MANAGEMENT PERSPECTIVE

New-onset diabetes after transplantation: focus on strategies to reduce risk

Adnan Sharif†

Practice Points

- New-onset diabetes after transplantation (NODAT) is one of the major medical complications associated with solid-organ transplantation.
- Risk factors for NODAT are both transplant specific and nonspecific.
- There are important similarities and differences between NODAT and diabetes mellitus that prevent simple translation of research findings between the two.
- Appreciation of non-modifiable NODAT risk factors will help devise individualized immunosuppressant regimens that balance the risks of graft rejection and cardio–metabolic complications.
- An understanding of modifiable NODAT risk factors should guide clinical decision-making processes to help reverse, attenuate or delay the onset or progression of NODAT.

SUMMARY New-onset diabetes after transplantation (NODAT) is a major and frequent complication post-solid-organ transplantation with significant adverse outcomes associated with its development. Focus amongst transplant clinicians has shifted towards strategies to both predict and prevent the onset of NODAT. Our approach to this problem must incorporate both transplant-specific and nonspecific strategies and appreciate the differences between NODAT and diabetes mellitus with regards to pathophysiology, risk factors, clinical course and management. The complexity of these patients warrants cooperation between clinicians involved within both fields of transplantation and diabetes. This article aims to discuss current strategies to reduce the risk of NODAT and proposes future directions for clinical research.

New-onset diabetes after transplantation (NODAT) is a major medical complication associated with solid-organ transplantation, with many adverse clinical outcomes attributed to its development [1–4]. Owing to its considerable prevalence amongst transplant recipients, with up to half of all nondiabetic transplant recipients (range: 2–53%) likely to be diagnosed with NODAT [5], the associated risk of morbidity, mortality, cost and adverse impact on patient quality of life (see **Figure 1**), attenuating the future risk of developing NODAT has become a clinical priority amongst transplant clinicians. Although there are parallels between such strategies in the transplant recipient and those in the general population, we should hesitate to

†Department of Nephrology & Transplantation, Renal Institute of Birmingham, Queen Elizabeth Hospital Birmingham, Edgbaston, Birmingham, UK;
Tel.: +44 121 371 3034; Fax: +44 121 627 5747; sharif_adnan@hotmail.com

part of future medicine fsg

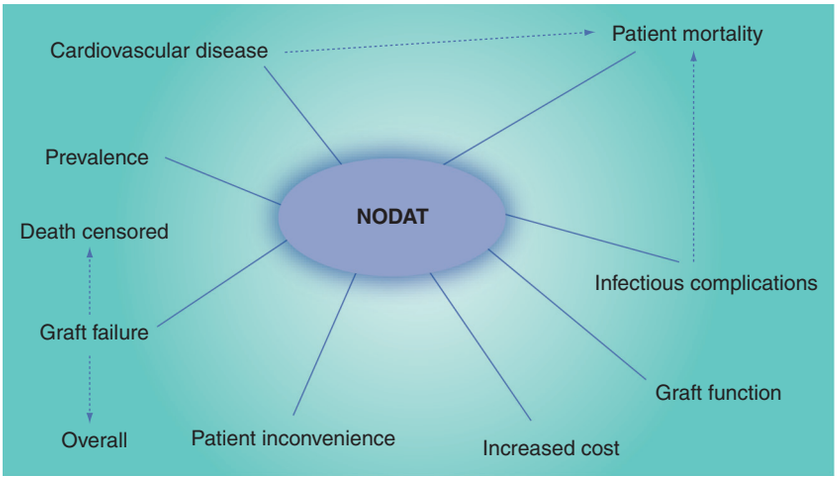

Figure 1. Why reduce the risk of new-onset diabetes after transplantation?
NODAT: New-onset diabetes after transplantation.

simply translate strategies from one population to another. NODAT and diabetes mellitus have many similarities but there are also important clinical and pathophysiological differences [2] that make transplant recipients a unique high-risk population (see **Table 1**). Although some of these individuals would have developed diabetes mellitus regardless of solid-organ transplantation, the transplant event itself provides a trigger and exacerbates underlying risk (e.g., similar to gestational diabetes) that justifies the term new-onset diabetes after transplantation (superseding the previously used term post-transplant diabetes mellitus).

Publication of NODAT consensus guidelines in 2003 provided transplant clinicians with clarification regarding screening, diagnosis and management options [6]. Prior to 2003 the diagnosis of NODAT lacked consistency owing to variable diagnostic criteria, center demographics and evolving immunosuppression regimens. The 2003 guidelines provided a consensus amongst transplant clinicians to adopt current American Diabetes Association (ADA) guidelines for the diagnosis of NODAT in line with the diagnosis of diabetes mellitus, and outlined treatment pathways with regards to management. However, in the current climate of new pharmacotherapy and clinical evidence, these guidelines are in need of urgent update with regards to preventative strategies. The purpose of this article is to review the transplantation literature, with the aim of discussing the evidence base behind strategies to reduce the risk of NODAT, and to suggest future directions. The aim is to assist clinicians in their attempts to devise focused and targeted risk-attenuation strategies for the development of NODAT in these high-risk patients. In the first half, the discussion will focus on how to predict the risk of developing NODAT. In the latter half of the article, the discussion will discuss strategies to attenuate or delay the development of NODAT and the evidence base for such therapeutic measures (see **Figure 2**).

Prediction of NODAT

■ Risk factors

Risk factors for the development of NODAT, both modifiable and non-modifiable, that are either transplant specific or nonspecific have been the subject of a recent comprehensive review [7] and are shown in **Box 1**. The importance of documenting these risk factors cannot be overstated. Knowledge of non-modifiable risk factors is important as it will allow individualization of immunosuppression to balance both graft and cardio–metabolic outcomes. Modifiable risk factors aid both prediction and prevention of NODAT and will be discussed in the second half of the article under preventative measures. In the context of predicting the risk of NODAT, it would be logical to assume a greater number of risk factors represents a higher likelihood of developing NODAT. In the general population, there are a variety of predictive risk factor models available that have epidemiologically demonstrated the ability to predict for the future risk of Type 2 diabetes mellitus [8]. No similar predictive models exist for a transplant-specific setting and it would be clinically advantageous to devise a specific NODAT predictive model for transplant recipients.

■ Abnormal glucose metabolism

Close surveillance of abnormal glycemia, regardless of timing or duration in the context of transplantation, identifies an individual with a heightened risk for the subsequent development of NODAT. Cosio *et al.* demonstrated an almost linear relationship between increasing levels of pre-transplantation fasting glycemia and subsequent post-transplantation risk of either impaired fasting glucose or NODAT [1]. From a postoperative perspective, Chakkera *et al.* recently demonstrated a relationship between inpatient hyperglycemia immediately post-transplantation and subsequent risk of developing NODAT [9]. Patients who

maintained normoglycemia whilst in hospital only had a 4% risk of NODAT at 1-year post-transplantation, in contrast with a 30% risk of NODAT for individuals with inpatient hyperglycemia requiring insulin therapy (patients with noninsulin-requiring hyperglycemia had an intermediate risk of developing NODAT of 18%). The considerable risk associated with insulin-requiring hyperglycemia is important as the authors have previously published work demonstrating that 66% of nondiabetic renal transplant recipients required insulin therapy upon discharge post-transplantation [10], although such percentages of insulin-on-discharge have not been observed from my own personal experience. Therefore the occurrence of hyperglycemia in any recipient post-transplantation, even if short term and self-limiting, should alert the clinician to the high-risk status of that individual for the subsequent development of NODAT. It should be highlighted that even self-limiting hyperglycemia that satisfies a diagnosis of diabetes but resolves should be classed as an episode of NODAT in accordance with the 2003 consensus guidelines, to allow appropriate risk stratification to be implemented to attenuate future NODAT risk.

■ Oral glucose tolerance tests

The oral glucose tolerance test (OGTT) should be considered the gold-standard diagnostic test post-transplantation on current evidence and diagnostic criteria are similar to the general population as suggested by the ADA (see **Table 2**). Its advantage lies in the ability to identify both fasting and postprandial hyperglycemia. Both are associated with disparate risks for development of diabetes and cardiovascular disease in the general population [11–13] due to their distinct pathophysiologies [14], with postprandial hyperglycemia having greater predictive power [11,15,16]. Similar epidemiological data for the predictive power of postprandial glucose is not available in transplant recipients and it remains to be seen whether postprandial hyperglycemia is a stronger risk factor than fasting hyperglycemia for clinical outcomes such as NODAT and cardiovascular disease post-transplantation.

The clinical benefit of identifying postprandial hyperglycemia with an OGTT pre-transplantation has been demonstrated by Bergrem and colleagues [17], where a diagnosis of impaired glucose tolerance pretransplantation was associated with a 26% increased risk of developing post-transplantation hyperglycemia. The advantage of an OGTT post-transplantation has been confirmed in a number of publications [18,19], as it can provide greater predictive power than fasting glucose alone by unmasking NODAT with postprandial glucose assessment.

■ Glycated hemoglobin

The role of the A1c assay from a screening and risk stratification perspective remains controversial in the general population, with an additional layer of complexity in the context of transplantation. Hoban *et al.* have previously demonstrated glycated hemoglobin to be superior to fasting glucose as a screening test for NODAT in renal transplant recipients [20]. Sharif and Baboolal have commented on the benefits and caveats of utilizing the A1c assay in the context of transplantation [21]. Notably, the accuracy of the assay will be mitigated in the setting of myelotoxic immuosuppression and post-transplantation anemia. However,

Table 1. Comparison of Type 2 diabetes mellitus with new-onset diabetes after transplantation.

Comparator	Type 2 diabetes mellitus	NODAT
Diagnosis	ADA criteria	2003 Consensus guidelines (incorporating ADA criteria)
Pathophysiology	Combination of β-cell dysfunction in context of insulin resistance	Combination of β-cell dysfunction in context of insulin resistance (exacerbated by immunosuppression)
Risk factors	General (e.g., age, obesity, family history and ethnicity)	General (but lack of evidence for some traditional risk like family history) Transplant specific
Management	Clinical evidence from randomized controlled trials	No randomized controlled trials available to guide management
Complications	Micro- and macro-vascular complications well documented	Unclear if similar degree or severity of complications

ADA: American Diabetes Association; NODAT: New-onset diabetes after transplantation.

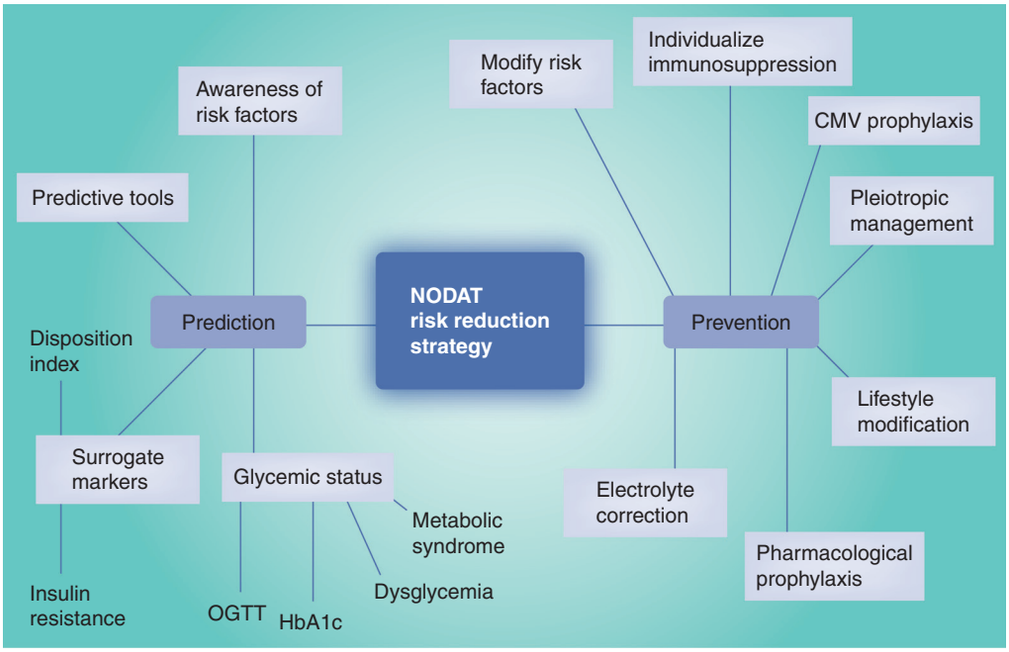

Figure 2. Strategies to reduce risk of new-onset diabetes after transplantation.
CMV: Cytomegalovirus; NODAT: New-onset diabetes after transplantation; OGTT: Oral glucose tolerance test.

the benefits are likely to outweigh the limitations and further work is required to validate the use of the assay for screening and diagnosis in a post-transplantation setting.

■ Metabolic syndrome

The metabolic syndrome is proposed as a cluster of known cardiovascular risk factors, inter-related by a common but speculative pathophysiological defect that symbolizes a heightened metabolic burden. The syndrome is not a disease itself but a marker of metabolic disturbance and a potential risk assessment tool for the development of diabetes and cardiovascular disease. The role of the metabolic syndrome is controversial with regards to NODAT risk stratification. Diagnosing metabolic syndrome in the context of solid-organ transplantation is associated with numerous adverse clinical outcomes and has been the subject of a comprehensive review article [22]. Notably, it is unclear whether there are pathophysiological differences between the metabolic syndrome in the general versus transplant population. There is emerging evidence of the utility of the metabolic syndrome in risk stratifying transplant recipients for future risk of NODAT, whether it is diagnosed pretransplantation [23] or post-transplantation [24]. Whether labeling transplant recipients with the metabolic syndrome has any clinical benefit over and above the presence of its individual components is unclear, but from an epidemiological viewpoint it certainly identifies high-risk patients who may merit further investigation or closer monitoring.

■ Insulin resistance indexes

New-onset diabetes after transplantation is characterized by the development of insufficient insulin secretion by the pancreatic β cell to compensate for the concomitant degree of insulin resistance [25–27]. Therefore, the development of insulin resistance is one of the early pathophysiological defects on the spectrum of dysglycemia and easy identification of deteriorating insulin resistance may be clinically advantageous. Gold standard techniques for assessing insulin sensitivity, such as euglycemic clamps or frequently sampled, intravenous glucose tolerance tests, are laborious and expensive academic tools. However, there are numerous surrogates available for estimation of insulin resistance in the context of transplantation, of which McAuley's index (calculated as: exp [2.63–0.28 ln (insulin [in microunits per milliliter]) – 0.31 ln (triglycerides [in millimoles per liter])) has been validated as one of the strongest

correlates (correlation r values ranging from 0.32–0.61; $p < 0.05$) [28,29]. Clinical application of these surrogates are lacking and there is no evidence to suggest continuous monitoring of these surrogates predicts for the development of NODAT.

■ Disposition index

Although surrogate insulin resistance indexes could be useful as screening tools, screening of this pathophysiological phenomenon may be difficult to interpret in isolation. As previously highlighted, NODAT develops due to β-cell dysfunction in the context of insulin resistance. This relationship is quantitatively represented as a mathematical constant (rectangular hyperbola) and qualitatively called the disposition index. In the context of falling insulin sensitivity (increasing insulin resistance), the pancreatic β cell secretes more insulin to compenstate in a reciprocal relationship. Despite these metabolic upheavals, the disposition index will remain constant and the patient remains normoglycemic. Only if the pancreatic β cells fails to adequately compensate for the degree of insulin resistance will the metabolic inter-relationship between insulin secretion and sensitivity fail and the disposition index falls, heralding the onset of hyperglycemia [26,30].

Therefore, as a more integrated representation of glycemic metabolism, surrogate markers for the disposition index itself may be better suited to track the evolution of glycemic abnormalities. In the general population, Utzschneider and colleagues demonstrated a surrogate for the disposition index that predicted for the development of future diabetes mellitus over and above that predicted by postprandial glucose [31]. In the transplant population, Sharif *et al.* have produced a surrogate formula for the disposition index ($DI = Insulin_0 \times [3.33/(glucose_0 - 3.5)] \times \exp[2.63 - (0.28 \times \ln\{insulin_0/6.945\}) - (0.31 \times \ln trigycerides_0)]$), calculated in standard international units, which correlates well with the intravenous glucose tolerance test-derived disposition index, is statistically consistent with a mathematical hyperbola and is valid in subgroups of transplant recipients [32]. The advantage of the Sharif index compared with the Utzschneider index is the ability to utilize fasting rather than postprandial blood sampling. There is evidence that a high carbohydrate–low glycemic index diet in the general population can modify the disposition index in patients with impaired glucose tolerance [33]. However, clinical application of this experimental surrogate post-transplantation is awaited and it remains to be seen whether serial monitoring of the disposition index is clinically advantageous.

Prevention of NODAT

■ Tailored immunosuppression

As previously discussed, an awareness of risk factors for NODAT is important for predicting the likelihood of its development [7]. An understanding of non-modifiable risk factors allows individualization of immunosuppressive regimens prior to transplantation, balancing the efficacy of graft survival with minimization of complications. In the current era of

Box 1. Risk factors for new-onset diabetes after transplantation.

Non-modifiable

- Age
- Ethnicity
- Family history of diabetes mellitus?
- *Cause of end-stage renal failure*
- Gender?
- *HLA mismatch?*
- Genetics
- *Innate immunity*
- *Donor characteristics?*
- Education

Modifiable

- Previous stress diabetes
- Obesity
- Metabolic syndrome
- Pre-transplant triglycerides
- *Cytomegalovirus*
- *Hepatitis C*
- *Immunosuppression*
  - Tacrolimus
  - Cyclosporin
  - Sirolimus
  - Corticosteroids
- *Rejection episodes?*
- Antihypertensives
  - β-blockers
  - Thiazide diuretics
- Biochemical abnormalities
  - Magnesium
  - Uric acid?
- Glomerular filtration rate?

Italics represent transplant-specific risk factors.

Table 2. Diagnosis of prediabetes based upon fasting glucose and oral glucose tolerance test (WHO).

Glycemic state	0 h glucose (mmol/l)	2 h glucose (mmol/l)
Normal	<6.1	<7.8
IFG	6.1†–6.9	–
IGT	–	7.8–11.0
NODAT	>6.9	>11.0

†5.6–6.9 mmol/l with American Diabetes Association.
IFG: Impaired fasting glycemia; IGT: Impaired glucose tolerance; NODAT: New-onset diabetes after transplantation.

immunosuppression there exists a variety of regimens providing comparable graft survival that could be appropriate for such patients at high risk of developing NODAT [34]. Examples of strategies with less diabetogenicity currently available include the use of cyclosporin rather than tacrolimus as the calcineurin inhibitor of choice [35], corticosteroid avoidance [36] or corticosteroid-sparing regimens [37]. The task for transplant clinicians is to balance the benefits of less diabetogenic immunosuppression with the potential increased risk of rejection with these strategies. Calcineurin inhibitor-free immunosuppression is one option but has its limitations. Transplant recipients poorly tolerate mTOR inhibitors and incidentally these agents are themselves associated with a risk of NODAT [38]. Newer immunosuppressant agents such as belatacept and tasocitinib are on the horizon, and awaiting regulatory approval, and have been shown to be less diabetogenic with equivalent graft survival, albeit at risk of increased allograft rejection [39,40].

Obesity/metabolic syndrome

Obesity, either alone or as a constituent of the metabolic syndrome, is one of the most important risk factors for the development of NODAT [23]. Putative evidence links pathophysiological mechanisms such as obesity, inflammation and adipocyte dysfunction as risk factors for NODAT [41]. A focus on obesity is important as it is common post-transplantation and associated with detrimental patient and graft outcomes [42]. However, there is currently no evidence to suggest pharmacologically or surgically targeting obesity post-transplantation has any favorable metabolic effects from a glycemic point of view.

With regards to the metabolic syndrome, although it has shown to be a useful risk stratification tool, it remains debateable whether the diagnosis provides any additional therapeutic advantage over its individual components. Controversy remains as to the merit of the metabolic syndrome [43,44] and what value it has as a therapeutic target. Until a definitive underlying pathophysiological mechanism is elucidated, the metabolic syndrome is likely to remain an epidemiological rather than a clinical or therapeutic tool.

■ Virus infection

Cytomegalovirus infection

Hjelmesaeth and colleagues have demonstrated an independent link between cytomegalovirus (CMV) infection and the development of NODAT, with putative mechanisms including direct virus-induced pancreatic β-cell damage [45]. This raises the possibility of prophylactic agents to prevent CMV infection also indirectly attenuating the risk of developing NODAT. Current transplantation practice is to administer 100 days of antiviral prophylaxis (e.g., oral valganciclovir) to patients at high risk for CMV (usually donor CMV positive and recipient CMV negative). The recent Improved Protection Against Cytomegalovirus in Transplant (IMPACT) study explored the benefits of utilizing a 200-day approach compared with 100 days in renal transplant recipients at high risk for NODAT [46]. Although there were advantages with regards to a reduced incidence of CMV with the prolonged 200-day prophylaxis, there was no significant difference in the secondary end point of incidence of NODAT (although the study was not adequately powered for this analysis). It should, however, be noted that not all groups have shown a link between CMV and NODAT and any putative link between the two remains pathophysiologically speculative [47].

Hepatitis C

Studies have shown that recipients with hepatitis C have a greater incidence of NODAT [48–50], although others have shown no statistically significant association and merely a trend [51]. Bloom *et al.* retrospectively performed multivariate logistic regression on 427 renal transplant recipients and identified hepatitis C as an independent risk factor, although a significant interaction existed between hepatitis C status and tacrolimus use [52]. The mechanism by which hepatitis C may cause NODAT is speculative but possible mechanisms suggested include impaired insulin action, defects in glucose

homeostasis secondary to liver disease or insulin resistance [52], with the latter emerging as the strongest causative factor [53]. This raises the possibility of antiviral treatment of hepatitis C attenuating the risk or progression of NODAT, although such evidence is lacking.

■ Correction of biochemical abnormalities

Biochemical abnormalities are common post-transplantation and likely secondary to both immunosuppression and tubular dysfunction (in the context of kidney transplantation). Van Laecke *et al.* demonstrated the detrimental effect of post-transplant hypomagnesemia on glucose metabolism in a retrospective single-center analysis of 254 renal transplant recipients [54]. Although this would suggest magnesium replacement may attenuate abnormal glucose metabolism, the authors paradoxically found the use of magnesium supplements to be associated with a risk of NODAT on a univariate analysis. Apart from hypomagnesemia, other common post-transplant biochemical abnormalities that may be associated with transplant-associated hyperglycemia include hyperuricemia and vitamin D deficiency [55]. Whether correction of any of these factors will attenuate abnormal glucose metabolism post-transplantation is unknown.

■ Antihypertensive therapy

The differing diabetogenicity of hypertensive agents is well documented in the general population, with β-blockers in particular noted for significant diabetogenic effects [56]. In the transplant population, Hjelmesaeth *et al.* observed detrimental effects of β-blockers and thiazide diuretics on glucose metabolism, although this proved nonsignificant in a multivariate analysis [57]. The pathophysiological effect of β-blockers on glucose metabolism post-transplantation may result from adipocyte dysfunction [58]. The choice of antihypertensive agents post-transplantation should be based on benefit on an individual basis but should acknowledge the possible diabetogenic risk attached to each agent in the context of pre-existing diabetic risk.

■ Lifestyle modification

Lifestyle modification has been shown to delay the onset of diabetes in nontransplant populations with abnormal glucose metabolism [59–62]. In a transplantation setting, Sharif *et al.* have demonstrated the successful use of aggressive lifestyle modifications [63]. Renal transplant recipients with abnormal postprandial glucose metabolism on an OGTT (impaired glucose tolerance and NODAT, n = 36) were selected to have aggressive lifestyle modifications (dietician referral, graded exercise program and weight loss advice), whilst renal transplant recipients with normal postprandial glucose metabolism (normal and impaired fasting glucose, n = 79) received leaflets advocating healthy lifestyle modifications alone. The dietary meal framework was derived from Diabetes UK advice [101] and consisted of 50% carbohydrate, 25% protein (meat, fish and beans) and 25% fiber (fruit and vegetables). A graded exercise program was commenced with the aim of maintaining 2 h of endurance exercise (e.g., walking, jogging or swimming) per week. Dieticians monitored all dietary and exercise diaries with reinforcement of lifestyle modification advice.

The intensive regimen resulted in a statistically significant reduction in postprandial glucose levels (10.2 mmol/l to 8.7 mmol/l, Δ = -15%, p = 0.012) and improved reclassification of glycemic status on re-evaluation by OGTT 6 months later. By contrast, simple lifestyle modification advice by leaflets alone in the group with normal glucose tolerance (n = 79) resulted in a significant deterioration of postprandial glucose levels (5.9 mmol/l to 6.6 mmol/l, Δ = +12%, p = 0.001) and worse glycemic status reclassification on follow-up OGTT.

■ Pharmacological prophylaxis for 'high risk' patients

Unlike in the general population [64–66], there is no evidence in the transplant population that the use of glucose-lowering agents as prophylaxis in patients deemed to be high risk for the development of NODAT or cardiovascular disease is beneficial. Randomized controlled trials targeting nondiabetic transplant recipients should be actively encouraged. In the context of overlapping metabolic disorders with shared pathophysiological mechanisms, it could be hypothesized that antiobesity or lipid-lowering agents may be beneficial owing to putative indirect effects on glucose metabolism, so-called pleiotropic effects.

■ Statins for pleiotropic benefits

Prasad *et al.* putatively suggested the link between the use of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) and a

reduced incidence of NODAT in a retrospective analysis of 314 renal transplant recipients [67]. Based on this hypothesis, Sharif *et al.* conducted a randomized controlled, double-blind, placebo-controlled crossover study comparing the effects of rosuvastatin 10 mg once daily and placebo in 20 nondiabetic renal transplant recipients with an indication for statin treatment [68]. Physiological parameters of glucose metabolism were assessed with the use of a frequently sampled, intravenous, glucose tolerance test and a meal tolerance test at the end of a 12-week crossover in each arm. Despite being an effective lipid-lowering agent and with clinically but not statistically significant anti-inflammatory action, the study demonstrated no significant influence of short-term rosuvastatin treatment on any physiological parameters of pancreatic β-cell function and insulin sensitivity. It could be argued that the pleiotropic effects of statin treatment only manifest after long-term administration, but in the absence of any clear evidence this hypothesis remains pure speculation.

Conclusion

This article highlights our current understanding on the strategies available for predicting and preventing the development of NODAT. In view of the significant advances made in both our knowledge base and available pharmacological armamentarium, it provides a clinical update to outdated NODAT guidelines. Although there remains a lack of randomized controlled trials, clinicians are in a better position today to make informed decisions regarding the prevention, attenuation and management of transplant-associated hyperglycemia in a clinical setting. We hope the summary provided here not only guides risk reduction of NODAT, but inspires further research and clinical trials into preventative strategies focussing specifically on solid-organ transplant recipients.

New-onset diabetes after transplantation is a major complication of solid-organ transplantation with associated morbidity, mortality and financial cost. Appropriate risk stratification should lead to adequate strategies to attenuate the risk of the development of NODAT – this requires close attention to risk factors for NODAT on an individual basis. Attention must be given to targeted research on the pathophysiology, progression and management of NODAT as simple translation of clinical data from the general population may not be appropriate. With patient expectations of a successful allograft heightened in the current era, focusing on attenuating the adverse complications of solid-organ transplantation, such as NODAT, will dominate the direction of transplantation medicine in the years to come.

Future perspective

Interest in this area is likely to direct attention to strategies attenuating the development of NODAT and focusing on how to predict and prevent NODAT. With regards to attenuating abnormal glycemic metabolism, it is clear that NODAT has many similarities but also important differences with diabetes mellitus and that simple translation of research from the general to transplant population should be avoided. Focused and targeted clinical trials are specifically required in this high-risk population to help guide strategies to both predict and prevent development of NODAT, including prophylaxis for high-risk recipients and targeting of obesity and the metabolic syndrome. Collaborations between transplant clinicans and diabetologists should therefore be encouraged to ensure transplant recipients receive optimum care for transplant-associated hyperglycemia. Evolving research domains such as utilizing genomics and genetic polymorphisms to identify high-risk population groups are likely to add to the knowledge base of NODAT risk stratification and will help shed light on some of the pathophysiological mysteries associated with the disease.

Transplant-specific randomized controlled trials are required to assess the potential for pharmacological prophylaxis to prevent the onset of NODAT in high-risk groups. Some agents such as metformin may be suitably attractive for their weight neutral properties, but close attention would need to be given to potential side effects. With the number of transplant recipients on the increase, future projects should be planned for by clinicians today.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

1 Cosio FG, Kudva Y, Velde MVD *et al.*: New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int.* 67, 2415–2421 (2005).

2 Crutchlow MF, Bloom RD: Transplant-associated hyperglycemia: a new look at an old problem. *Clin. J. Am. Soc. Nephrol.* 2, 343–355 (2007).

3 Moore R, Ravindran V, Baboolal K: The burden of new-onset diabetes mellitus after transplantation. *Clin. Transplant.* 20(6), 755–761 (2006).

4 Bodziak KA, Hricik DE: New-onset diabetes mellitus after solid organ transplantation. *Transpl. Int.* 22(5), 519–530 (2009).

5 Davidson JA, Wilkinson A: New-Onset Diabetes after Transplantation 2003 International Consensus Guidelines: an endocrinologist's view. *Diabetes Care* 27(3), 805–812 (2004).

6 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* 75(Suppl. 10), SS3–S24 (2003).

7 Sharif A, Baboolal K: Risk factors for new-onset diabetes after kidney transplantation. *Nat. Rev. Nephrol.* 6(7), 415–423 (2010).

8 Schwarz PE, Li J, Lindstrom J, Tuomilehto J: Tools for predicting the risk of Type 2 diabetes in daily practice. *Horm. Metab. Res.* 41(2), 86–97 (2009).

9 Chakkera HA, Knowler WC, Devarapalli Y *et al.*: Relationship between inpatient hyperglycemia and insulin treatment after kidney transplantation and future new onset diabetes mellitus. *Clin. J. Am. Soc. Nephrol.* 5(9), 1669–1675 (2010).

10 Chakkera HA, Weil EJ, Castro J *et al.*: Hyperglycemia during the immediate period after kidney transplantation. *Clin. J. Am. Soc. Nephrol.* 4(4), 853–859 (2009).

11 Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC: Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet. Med.* 17(6), 433–440 (2000).

12 Unwin N, Shaw J, Zimmet P, Alberti KG: Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet. Med.* 19(9), 708–723 (2002).

13 Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata Diabetes Study. *Diabetes Care* 22(6), 920–924 (1999).

14 Meyer C, Pimenta W, Woerle HJ *et al.*: Different mechanisms for impaired fasting glucose and impaired postprandial glucose tolerance in humans. *Diabetes Care* 29(8), 1909–1914 (2006).

15 Santaguida PL, Balion C, Hunt D *et al.*: Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. *Evid. Rep. Technol. Assess. (Summ.)* 128, 1–11 (2005).

16 Zhang YF, Hong J, Zhan WW *et al.*: Hyperglycaemia after glucose loading is a major predictor of preclinical atherosclerosis in nondiabetic subjects. *Clin. Endocrinol. (Oxf.)* 64(2), 153–157 (2006).

17 Bergrem HA, Valderhaug TG, Hartmann A, Bergrem H, Hjelmesaeth J, Jenssen T: Glucose tolerance before and after renal transplantation. *Nephrol. Dial. Transplant.* 25(3), 985–992 (2010).

18 Sharif A, Moore RH, Baboolal K: The use of oral glucose tolerance tests to risk stratify for new-onset diabetes after transplantation: an underdiagnosed phenomenon. *Transplantation* 82(12), 1667–1672 (2006).

19 Armstrong KA, Prins JB, Beller EM *et al.*: Should an oral glucose tolerance test be performed routinely in all renal transplant recipients? *Clin. J. Am. Soc. Nephrol.* 1, 100–108 (2006).

20 Hoban R, Gielda B, Temkit M *et al.*: Utility of HbA1c in the detection of subclinical post renal transplant diabetes. *Transplantation* 81(3), 379–383 (2006).

21 Sharif A, Baboolal K: Diagnostic application of the A(1c) assay in renal disease. *J. Am. Soc. Nephrol.* 21(3), 383–385 (2010).

22 Sharif A: Metabolic syndrome and solid-organ transplantation. *Am. J. Transplant.* 10(1), 12–17 (2010).

23 Bayer ND, Cochetti PT, Anil Kumar MS *et al.*: Association of metabolic syndrome with development of new-onset diabetes after transplantation. *Transplantation* 90(8), 861–866 (2010).

24 Porrini E, Delgado P, Bigo C *et al.*: Impact of metabolic syndrome on graft function and survival after cadaveric renal transplantation. *Am. J. Kidney Dis.* 48(1), 134–142 (2006).

25 Nam JH, Mun JI, Kim SI *et al.*: β-cell dysfunction rather than insulin resistance is the main contributing factor for the development of postrenal transplantation diabetes mellitus. *Transplantation* 71(10), 1417–1423 (2001).

26 Pacini G: The hyperbolic equilibrium between insulin sensitivity and secretion. *Nutr. Metab. Cardiovasc. Dis.* 16(Suppl. 1), S22–S27 (2006).

27 Hjelmesaeth J, Hagen M, Hartmann A, Midtvedt K, Egeland T, Jenssen T: The impact of impaired insulin release and insulin resistance on glucose intolerance after renal transplantation. *Clin. Transplant.* 16(6), 389–396 (2002).

28 Sharif A, Ravindran V, Moore RH *et al.*: Insulin resistance indexes in renal transplant recipients maintained on tacrolimus immunosuppression. *Transplantation* 89(3), 327–333 (2010).

29 Oterdoom LH, de Vries AP, van Son WJ *et al.*: Validation of insulin resistance indexes in a stable renal transplant population. *Diabetes Care* 28(10), 2424–2429 (2005).

30 Ekstrand AV, Eriksson JG, Gronhagen-Riska C, Ahonen PJ, Groop LC: Insulin resistance and insulin deficiency in the pathogenesis of posttransplantation diabetes in man. *Transplantation* 53(3), 563–569 (1992).

31 Utzschneider KM, Prigeon RL, Faulenbach MV *et al.*: Oral disposition index predicts the development of future diabetes above and beyond fasting and 2-h glucose levels. *Diabetes Care* 32(2), 335–341 (2009).

32 Sharif A, Ravindran VK, Dunseath G, Luzio SD, Owens DR, Baboolal K: Impending hyperglycemia in normoglycemic renal transplant recipients – an experimental predictive surrogate. *Transplantation* 89(11), 1341–1346 (2010).

33 Wolever TM, Mehling C: High-carbohydrate-low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance. *Br. J. Nutr.* 87(5), 477–487 (2002).

34 Chadban S: New-onset diabetes after transplantation – should it be a factor in choosing an immunosuppressant regimen for kidney transplant recipients. *Nephrol. Dial. Transplant.* 23(6), 1816–1818 (2008).

35 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.* 7(6), 1506–1514 (2007).

36 Woodle ES, First MR, Pirsch J, Shihab F, Gaber AO, Van Veldhuisen P: A prospective, randomized, double-blind, placebo-controlled multicenter trial comparing early (7 day) corticosteroid cessation versus long-term, low-dose corticosteroid therapy. *Ann. Surg.* 248(4), 564–577 (2008).

37 Knight SR, Morris PJ: Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk. A meta-analysis. *Transplantation* 89(1), 1–14 (2010).

38 Johnston O, Rose CL, Webster AC, Gill JS: Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J. Am. Soc. Nephrol.* 19(7), 1411–1418 (2008).

39 Vincenti F, Charpentier B, Vanrenterghem Y *et al.*: A Phase III study of Belatacept-based Immunosuppression Regimens versus Cyclosporine in Renal Transplant Recipients (BENEFIT study). *Am. J. Transplant.* 10(3), 535–546 (2010).

40 Busque S, Leventhal J, Brennan DC *et al.*: Calcineurin-inhibitor-free immunosuppression based on the JAK inhibitor CP-690,550: a pilot study in *de novo* kidney allograft recipients. *Am. J. Transplant.* 9(8), 1936–1945 (2009).

41 Bayes B, Granada ML, Pastor MC *et al.*: Obesity, adiponectin and inflammation as predictors of new-onset diabetes mellitus after kidney transplantation. *Am. J. Transplant.* 7(2), 416–422 (2007).

42 Potluri K, Hou S: Obesity in kidney transplant recipients and candidates. *Am. J. Kidney Dis.* 56(1), 143–156 (2010).

43 Alberti KG, Zimmet PZ: Should we dump the metabolic syndrome? No. *BMJ* 336(7645), 641 (2008).

44 Gale EA: Should we dump the metabolic syndrome? Yes. *BMJ* 336(7645), 640 (2008).

45 Hjelmesaeth J, Sagedal S, Hartmann A *et al.*: Asymptomatic cytomegalovirus infection is associated with increased risk of new-onset diabetes mellitus and impaired insulin release after renal transplantation. *Diabetologia* 47(9), 1550–1556 (2004).

46 Humar A, Lebranchu Y, Vincenti F *et al.*: The efficacy and safety of 200 days valganciclovir cytomegalovirus prophylaxis in high-risk kidney transplant recipients. *Am. J. Transplant.* 10(5), 1228–1237 (2010).

47 Gourishankar S, Jhangri GS, Tonelli M, Wales LH, Cockfield SM: Development of diabetes mellitus following kidney transplantation: a Canadian experience. *Am. J. Transplant.* 4(11), 1876–1882 (2004).

48 Soule JL, Olyaei AJ, Boslaugh TA *et al.*: Hepatitis C infection increases the risk of new-onset diabetes after transplantation in liver allograft recipients. *Am. J. Surg.* 189(5), 552–557; discussion 557 (2005).

49 Finni PE, Souza ER, Rioja S *et al.*: Is hepatitis C a risk factor to posttransplant diabetes mellitus after renal transplantation in patients using tacrolimus? *Transplant. Proc.* 36(4), 884–885 (2004).

50 Fabrizi F, Messa P, Martin P, Takkouche B: Hepatitis C virus infection and post-transplant diabetes mellitus among renal transplant patients: a meta-analysis. *Int. J. Artif. Organs* 31(8), 675–682 (2008).

51 Sens YA, Silva VD, Malafronte P, Souza JF, Miorin LA, Jabur P: Posttransplant diabetes mellitus in renal transplant patients with hepatitis C virus. *Transplant. Proc.* 36(4), 886–888 (2004).

52 Bloom RD, Rao V, Weng F, Grossman RA, Cohen D, Mange KC: Association of hepatitis C with posttransplant diabetes in renal transplant patients on tacrolimus. *J. Am. Soc. Nephrol.* 13(5), 1374–1380 (2002).

53 Baid-Agrawal S, Frei U, Reinke P *et al.*: Impaired insulin sensitivity as an underlying mechanism linking hepatitis C and posttransplant diabetes mellitus in kidney recipients. *Am. J. Transplant.* 9(12), 2777–2784 (2009).

54 Van Laecke S, Van Biesen W, Verbeke F, De Bacquer D, Peeters P, Vanholder R: Posttransplantation hypomagnesemia and its relation with immunosuppression as predictors of new-onset diabetes after transplantation. *Am. J. Transplant.* 9(9), 2140–2149 (2009).

55 Sharif A: Predictors of new-onset diabetes after transplantation: the overlooked confounders. *Am. J. Transplant.* 9, 2858 (2009).

56 Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for Type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N. Engl. J. Med.* 342(13), 905–912 (2000).

57 Hjelmesaeth J, Midtvedt K, Jenssen T, Hartmann A: Insulin resistance after renal transplantation: impact of immunosuppressive and antihypertensive therapy. *Diabetes Care* 24(12), 2121–2126 (2001).

58 Hjelmesaeth J, Flyvbjerg A, Jenssen T *et al.*: Hypoadiponectinemia is associated with insulin resistance and glucose intolerance after renal transplantation: impact of immunosuppressive and antihypertensive drug therapy. *Clin. J. Am. Soc. Nephrol.* 1(3), 575–582 (2006).

59 Uusitupa M: Lifestyles matter in the prevention of Type 2 diabetes. *Diabetes Care* 25(9), 1650–1651 (2002).

60 Lindstrom J, Eriksson JG, Valle TT *et al.*: Prevention of diabetes mellitus in subjects with impaired glucose tolerance in the Finnish Diabetes Prevention Study: results from a randomized clinical trial. *J. Am. Soc. Nephrol.* 14(7 Suppl. 2), S108–S113 (2003).

61 Tuomilehto J, Lindstrom J, Eriksson JG *et al.*: Prevention of Type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N. Engl. J. Med.* 344(18), 1343–1350 (2001).

62 Pan XR, Li GW, Hu YH *et al.*: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 20(4), 537–544 (1997).

63 Sharif A, Moore R, Baboolal K: Influence of lifestyle modification in renal transplant recipients with postprandial hyperglycemia. *Transplantation* 85(3), 353–358 (2008).

64 Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290(4), 486–494 (2003).

65 Knowler WC, Barrett-Connor E, Fowler SE *et al.*: Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346(6), 393–403 (2002).

66 Gerstein HC, Yusuf S, Bosch J *et al.*: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368(9541), 1096–1105 (2006).

67 Prasad GV, Kim SJ, Huang M *et al.*: Reduced incidence of new-onset diabetes mellitus after renal transplantation with 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors (statins). *Am. J. Transplant.* 4(11), 1897–1903 (2004).

68 Sharif A, Ravindran V, Moore R *et al.*: The effect of rosuvastatin on insulin sensitivity and pancreatic β-cell function in nondiabetic renal transplant recipients. *Am. J. Transplant.* 9(6), 1439–1445 (2009).

■ Website

101 Diabetes UK: Eating well – Food and diabetes (2006) http://diabetes.org.uk/Guide-to-diabetes/Food_and_recipes