# Diagnosis and management of new-onset diabetes after transplantation

Joanne Buchanan

**New-onset diabetes after transplantation (NODAT) is recognised as one of the most important complications of solid organ transplantation. In this article, the author describes the aetiology and diagnosis of NODAT, and discusses options for treatment and management of the condition.**

**Article points**

1. New-onset diabetes after transplant (NODAT) occurs in up to 50% of transplant patients.
2. The risk of graft rejection, graft loss and graft infection is greater in post-transplant individuals who have pre-existing or NODAT.
3. Diabetes is a major complication of transplantation, and immunosuppressive therapy may play a part in its development.

**Key words**

- Diagnosis
- New-onset diabetes after transplant
- Management

The aetiology and natural history of new-onset diabetes after transplant (NODAT) are highly variable, but the condition is generally believed to result from a combination of insulin resistance and insulin deficiency (Chadban, 2008), which is then aggravated by immunosuppressive treatment post-transplant.

NODAT occurs in up to 50% of transplant patients (Davidson et al, 2003). On average, in the author's Trust, 22% of transplant patients are diagnosed with NODAT, and this is often within the first 6 months post-transplant. Individuals diagnosed with NODAT have a 22% higher risk of death compared with the general post-transplant population (Cosio et al, 2002). Due to the type of immunosuppressants used in all types of transplant, the figures are very similar for whichever organ is being transplanted.

## What is the impact of NODAT?

Diabetes increases the risk of macrovascular complications, for example coronary heart disease and stroke, and microvascular complications, such as neuropathy, retinopathy and nephropathy (Laing et al, 2003; Paterson et al, 2007). The risk of graft rejection, graft loss and graft infection is greater in post-transplant individuals who have pre-existing or new-onset diabetes (Bayés et al, 2004). In addition, the micro- and macrovascular complications of chronic hyperglycaemia further increase morbidity in these individuals (Fowler, 2008).

The author believes that all UK transplant units should include assessment of NODAT in audits of transplant outcome, especially as the disorder is likely to become more prevalent given the association of type 2 diabetes with age, and the increasing age of transplant recipients in the UK.

The majority of individuals on the transplant waiting list have a random venous blood glucose test annually. Unfortunately, experience has shown that the results are unlikely to be followed up, and referrals to the diabetes team are very few in this group of individuals within the Portsmouth area.

## Diagnostic criteria

Diagnosis of NODAT is based on UK diagnostic criteria for diabetes in the general population, which follows recommendations

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**Page points**

1. All transplant healthcare professionals should be aware of the factors associated with an increased risk of new-onset diabetes after transplanatation (NODAT).
2. If screening for diabetes is carried out preoperatively and diabetes is diagnosed, early intervention could be introduced.
3. If NODAT occurs after 6 months during long-term follow up, treatment will need to be individualised, and will generally follow the approach of somebody with type 2 diabetes.

from the WHO (1980), the International Diabetes Federation (2005) and the American Diabetes Association (2009).

In Portsmouth, individuals with impaired glucose tolerance post-transplant are also recognised and the relevant education given – for example, dietary advice and blood glucose monitoring at home and explaining the risk factors of developing diabetes. Random capillary blood glucose test results will then be monitored, and insulin therapy commenced if required. At the author's institution, insulin is used to optimise blood glucose levels, but, in some institutions, gliclazide is used.

All transplant healthcare professionals should be aware of the factors associated with an increased risk of NODAT – this would hopefully encourage them to screen for diabetes using a fasting glucose prior to transplant. If screening for diabetes is carried out preoperatively and diabetes is diagnosed, early intervention could be introduced. If an individual is diagnosed with diabetes, it may affect the decisions regarding which immunosuppressant medication is used post-transplant. Studies have shown tacrolimus is associated with a higher risk of developing post-transplant diabetes than ciclosporin (Pirsch et al, 1997). Therefore, the decision to use ciclosporin potentially could be made if diabetes has previously been diagnosed.

## Treatment of NODAT

The initial aim of NODAT treatment is to ameliorate symptoms and metabolic abnormalities and then to reduce the potential long-term impact of diabetes through adjustment of immunosuppressive therapy. Although neither NICE (2008) nor the national service framework (NSF) for renal services (Department of Health [DH], 2004) specifically consider the adjustment of immunosuppressive therapy to resolve symptoms of NODAT, the NSF's markers of good practice include effective monitoring and treatment to minimise the risks of adverse effects on immunosuppressive treatment. There are several factors associated with an increased risk of NODAT, both modifiable and non-modifiable, and these are listed in *Box 1*.

The second aim of treatment is to prevent the complications of diabetes through appropriate management of the condition. Individuals at the author's institution who develop NODAT with hyperglycaemia postoperatively (more than one random venous blood glucose level above 10 mmol/L) receive insulin. In Portsmouth, the team currently use short-acting human insulin with lunch and evening meals only, as they are trying to follow the steroid pattern of high blood glucose levels. Experience has shown, therefore, that waking blood glucose levels are good, and as the day continues blood glucose levels increase. This could potentially then be stepped down to oral hyperglycaemic agents, or withdrawal of treatment altogether if blood glucose levels become normal (<6 mmol/L; World Health Organization, 1980).

If NODAT occurs after 6 months during long-term follow-up, treatment will need to be individualised, and will generally follow the approach of somebody with type 2 diabetes – starting with improved diet and increased physical activity. However, the majority of people developing NODAT will require drug treatment. The use of metformin following kidney transplant is a grey area, and depends on post-transplant kidney function; this would be a decision made between the nephrologists and the diabetes team. Blood glucose control should be measured using $HbA_{1c}$ every 3 months.

Individuals with NODAT should receive intensive treatment for hypertension and hyperlipidaemia, and smoking cessation advice to reduce their risk of macrovascular

**Box 1. The factors associated with an increased risk of developing NODAT.**

- Age >40 years
- Black/Hispanic ethnicity
- Cadaver kidney
- Family history of diabetes
- Glucose intolerance
- Hepatitis C infection
- Immunosuppresive therapy
- Metabolic syndrome
- Obesity

complications. Most people with NODAT will also require treatment with antihypertensive and lipid-lowering drugs in addition to their immunosuppressive and hypoglycaemic therapy.

Patients with NODAT in Portsmouth are followed up for 3 months post-transplant by a DSN, but following this a referral to the diabetes centre is made for ongoing, annual follow-up. The diabetes service provides follow-up and annual screening for diabetes complications, including eye examinations for retinopathy, urinalysis for nephropathy, blood tests, and foot check-ups for neuropathy and peripheral artery disease.

Consistent management both by the transplant and diabetes teams is important and, ideally, patients should be followed-up by joint transplant–diabetes clinics if possible.

## Pre-transplant risk factors

Diabetes is a major complication of transplantation, and immunosuppressive therapy may play a part in its development. A number of pre-transplant risk factors predict the development of diabetes in some individuals, including age >40 years, high BMI, high fasting glucose levels, high plasma insulin levels and increased insulin resistance (Cho et al, 2003). Attempts should be made to reduce the incidence of NODAT by tailoring immunosuppression, lifestyle modification and selecting non-diabetogenic medications (Joss et al, 2007). Early detection and treatment of the modifiable factors can help prevent complications of diabetes, so screening is paramount to help these individuals lead healthy lives with their new organs.

Improvements in management of people at high risk of NODAT may help reduce the incidence of deaths with a functioning graft. Lifestyle modification is recommended as first-line therapy to manage NODAT. Management of the condition is very similar to that of type 2 diabetes (*Table 1*), along with titration of steroids and anti-rejection medication.

Management of NODAT is an ongoing process. If diabetes treatment is withdrawn at any point – usually due to a reduction in blood glucose levels – annual reviews are still required. Individuals should be made aware that they are at risk of developing type 2 diabetes in the future. As in type 2 diabetes, weight and lifestyle management is still essential and should continue.

**Page points**

1. Patients with new-onset diabetes after transplantation in Portsmouth are followed up for 3 months post-transplant by a DSN, but following this a referral to the diabetes centre is made for ongoing annual follow-up.
2. Consistent management both by the transplant and diabetes teams is important and, ideally, patients should be followed up by joint transplant–diabetes clinics if possible.
3. Diabetes is a major complication of transplantation, and immunosuppressive therapy may play a part in its development.

**Table 1. Management of people with new-onset diabetes after transplantation.**

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|---|---|---|
| **Pre-transplant baseline evaluation** | Screening<br>Complete medical history<br>Glucose history<br>Diabetes risk factors | Counselling<br>Weight control<br>Appropriate diet<br>Regular exercise<br>Compliance |
| **Individualisation of therapy** | Consider the following, particularly for high-risk individuals:<br>– Decrease corticosteroid dosage as soon as possible (after discussion with renal team)<br>– Use steroid-sparing regimens<br>– Consider switching to ciclosporin in tacrolimus-treated individuals with poorly controlled diabetes | |
| **Post-transplant monitoring for diabetes or abnormal glucose metabolism** | – Fasting plasma glucose testing<br>– Weekly for 4 weeks post-transplant<br>– At 3 months post-transplant<br>– At 6 months post-transplant<br>– Annually<br>– Also, administer regular oral glucose tolerance tests | |

***"The author plans to become more involved, as a DSN, in the pre-transplant clinics, and also to run all pre-transplant patients through a screening programme."***

In Portsmouth, the team run a low clearance renal clinic to see people with diabetes with an estimated glomerular filtration rate below 45 mL/min/1.73m$^2$. The aim of this clinic is to aid individuals in gaining good glycaemic control prior to surgery to help with their recovery and the life of their potential new kidney.

## Summary

The author plans to become more involved, as a DSN, in the pre-transplant clinics, and also to run all pre-transplant patients through a screening programme, whereby they have a fasting glucose test every 6 months. This should enable the diabetes team to commence any treatment necessary prior to surgery, thus giving the person with NODAT an increased chance of a speedy recovery. ■


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