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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

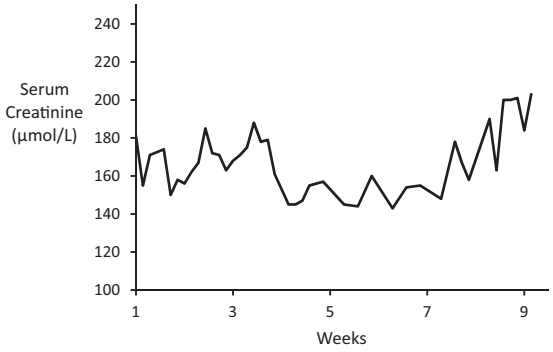
A 49-year-old man with end-stage renal failure secondary to reflux nephropathy underwent elective primary renal transplantation. Pre-transplant creatinine was 857 μmol/L with an estimated glomerular filtration rate of 6 mL/min/1.73m^2, calculated using the abbreviated modification of diet in renal disease 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/m^2. 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,

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

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]

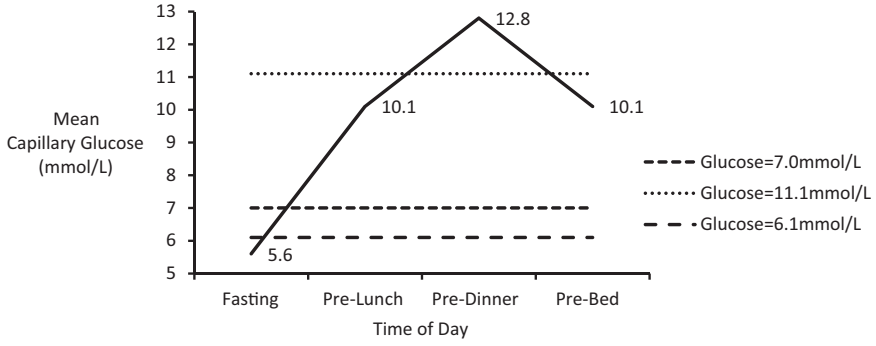
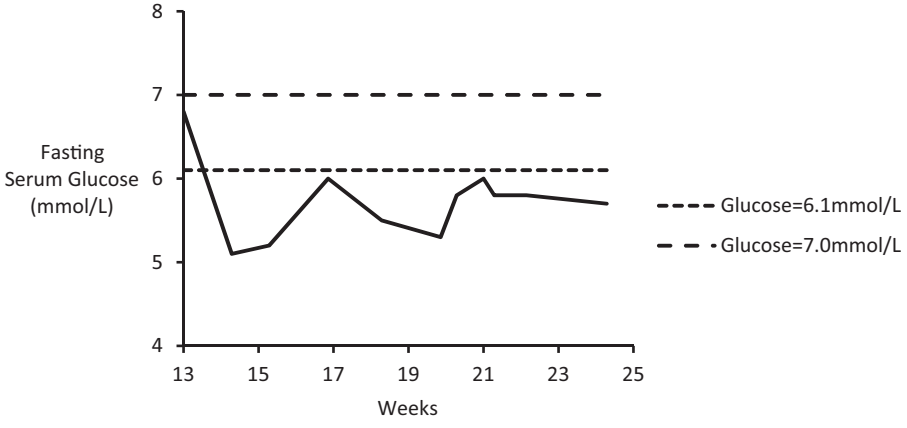


Figure 3. Fasting serum glucose concentration (mmol/L) since commencing on oral hypoglycaemic agents. Dashed lines show the venous glucose WHO cut-offs for impaired fasting glucose (≥6.1 mmol/L), and diabetes (fasting glucose ≥7.0 mmol/L and random glucose ≥11.1 mmol/L).[4]



The main cause of death following renal transplantation is cardiovascular disease.[6] 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).[7] 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.[8] The increased mortality is independent of graft malfunction.[9]

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.[2] Genetic factors are also relevant, with a threefold increased risk seen in recipients with autosomal dominant polycystic kidney disease[10] and an association demonstrated with the *TCF7L2* polymorphism.[11]

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.[12] The prediction of patients who may develop NODAT is imprecise, however two risk scores have shown some utility.[13,14]

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.[15,16] 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.[17,18] 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 signalling, suppression of insulin secretion and induction of islet-cell apoptosis at higher doses.[19] 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.[20]

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,[21] cardiovascular disease events,[22] and cancer incidence,[23] all of which are increased in transplant recipients.[6] Metformin reduces hepatic glucose production by phosphorylation of the transcriptional coactivator cAMP response element-binding (CREB) protein, reducing the expression of genes inducing gluconeogenesis.[24] It is eliminated via renal excretion, with excretion decreased in proportion to decreased creatinine clearance.[25] Caution is advised in using metformin in patients with renal impairment with an eGFR <60 mL/min/1.73 m^2 and a creatinine <150 μmol/L and discontinuation is advised in advanced renal impairment with an eGFR <30 mL/min/1.73 m^2 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.[26]

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 mediating 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.[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.[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

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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.

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References

1. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130: 461–470.
2. Vincenti F, Friman S, Scheuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 2007; 7: 1506–1514.
3. Cosio FG, Kudva Y, van der Velde M, et al. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; 67: 2415–2421.
4. World Health Organisation. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation*, 1st ed. Geneva: World Health Organisation, 2006.
5. Sharif A and Baboolal K. Diagnostic application of the A(1c) assay in renal disease. *J Am Soc Nephrol* 2010; 21: 383–385.
6. Pilmore H, Dent H, Chang S, et al. Reduction in cardiovascular death after kidney transplantation. *Transplantation* 2010; 89: 851–857.
7. Lindholm A, Albrechtsen D, Frodin L, et al. Ischemic heart disease – major cause of death and graft loss after renal transplantation in Scandinavia. *Transplantation* 1995; 60: 451–457.
8. Burroughs TE, Swindle J, Takemoto S, et al. Diabetic complications associated with new-onset diabetes mellitus in renal transplant recipients. *Transplantation* 2007; 83: 1027–1034.
9. Cole EH, Johnston O, Rose CL, et al. Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival. *CJASN* 2008; 3: 814–821.
10. de Mattos AM, Olyaei AJ, Prather JC, et al. Autosomal-dominant polycystic kidney disease as a risk factor for diabetes mellitus following renal transplantation. *Kidney Int* 2005; 67: 714–720.
11. Ghisdal L, Baron C, Le Meur Y, et al. TCF7L2 polymorphism associates with new-onset diabetes after transplantation. *J Am Soc Nephrol* 2009; 20: 2459–2467.
12. Nagaraja P, Ravindran V, Morris-Stiff G, et al. Role of insulin resistance indices in predicting new-onset diabetes after kidney transplantation. *Transplant Int* 2013; 26: 273–280.
13. Rodrigo E, Santos L, Pinera C, et al. Prediction at first year of incident new-onset diabetes after kidney transplantation by risk prediction models. *Diabetes Care* 2012; 35: 471–473.
14. Chakkera HA, Weil EJ, Swanson CM, et al. Pretransplant risk score for new-onset diabetes after kidney transplantation. *Diabetes Care* 2011; 34: 2141–2145.
15. Davidson J, Wilkinson A, Dantal J, et al. New-onset diabetes after transplantation: 2003 international consensus guidelines. Proceedings of an international expert panel meeting. Barcelona, Spain, 19 February 2003. *Transplantation* 2003; 75(10 Suppl): SS3–SS24.
16. Wilkinson A, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. *Clin Transplant* 2005; 19: 291–298.

17. Caillard S, Eprinchard L, Perrin P, et al. Incidence and risk factors of glucose metabolism disorders in kidney transplant recipients: role of systematic screening by oral glucose tolerance test. *Transplantation* 2011; 91: 757–764.
18. Valderhaug TG, Jenssen T, Hartmann A, et al. Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. *Transplantation* 2009; 88: 429–434.
19. Tappy L, Randin D, Vollenweider P, et al. Mechanisms of dexamethasone-induced insulin resistance in healthy humans. *J Clin Endo Metabol* 1994; 79: 1063–1069.
20. End of Life Diabetes Care Working Group. *End of Life diabetes care: a strategy document commisioned by Diabetes UK. Promoting appropriate and sensitive high quality diabetes care for all adults at the end of life*, 1st ed. London: Diabetes UK, 2012.
21. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352: 837–853.
22. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–1589.
23. Libby G, Donnelly LA, Donnan PT, et al. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 2009; 32: 1620–1625.
24. He L, Sabet A, Djedjos S, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. *Cell* 2009; 137: 635–646.
25. Sambol NC, Chiang J, Lin ET, et al. Kidney function and age are both predictors of pharmacokinetics of metformin. *J Clin Pharmacol* 1995; 35: 1094–1102.
26. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2010; 4: 002967.
27. Hecking M, Haidinger M, Doller D, et al. Early basal insulin therapy decreases new-onset diabetes after renal transplantation. *J Am Soc Nephrol* 2012; 23: 739–749.