NODAT: A disease in its own right or type 2 diabetes waiting to happen?

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There has been much discussion in recent years about the existence of new onset diabetes after transplantation (NODAT) as a disease in its own right. A 2003 consensus document for NODAT combined diagnostic criteria from the World Health Organization and the American Diabetes Association (Davidson et al, 2003). This debate outlines two schools of thought: The first point of view, put forward by Karen Marchant, is that NODAT should be considered as a separate disease to type 2 diabetes and the second viewpoint, argued by Julie Brake, is that NODAT is actually undiagnosed type 2 diabetes.

NODAT is an independent risk factor associated with transplantation, not just type 2 diabetes waiting to happen.

Karen Marchant

New onset diabetes after transplant (NODAT) is a serious condition constituting a distinct metabolic entity with unique pathophysiology that differs from type 2 diabetes (Hecking et al, 2013a). The diagnosis implies a raised mortality and morbidity risk due to increased rates of cardiovascular disease and infection, and is a leading cause of death in renal transplant recipients. Evidence suggests that NODAT decreases long-term allograft survival from any cause, with one-year survival at 83%, compared to 98% for those without NODAT.

While clinicians will agree some of the risk factors are similar to that of type 2 diabetes (age, obesity, family history, ethnicity and impaired glucose tolerance), there are independent risk factors associated with having a renal transplant that expose these individuals to a far greater risk of NODAT, either in the immediate post-operative period or within the first 12 months post-transplant. These include infection, immunosuppressant medication, underlying renal disease such as adult polycystic kidney disease, human leukocyte antigen mismatch and donor gender. If these individuals were not subjected to a transplant, they would not develop diabetes at this time, firmly establishing that NODAT is a different disease to type 2 diabetes.

The incidence of NODAT varies due to the time of the transplant, the study population and immunosuppressive agents used. The diagnosis of NODAT is made when individuals are on a maintenance immunosuppression dose, clear of infection with stable graft function, which generally occurs at three months of transplantation.

Diagnosis criteria incorporate both the World Health Organization and American Diabetes Association criteria for diabetes, which have been combined to form the International Consensus Guidelines (Davidson et al, 2003).

HbA_{1c} is not an accurate marker for diagnosis, but is useful for identifying any trends that are occurring and as a marker to alert the healthcare professional towards a diagnosis of NODAT within 12 months of a transplant. NODAT is diagnosed after 12 months. An updated guideline now suggests that the term NODAT is no longer used, but PTDM be adopted to describe all newly diagnosed diabetes in the post-transplant setting (Sharif et al, 2014).

A substantial number of people originally diagnosed with NODAT become normoglycaemic without medical intervention, or with medical intervention that can be stopped after only a few weeks, which suggests their hyperglycaemia was transient due to the higher dose immunosuppressive medication used in the earlier weeks of transplantation. These individuals should not be classified as having diabetes.

The evidence suggests that immunosuppressant medication is responsible for 74% of the NODAT diagnoses (Kaposztas et al, 2011), with tacrolimus appearing to be the most islet cell toxic.

"Screening for those with diabetes prior to transplant is crucial, as well as for those at risk of developing diabetes."

In those individuals converting from tacrolimus to sirolimus, significant deterioration in insulin resistance was noted, suggesting that cyclosporine is the least diabegenic medication. Hepatitis C virus (HCV) infection correlates with a four-fold increase in NODAT. HCV combined with tacrolimus increases this risk due to potential islet cell dysfunction, insulin resistance due to liver dysfunction and abnormalities in glucose metabolism. Cytomegalovirus (CMV) infection, a common occurrence post-transplant, may also increase the risk of NODAT

Overall, studies suggest about one-third of non-diabetic kidney transplant recipients develop impaired glucose metabolism six months post-transplant and those with transient hyperglycaemia may be at higher risk of NODAT at a later date (Chakkera et al, 2010). Therefore, healthcare professionals must remain vigilant to this high-risk group. The need to screen for diabetes is crucial, alongside patient education prior to transplant about the risk of developing NODAT within twelve months of transplantation or in the future. This information will help to prepare transplant patients, should this occur.

Screening in our cohort showed 138 people were listed as having developed NODAT post-transplant between January 1992 and February 2015. This number seems extraordinarily low and suggests poor data entry. Of these, 49% (67 people) did not have an HbA_{1c} check prior to transplantation. Of those with results, 38% had a raised HbA_{1c} (>42 mmol/mol [6%]) prior to transplantation. Of these, 59% also had a raised body mass index of 26–38 kg/m^2. Out of the remaining 44 individuals, 62% had a normal HbA_{1c} (<42 mmol/mol [6%]) and of these, 54% had a raised BMI between 26–38 kg/m^2. For those given an initial diagnosis of NODAT, 31% (43 people) had the diagnosis resolved within the first 12 months post-transplant (author's own data, unpublished).

Early intervention may be important. As Hecking et al (2013b) suggested, early use of insulin less than three weeks post-transplant could reduce the odds of developing NODAT within the first year by 73%.

Screening for those with diabetes prior to transplant is crucial, as well as for those at risk of developing diabetes. It is clear that within my own unit we need to make extra effort in this regard.

We also need to ensure better data entry to allow for a full and meaningful audit. Importantly, we need to ensure that those with resolved NODAT receive an annual follow-up to ensure they do not develop glucose intolerance or diabetes that goes unnoticed and therefore untreated.

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Diabetes by any other name.

Julie Brake

Is this really another type of diabetes that requires its own sub-category or name? Call me a sceptic, but is it not just secondary diabetes in the same way that post-pancreatitis diabetes or steroid-induced diabetes or even diabetes presenting post-myocardial infarction (MI) is? If not, then surely we should have NODAT, NODAMI (new onset diabetes post MI), NODAP (new onset diabetes post pancreatitis) and NODAS (new onset diabetes post steroids). It is also important to recognise that a considerable amount of "NODAT" could actually be previously undiagnosed type 2 diabetes picked up after a transplant. In many of the above "types" of diabetes, one could argue that the diabetes could have been present but undiagnosed prior to the event (MI, pancreatitis, steroid treatment) and this can also be true of NODAT.

Testing for diabetes prior to transplant can be sporadic. It can consist of a fasting blood glucose level only and is often not robust enough to detect undiagnosed type 2 diabetes in many people.

In one study by Bergrem et al (2010) looking at pre-transplant oral glucose tolerance testing in individuals without previously diagnosed diabetes, they found that 8.1% of individuals had undiagnosed diabetes and only 22% of these had a fasting plasma glucose of over 7.0 mmol/L. This

"It is also important to remember that people with pre-transplant diabetes fair far worse than those who develop diabetes post-transplant and have a higher cardiovascular mortality risk."

suggests that most undiagnosed diabetes in pre-transplant individuals would be missed on routine blood tests prior to transplant. This begs the question that as HbA_{1c} cannot be used in this group of individuals to diagnose diabetes, maybe all pre-transplant individuals should have a more thorough screen for diabetes?

It is also important to remember that people with pre-transplant diabetes fair far worse than those who develop diabetes post-transplant and have a higher cardiovascular mortality risk (Kuo et al, 2010), which is another reason why diabetes status should be confirmed prior to surgery.

The incidence of NODAT varies widely in the medical press and pre-transplant testing for diabetes is not consistent across the UK. This could account for the wide variation. In the literature, incidence of NODAT is between 2% and 53%. In Luan et al's study looking at incidence of NODAT in over 25 000 people, an overall incidence of approximately 16% after 3 years was found (Luan et al, 2011). In the previously mentioned study by Bergrem et al (2010), 8% of individuals having a transplant had undiagnosed type 2 diabetes. Therefore, it is impossible to know, retrospectively, how many of these diagnoses are type 2 diabetes.

The fact that NODAT results from the same metabolic risk factors as type 2 diabetes, and these are enhanced by the transplantation, is similar to the occurrence of post-MI diabetes. Studies do suggest, however, that the immunosuppressive regimens probably account for the increased risk of developing diabetes post transplant.

As Karen pointed out, immunosuppressants are responsible for 74% of NODAT (Kaposztas et al, 2011) with tacrolimus appearing to be the most islet cell toxic. Also, Karen noted that converting from tacrolimus to sirolimus led to significant deterioration in insulin resistance, suggesting cyclosporine is the least diabegenic. This re-enforces the theory that the person has diabetes secondary to immunosuppressant therapy, not necessarily diabetes due to the transplant.

This is also supported in a study by Depczynski et al (2000) looking at individuals who underwent heart transplantation. In this study, people who developed diabetes after transplant had received higher mean doses of prednisolone, pointing towards steroid-induced diabetes rather than NODAT.

Glucose profiles in people with NODAT are generally very similar to those with prednisolone-induced hyperglycaemia or diabetes, being especially raised through the afternoon and evening and commonly much improved fasting glucose levels the following day.

I feel that in order to identify the best treatment for people with diabetes post transplant, we need to establish the cause of their diabetes and, rather than lumping their diabetes under the umbrella of NODAT, surely we should have better screening prior to transplant in order to identify pre-transplant diabetes. As a result, any diabetes diagnosed post transplant can be seen for what it is, either a reaction to the surgery or a response to steroid or immunosuppressant therapy.

I do not disagree that some people diagnosed with NODAT do not have type 2 diabetes but have secondary diabetes. However, some individuals probably did have previously undiagnosed type 2 diabetes, or impaired glucose regulation that develops into type 2 diabetes due to the stress of major surgery or, more likely, they have secondary diabetes due to immunosuppressive therapy.

It is, therefore, fairly reasonable to consider how many people had undiagnosed type 2 diabetes prior to transplant. It is also reasonable to consider how many have diabetes due to the increased metabolic effects of surgery and how many have diabetes due to the post-transplant treatment (steroids and immunosuppressant therapy) and whether these different causations carry differing risks and require different treatments.

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