New-onset diabetes after transplantation

New-onset diabetes after transplantation is a serious complication of organ transplantation that is becoming increasingly more common. New-onset diabetes after transplantation has implications for graft and patient survival. This article reviews the pathogenesis, diagnosis and management of new-onset diabetes after transplantation.

It is now more than half a century since the first successful patient–patient solid-organ transplant. Transplantation has evolved into a routine treatment for many types of organ failure. With improvements in clinical outcomes the aim is no longer only to ensure short-term graft and patient survival. Reducing the risk of long-term complications that result in premature death with a functioning graft presents a new challenge.

Diabetes mellitus developing de novo after transplantation is recognized as one of the most important of these complications (EBPG Expert Group on Renal Transplantation, 2002; British Transplantation Society, 2003; National Institute for Clinical Excellence, 2004; Krentz and Wheeler, 2005). While it may be possible to reduce the impact of this undesirable metabolic consequence of transplantation this will only be achievable if health-care professionals are aware of likely contributory factors and able to intervene to reduce the risks for their recipients. While some of these factors, e.g. age and race, are immutable, others, e.g. obesity and aspects of immunosuppressive drug therapy, are potentially modifiable.

Table 1. Diagnostic criteria for identifying patients with diabetes or impaired glucose tolerance after transplantation

Criteria for diabetes*	Symptoms of diabetes (polyuria, polydipsia, unexplained weight loss) plus non-timed concentration ≥ 11.1 mmol/litre or	
	FPG ≥ 7.0 mmol/litre (fasting = no caloric intake for at least 8 hours) or	
	2-hour PG ≥ 11.1 mmol/litre during OGTT using glucose load containing at least 75 g anhydrous glucose dissolved in water	
Criteria for diagnosis of IFG and IGT †	By fasting plasma glucose concentration:	Normal <5.6 mmol/litre‡
		IFG ≥5.6–6.9 mmol/litre
	By OGTT:	Normal glucose tolerance = 2-hour glucose <7.8 mmol/litre
		IGT = 2-hour glucose ≥7.8 mmol and <11.1 mmol/litre

* A confirmatory test based on measurements of venous plasma glucose must be carried out on another day in the absence of unequivocal hyperglycaemia with acute metabolic decompensation. Urine should also be tested for ketones: the combination of hyperglycaemia and ketosis usually indicates a need for prompt insulin treatment. Diabetic ketoacidosis and hyperosmolar non-ketotic hyperglycaemia are metabolic emergencies requiring treatment with intravenous fluids, insulin and electrolytes †It is important to specify the test, since 2-hour OGTT cut-off will identify more people with IGT than those identified with IFG from the FPG test. OGTT = oral glucose tolerance test; IFG = impaired fasting glucose; IGT = impaired glucose tolerance. ‡ as recommended by American Diabetes Association (2006). From World Health Organization (1999); Davidson et al (2003); American Diabetes Association (2006)

Dr David C Wheeler *is Reader in Nephrology and Honorary Consultant Nephrologist, Centre for Nephrology, Royal Free and University College Medical School, London and* **Dr Andrew J Krentz** *is Consultant in Diabetes and Endocrinology, Honorary Senior Clinical Lecturer, Southampton University Hospitals, Southampton SO16 6YD*

Correspondence to: Dr AJ Krentz

Clinical significance of post-transplant diabetes

New-onset diabetes after transplantation (NODAT) is characterized by a variable combination of impaired insulin secretion in concert with resistance to the actions of insulin on key target tissues such as skeletal muscle (Krentz et al, 1995). While these defects are reminiscent of the key metabolic abnormalities of type 2 diabetes subtle differences in intermediary metabolism have been reported (Krentz at al, 1995). A proportion of NODAT cases may be more appropriately be categorized as type 3 diabetes (American Diabetes Association, 2006). However, differentiating transplant-induced diabetes from type 2 diabetes that would have developed independently of transplantation is problematic in practice. International consensus guidelines recommend that diagnosis of NODAT be based on criteria that are used to diagnose diabetes in the general population (*Table 1*) (Davidson et al, 2003). This also permits identification of individuals with lesser degrees of hyperglycaemia, i.e. impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). In the general population the latter categories are associated with an increased risk of progression to diabetes and with the development of atherosclerotic cardiovascular disease (Heldgaard et al, 2004). While the prognostic implications of these categories of glucose intolerance specifically in transplant recipients have not been determined, they provide a basis for reliable comparisons of incidence rates between transplant centres.

NODAT increases the risk that transplant recipients face from premature mortality (Friedman et al, 1985; Jindal and Hjelmesaeth, 2000; Revanur et al, 2001) and graft loss (Roth et al, 1989; Revanur et al, 2001; John and Thuluvath, 2002; Valantine, 2004) (*Figures 1* and *2*). NODAT adds to an already high risk of cardiovascular disease in recipients of renal and heart grafts. Predictably, inferior clinical outcomes are associated with higher health-care costs (Woodward et al, 2003). However, the incidence and prevalence of NODAT remains uncertain, since the reported incidence in the literature varies from ~2% to ~50% (Montori et al, 2002). In part, these widely varying estimates reflect the use of arbitrary definitions of diabetes, imprecise identification of unrecognized hyper-

glycaemia pre-dating transplantation in some patients, and a failure to acknowledge the progressive increase in risk of diabetes that follows transplantation (Kasiske et al, 2003). The American Diabetes Association has lowered the threshold for diagnosing IFG to 5.6 from 6.0 mmol/litre (American Diabetes Association, 2006); the relative predictive value of these thresholds for the development of diabetes and cardiovascular disease remain uncertain, both in the general population and in patients with NODAT.

Role of immunosuppression

Factors that are associated with an increased risk of NODAT are shown in *Table 2*. Of these, immunosuppression is particularly relevant, explaining ~70% of the variability in incidence of diabetes (Montori et al, 2002). Corticosteroids remain an important component of most immunosuppressive regimens; their association with NODAT was clearly established at the inception of clinical transplantation in the 1960s. A dose–response link is evident with each increment 0.01 mg/kg/day prednisolone increasing the risk of NODAT by ~5% and glucose intolerance to a similar degree (Hjelmesaeth et al, 1997).

Use of calcineurin inhibitors, e.g. cyclosporin and tacrolimus, is also associated with an increased risk of developing NODAT. These agents bind to specific intracellular target proteins, modulating key aspects of T lymphocyte function (Halloran, 2004). Both drugs reportedly induce insulin resistance and impair insulin secretion in animal models and in humans through incompletely understood mechanisms (Krentz et al, 1995). The risk of developing NODAT may be higher with tacrolimus (British Transplantation Society, 2003). Woodward et al (2003) reported incremental incidences with cyclosporin and tacrolimus of respectively 9.4% *vs* 15.4% at 1 year and 8.4% *vs* 17.7% at 2 years in renal transplant patients (*Figure 3*). These observations were strengthened by a meta-analysis of prospective studies in kidney, heart and liver transplant recipients found a higher risk of NODAT in patients treated with tacrolimus (Heisel et al, 2004). In contrast, some other drugs, e.g. azathioprine, appear to be devoid of diabetogenic potential.

Table 2. Risk factors for developing new-onset diabetes after transplantation

Age > 40 years
African or Hispanic ancestry/ethnicity
History of diabetes in first-degree relative and/or personal history of gestational diabetes
Immunosuppressive therapy (see text)
Central obesity (see *Table 4*)
Hepatitis C viral infection
Abnormal glucose regulation before transplantation
Presence of other major cardiovascular risk factors (hyperlipidaemia, hypertension)
Cadaver kidney

based on Davidson et al (2003)

Pre-transplant review of risk factors for NODAT

Risk factors for NODAT may be identified during pre-transplant review of the potential recipient's medical history; this should include specific questioning about any relevant personal history of glucose intolerance or diabetes, e.g. gestational diabetes, and family history of diabetes in a first degree relative. Current guidelines recommend screening for abnormal glucose metabolism by measuring fasting plasma glucose (FPG) concentrations as outlined in *Table 3* (World Health Organization, 1999; Davidson et al, 2003; American Diabetes Association, 2006). While screening using oral glucose tolerance tests would be more sensitive this approach is

Figure 1. Patient survival by diabetic status. From Revanur et al (2001). DM = diabetes mellitus; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; PTDM = post-transplant diabetes mellitus.

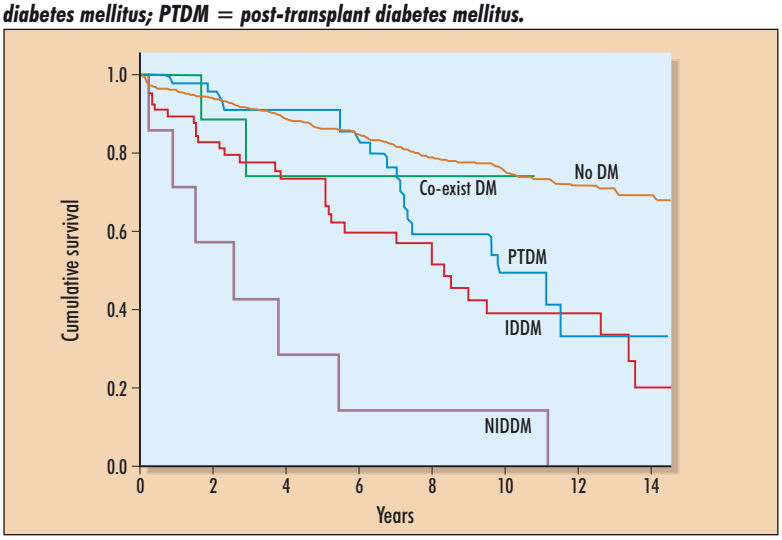
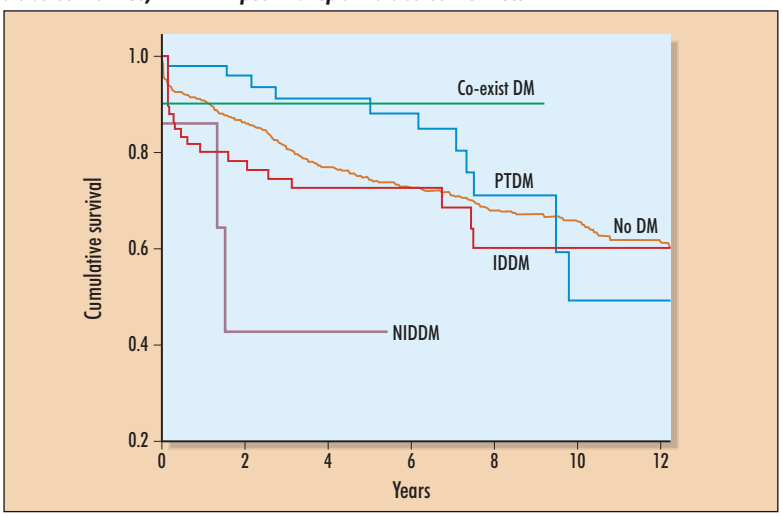


Figure 2. Graft survival by diabetic status. From Revanur et al (2001). DM = diabetes mellitus; IDDM = insulin-dependent diabetes mellitus; NIDDM = non-insulin dependent diabetes mellitus; PTDM = post-transplant diabetes mellitus.



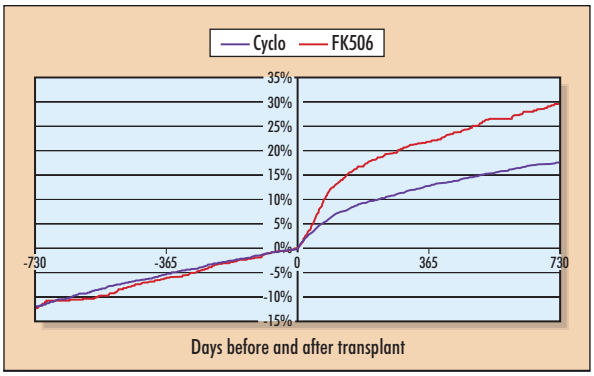


Figure 3. Incidence of diabetes before and after transplantation in patients receiving cyclosporin or tacrolimus. The incremental incidence of diabetes for cyclosporin was 9.4% at 1 year and 8.4% at 2 years, and for tacrolimus was 15.4% at 1 year and 17.7% at 2 years. From Woodward et al (2003).

unwieldy in clinical practice. The guidelines also recommend that clinical and biochemical measures are used to identify patients with additional components of the metabolic syndrome (*Table 4*). The metabolic syndrome increases the risk of cardiovascular disease ~3-fold in non-transplant populations (Grundy et al, 2006). Other risk factors for atherosclerosis, e.g. tobacco use and family history of premature cardiovascular disease, should be identified (Davidson et al, 2003).

These assessments should help to inform patients about their likely personal risk of developing NODAT (Davidson et al, 2003). The importance of minimizing weight gain following transplantation through healthy eating and maintaining adequate levels of physical activity should be stressed. This advice should be reinforced with clear written information; referral to a dietician may be appropriate. To date, no clinical trials have addressed the impact of lifestyle modification on the risk of NODAT in organ transplant recipients.

Table 3. Recommended pre-transplant screening and counselling

Complete medical history	
Glucose screening at regular intervals:	Fasting plasma glucose < 6.1 mmol/litre: every 3 years Fasting plasma glucose 6.1–7.0 mmol/litre: every year
Determination of risk factors for new-onset diabetes after transplantation (*Table 2*)	
Inform patients of their risk factor profile and counsel on the importance of weight control, diet and regular exercise. Referral to a dietician should be considered	

From Davidson et al (2003)

Table 4. The metabolic syndrome

The metabolic syndrome is present if there are three or more of the following*:
Waist circumference > 102 cm in men and > 88 cm in women
Serum triglyceride >1.7 mmol/litre
High-density lipoprotein cholesterol <1.0 mmol/litre in men, <1.3 mmol/litre in women
Blood pressure >130/>85 mmHg
Serum glucose > 6.1 mmol/litre
The International Diabetes Federation has proposed an alternative approach to the diagnosis of the metabolic syndrome (Alberti et al, 2005)

*These criteria have not been studied in relation to cardiovascular outcomes in patients with new-onset diabetes after transplantation. From Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001)

If lifestyle modification such as diet and exercise is not feasible, e.g. because of the presence of co-morbidity, attention should focus on reducing cardiovascular risk through other measures, e.g. support in quitting smoking and optimization of glycaemia, blood pressure and dyslipidaemia using safe and effective drugs (see below).

Managing NODAT

Blood glucose levels should be monitored periodically in all patients after transplantation (*Table 5*). The development of IFG – or IGT (the diagnosis of which requires a 75 g oral glucose tolerance test) – should trigger intervention with a redoubling of efforts directed towards effective lifestyle modification. For patients who develop overt NODAT, the guidelines recommend a step-wise approach to therapy (see below); in the absence of clinical trials in patients with NODAT these recommendations have been adapted from the management of type 2 diabetes (Davidson et al, 2003).

In the absence of metabolic decompensation – i.e. marked hyperglycaemia with or without ketosis and/or symptoms that require immediate insulin therapy – the basis of treatment is lifestyle modification followed by oral monotherapy and combination antidiabetic therapy as required. Insulin, as monotherapy or in combination with one or more oral antidiabetic agents, may be required to achieve an optimal target haemoglobin A_{1c} (HbA_{1c}) <6.5%. As for all forms of diabetes, avoidance of iatrogenic hypoglycaemia and minimizing the potential for drug-induced weight gain are important. The prevalence of co-morbidity is relatively high in transplant recipients; issues of drug safety and tolerability remain paramount when tailoring antidiabetic therapy to the individual. Currently, there is very little information about the relative merits of different oral antidiabetic agents for the treatment of NODAT. For some patients, this may mean that monotherapy with insulin is the best long-term option. *Table 6* gives a step-wise approach to the management of hyperglycaemia in patients with NODAT.

Table 5. Suggested monitoring blood glucose after transplantation

Screen by measuring FPG at the following intervals:	At least once-weekly for the first 4 weeks after transplantation
	At 3, 6 and 12 months post-transplant
	Annually thereafter
Measure random (untimed) plasma glucose at regular intervals, e.g. when blood is drawn for monitoring of immunosuppressant levels	
Consider OGTT in patients with normal FPG and impaired glucose tolerance; post-challenge hyperglycaemia has been shown to be a better risk marker for cardiovascular disease than fasting hyperglycaemia in other groups; comparable data are not available for organ transplant recipients (but OGTT is relatively time- and labour-intensive; day-to-day variability is another potential limitation)	

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test. From Davidson et al (2003)

When monitoring the response to treatment a potential caveat exists with regard to HbA_{1c} concentrations. These may be falsely lowered by anaemia or renal impairment; self-monitoring of capillary blood glucose pre- and post-prandially at a frequency dictated by individual circumstances may provide complementary information to guide changes in therapy.

Control of other modifiable cardiovascular risk factors, e.g. hypertension and dyslipidaemia, should be guided by the fact that diabetes is regarded as a 'coronary risk equivalent' (British Cardiac Society et al, 2005). Aggressive multifactorial intervention aimed at primary prevention of vascular disease is warranted in these high-risk patients. Targets for blood pressure and lipids should reflect the stricter goals for secondary prevention in high-risk patients (*Table 7*) (Williams et al, 2004; British Cardiac Society et al, 2005). Adherence to risk factor targets should be monitored regularly and drug therapy adjusted as required. The risks and benefits of antiplatelet therapy have not been clearly established in organ transplant recipients.

Transplant clinicians should also ensure that patients receive regular surveillance so that long-term microvascular complications such as retinopathy and neuropathy are detected in their early stages when they are asymptomatic. Transplantation may add to the risk of developing these complications, e.g. renal impairment and certain immunosuppressive drugs can increase the risk of polyneuropathy. The place of screening for microalbuminuria in patients with NODAT is presently uncertain (Davidson et al, 2003). Well-recognized nephrotoxic effects of immunophilins may increase the risk of renal dysfunction in patients with or without NODAT.

In general, immunosuppressive drug protocols should allow for individualization of standard triple therapy (calcineurin inhibitor, antiproliferative agent and corticosteroid) taking into account each patient's risk of NODAT and other adverse events. This is incorporated in the NICE guidance on immunosuppression for renal transplantation in adults (NICE, 2004). For patients who develop NODAT, there is presently little evidence that changing from one calcineurin inhibitor to another is beneficial in terms of glycaemia. However, reduction or withdrawal of corticosteroids may be appropriate; more data are required on this. This requires careful consideration since the risk of organ rejection may be increased, although steroid withdrawal is routine in some UK centres. At present, there is no consensus on steroid withdrawal; some patients will need to restart corticosteroids because of acute rejection (Hollander et al, 1997; Ahsan et al, 1999; Jordan et al, 2000; Felkel et al, 2002; Greig et al, 2003). This risk is higher among black than among white recipients (Hollander et al, 1997; Felkel et al, 2002).

As mentioned earlier, some transplant recipients may develop marked hyperglycaemia in the early postoperative phase that requires prompt treatment with insulin. In these circumstances, discharge from hospital on twice-daily biphasic insulin or multiple daily injections (i.e. basal-bolus regimen) can be followed by a re-assessment of the need for insulin after 2–3 months. It may be possible to reduce or withdraw insulin therapy as corticosteroid doses are reduced (Jardine et al, 2005). Similarly, improvements in glycaemic control have been reported when doses of corticosteroids are gradually tapered and withdrawn within the first few years of transplantation (Hollander et al, 1997; Jordan et al, 2000). For patients treated with oral antidiabetic drugs, management of NODAT with lifestyle measures alone may be possible at this stage. However, continuing periodic monitoring is required in the light of the cumulative risk of developing NODAT with time.

Table 6. Treatment of hyperglycaemia in patients with new-onset diabetes after transplantation

If the patient has symptomatic hyperglycaemia, metabolic decompensation or ketosis, move directly to step 5	
Step 1: Lifestyle modification plus education. If individualized goals for glucose are not achieved in 2–4 months, reassess lifestyle interventions and move to Step 2	
Step 2: Monotherapy with an oral antidiabetic agent such as	Sulphonylurea (associated with weight gain. Reduce dose if serum creatinine is elevated and avoid if glomerular filtration rate <10 ml/minute)
	Meglitinide analogue, e.g. repaglinide (may carry a lower risk of hypoglycaemia than sulphonylureas; relatively safe in lesser degrees of renal impairment)
	Thiazolidinedione (associated with weight gain and contraindicated in heart failure; caution in combination with insulin – increased risk of fluid retention)
	Alpha-glucosidase inhibitors (acarbose in the UK; may not be tolerated because of gastrointestinal side-effects)
	Metformin (avoid if creatinine clearance <40 ml/min or risk of tissue hypoxia)
If individualized goals for glucose are not achieved in 2–4 months, reassess lifestyle interventions and move to Step 3	
Step 3: Oral combination therapy to the maximum dose of agent in each class, if safety considerations permit. If goals are not achieved in 2–4 months, reassess lifestyle interventions and move to Step 4	
Step 4: Insulin ± an oral agent (this combination has not been assessed in patients with new-onset diabetes after transplantation)	
Step 5: Insulin monotherapy adjusted to achieve target glucose levels, possibly in conjunction with an oral antidiabetic agent. Reassess need for insulin periodically	

Table 7. Optimal targets for blood pressure and lipids in patients with diabetes

Blood pressure <130/80 mmHg
Total cholesterol <4.0 mmol/litre or lower by 25%, which is greater
Low-density lipoprotein cholesterol <2.0 mmol/litre or lower by 30%, whichever is greater
High-density lipoprotein cholesterol >1.0 mmol/litre
Triglycerides <2.3 mmol/litre

From Williams et al (2004); British Cardiac Society et al (2005)

Conclusions

The development of NODAT has potentially serious clinical implications for patients receiving solid organ transplants; evidence suggests that NODAT adds to the current high costs of treatment. Given the adverse impact of NODAT on graft and patient survival health-care professionals should recognize opportunities to modify known risk factors for its development. Transplant recipients should be assessed before transplantation and monitored carefully postoperatively for the development of glucose intolerance and diabetes. Appropriate lifestyle measures and drug therapy should be instituted pre- and post-transplantation as necessary. Clinical trials of antidiabetic medications have yet to be performed specifically in patients with NODAT. For the time being, clinicians must rely on incomplete data and extrapolations. More information is needed on the pathogenesis of NODAT and its long-term clinical implications. Ideally, future research should include randomized trials in which the impact of altering modifiable risk factors for NODAT is assessed. **BJHM**

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KEY POINTS

- New-onset diabetes after transplantation (NODAT) is a serious complication of solid organ transplantation.
- Development of NODAT has an adverse impact on graft and patient survival.
- Steps should be taken to identify patients at increased risk of NODAT.
- In the absence of acute metabolic decompensation a stepped care approach to mangaging NODAT is proposed.
- Follow up requires attention to the likely enhanced risk of vascular disease assocated with NODAT.

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