. After the first month, a fasting plasma glucose measurement (+/−OGTT) and/or an HbA1c should be checked every three months for the first year post-transplant and annually thereafter. However, the use of fasting plasma glucose measurements has been shown to miss (as would have occurred in our case) approximately 20–25% of NODAT patients who would be diagnosed if an OGTT was also performed. In our unit, we use a 2-h post prandial measurement performed every day during routine clinic visits during the first month post-transplantation.

Glucocorticoids are commonly used as part of the immunosuppression regimen following transplantation. They probably contribute to the development of NODAT and, in the non-transplant setting, are associated with the development of steroid-induced diabetes. They contribute to hyperglycaemia via increased insulin resistance and decreased insulin secretion. They cause decreased suppression of hepatic gluconeogenesis and inhibition of peripheral glucose uptake; probably mediated via a variety of receptor and post-receptor effects on insulin signaling, suppression of insulin secretion and induction of islet-cell apoptosis at higher doses. The peak effect on glycaemia tends to occur 4 to 12 h after administration of glucocorticoid and with once daily dosing effects may not last for the whole 24 h. It is therefore possible with the recommended morning administration of steroid to measure normal fasting plasma glucose concentrations, but have markedly elevated plasma glucose concentrations at other time points throughout the day. Therefore similarly to NODAT, a reliance on fasting plasma glucose concentrations may miss a diagnosis of steroid-induced diabetes. Guidance on the management of steroid-induced diabetes is mostly based on expert opinion. Recently, a protocol for management of steroid-induced and steroid-exacerbated diabetes has been compiled by Diabetes UK which advocates the early use of sulphonylurea agents.

Metformin is an insulin sensitising agent which was not used in our case for its hypoglycaemic effects, but for its potential beneficial effects on total mortality, cardiovascular disease events, and cancer incidence, all of which are increased in transplant recipients. Metformin reduces hepatic glucose production by phosphorylation of the transcriptional coactivator cAMP response element-binding (CREB) protein, reducing the expression of genes inducing gluconeogenesis. It is eliminated via renal excretion, with excretion decreased in proportion to decreased creatinine clearance. Caution is advised in using metformin in patients with renal impairment with an eGFR <60 mL/min/1.73 m² and a creatinine <150 μmol/L and discontinuation is advised in advanced renal impairment with an eGFR <30 mL/min/1.73 m² and a creatinine >150 μmol/L. This is due to a risk of lactic acidosis, a rare diagnosis associated with high mortality. This risk appears to be largely due to co-morbidities and resultant tissue hypoxia, with a meta-analysis showing no evidence of an increased risk of lactic acidosis associated with the use of metformin compared with non-metformin regimens.

It is unlikely that the beneficial effects of metformin may be due to reduced weight, improvements in lipids and reduction of hypercoagulability. Indeed, it is probable that there are other, as yet unknown, mechanisms mediates these beneficial effects. As renal transplant recipients have markedly increased incidences of cardiovascular events and cancer, there are potentially theoretical benefits to the continued use of metformin in this group. We therefore suggest that, with careful monitoring, metformin may be continued.
Current treatment guidelines for the management of NODAT advise a stepwise progression from lifestyle to oral medications to insulin.\(^\text{15,16}\) In our unit, we are keen to achieve glycaemic control promptly and initiate sulphonylureas and insulin early. Unless metformin is not tolerated by the patient this is commenced when diagnosed with NODAT. A recent trial using early introduction of basal insulin demonstrated reduced incidence of NODAT, reduced HbA1c and improved beta-cell secretory function when compared to participants treated conventionally.\(^\text{27}\) This was a small trial and a large multicentre randomised controlled trial (Insulin therapy for the prevention of NODAT (ITP-NODAT) is presently in progress.

In conclusion, our case highlights NODAT, a common complication post transplantation associated with poorer outcomes for the patient and for the graft. We discuss current diagnostic and treatment guidelines and highlight a potential problem in the reliance on fasting glucose measurement for diagnostic purposes of NODAT, and the more common scenario of steroid-induced diabetes. For the clinician who may not encounter many transplant patients, this case highlights the importance of screening for NODAT, the potential utility of continued use of metformin in patients with renal impairment and the pattern of steroid effects on hyperglycaemia.

**Declarations**

**Competing interests:** None declared

**Funding:** None declared

**Ethical approval:** Written informed consent has been obtained from the patient for publication of this anonymised case report.

**Guarantor:** FW

**Contributorship:** All authors contributed to the clinical management of this patient. HP was the consultant nephrologist who managed the patient through his transplantation. IRW and NHW were the junior doctors who managed the patient’s NODAT under supervision from consultant diabetologists PLD and FW. All authors contributed to the writing and editing of this case report. IRW was the primary author of this case report, and was assisted with the literature search and initial drafting by NHW, under supervision by HP, PLD and FW. Subsequent editing was by all authors.

**Acknowledgements:** None

**Provenance:** Not commissioned; peer-reviewed by Layla Alhyas

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