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REVIEW

Dysglycemia after renal transplantation: Definition, pathogenesis, outcomes and implications for management

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Abstract

New-onset diabetes after transplantation (NODAT) is major complication following renal transplantation. It commonly develops within 3-6 mo post-transplantation. The development of NODAT is associated with significant increase in risk of major cardiovascular events and cardiovascular death. Other dysglycemic states, such as impaired glucose tolerance are also associated with increasing risk of cardiovascular events. The pathogenesis of these dysglycemic states is complex. Older recipient age is a consistent major risk factor and the impact of calcineurin inhibitors and glucocorticoids has been well described. Glucocorticoids likely cause insulin resistance and calcineurin inhibitors likely cause β-cell toxicity. The impact of transplantation in incretin hormones remains to be clarified. The oral glucose tolerance test remains the best diagnostic test but other tests may be validated as screening tests. Possibly, NODAT can be prevented by administering insulin early in patients identified as high risk for NODAT. Once NODAT has been diagnosed altering immunosuppression may be acceptable, but creates the difficulty of balancing immunological with metabolic risk. With regard to hypoglycemic use, metformin may be the best option. Further research is needed to better understand the pathogenesis, identify high risk patients and to improve management options given the significant increased risk of major cardiovascular events and death.

Key words: Management; Epidemiology; Pathogenesis; Renal transplantation; Diabetes

Core tip: New-onset diabetes after transplantation (NODAT) carries a significant cardiovascular burden. Its pathogenesis is multifactorial and includes modifiable factors. New insights into glucose and insulin homeostasis may lead to improved ability to identify high risk patients and to the development of management strategies that do not require alteration in immunosuppression, whilst simultaneously reducing the risk of NODAT.

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INTRODUCTION

Dysglycemia post renal transplantation, encompassing new onset diabetes after transplant (NODAT), impaired fasting glucose (IGF) and impaired glucose tolerance (IGT), is a challenging clinical problem. However, despite more than two decades of research the pathogenesis of post-transplant dysglycemia is incompletely understood and a consensus on approach to screening, diagnosis and management is lacking. This review will outline the issues of defining the clinically important states, detecting and predicting their development, the progress that has been made in understanding their pathogenesis and relationship to described risk factors (particularly immunosuppression therapies) and the implications for management and further research into this significant post-transplant complication.

DEFINITION

There have been several changes in the definition of dysglycemia post transplantation over time. Initially referred to as diabetes after renal transplantation, this name failed to capture the important distinction of those who were diabetic pre-transplant from those who developed diabetes after transplant. The term post-transplant diabetes mellitus (PTDM) also failed to clearly distinguish between the two states. The most common term currently used is new-onset diabetes after transplant (NODAT); however, this too fails to capture those with new onset IGT, which is also associated with poorer outcomes (see below). Some have proposed the term "transplant associated hypergylcemia"[1], which captures the impact of dysglycemia, as opposed to the worst category of dysglycemia alone (diabetes), however it does not to make a distinction between those who came to transplant with a dysglycemic state and those who developed it after transplantation.

Prior to 2003 the most common criteria used for the diagnosis of post-transplant diabetes was use of hypoglycemic agents. However, this is reliant upon clinician awareness of the results of appropriately timed and collected glucose testing and remains an insensitive marker of NODAT. With enhanced understanding of the pathophysiology of post-transplant dysglycemia and its clinical significance a more sensitive and clinical useful definition is needed. In 2003 an international expert panel devised a consensus document[2] that adopted the World Health Organisation/American Diabetes Association (WHO/ADA) guidelines for the testing and defining of dysglycemic states post-transplant [fasting blood glucose level (F BGL) $\geqslant$ 7.0 mol/L; 2-h BGL $\geqslant$ 11.1 mmol/L], based on the definitions used for the general population. However, whilst there is consensus on the interpretation of blood glucose levels, there is no consensus on who to test, when to test and which test to use. Table 1 shows the wide range of tests used and timing of these in studies that have reported NODAT outcomes: F BGL, random blood glucose level (R BGL), 2-h 75 g oral glucose tolerance test (oGTT), HbA1c at 10 wk, 3 mo, 6 mo, 1 year and use of hypoglycemic agents at 30 d. Furthermore, there is little recognition in the literature of the importance of reporting and understanding the significance of dysglycemic states other than NODAT such as IGT or IFG. Few studies report incident rates and/or outcomes of such dysglycemic states. As a result, drawing conclusions based on research in this area has unavoidable caveats, which can only be addressed by large multi-centred well designed trials with post-transplant dysglycemia as the primary outcome.

EPIDEMIOLOGY

One of the confounders in any study of NODAT is the rate of pre-transplant unrecognised dysglycemia. Table 2 shows the rates of unrecognised dysglycemia in patients on the transplant waiting list. Bergrem *et al*[30] investigated 889 Norwegian transplant wait listed candidates who were not clinically suspected to have diabetes. The majority of patients (62%) were not on dialysis and only 12% were on glucocorticoids. All patients underwent an oGTT. Using WHO/ADA diagnostic criteria, 330 (37.1%) patients were found to have dysglycemia, in addition to which, 72 (8.1%) were found to have diabetes. Importantly, of those patients found to be diabetic on oGTT, only 22% were identified by F BGL testing alone. Further receiver operating curve (ROC) analysis demonstrated that using a cut-off of 92 mg/dL (5.1 mmol/L) for F BGL testing as the threshold for initiating an oGTT detected 90% of the diabetic patients, requiring 53% of the wait listed patients to be tested.

It is interesting to note that not all patients with dysglycemia pre-transplant develop persistent post-transplant dysglycemia (IGF, IGT or NODAT). Caillard *et al*[31] screened 243 patients at time of wait listing with oGTT and found 37 (15.2%) dysglycemic patients and eight (3.3%) newly diagnosed diabetic patients. The time from pre-transplant oGTT to transplantation was not documented; however, 50% of the dysglycemic patients developed NODAT, 23% remained dysglycemic and 14% become normoglycemic post transplantation. In 26% of those diagnosed with NODAT, this abnormality could only be detected by oGTT. A Japanese study in which patients with no known history of diabetes were administered an oGTT two weeks before receipt of a living donor transplant, found that 30.4% were dysglycemic with an additional 4.0% found to be diabetic[32]. Hornum *et al*[33] found 33% dysglycemia rate pre-transplant (n = 57) and over 12-mo follow up the pre-transplant dysglycemia was not associated with the development of NODAT. Interestingly, they too

Table 1 Selection of studies that reported rates of new-onset diabetes after transplantation or other dysglycemic states

Ref.	Criteria	*n*	Rates
Cosio *et al*[3]	Use of medications, F BGL	490	13% at 1 yr 33% dysglycemic
Hjelmesaeth *et al*[4]	Use of medications, F BGL, oGTT	201	20% at 3 mo
Vincenti *et al*[5]	oGTT	682	30% at 6 mo dysglycemic
Delgado *et al*[6]	oGTT, F BGL	374	6.7% at 4.1 yr 25.1% dysglycemic
Ramesh Prasad *et al*[7]	F BGL or R BGL	151	20.5%
Luan *et al*[8]	oGTT	203	11.8% at 10 wk 47.8% dysglycemic
Bayer *et al*[9]	Use of medications, F BGL, R BGL	640	31.4% at 1 yr
Bergrem *et al*[10]	Use of medications, F BGL, R BGL	301	13% at 10 wk
Valderhaug *et al*[11]	oGTT	1410	17% at 10 wk 38% dysglycemic
Ciancio *et al*[12]	Use of medications	150	15%-22% at 4 yr
Israni *et al*[13]	Medications, F BGL	1840	13% at 5 yr
Wauters *et al*[14]	Use of medications, F BGL	1146	14.1% at 1 mo, 11.1% at 4 mo, 13.4% at 1 yr 27%, 34.3% and 29.8% dysglycemic
Chan *et al*[15]	oGTT	292	24% at 6 mo
Vacher-Coponat *et al*[16]	Use of medications	289	16.8%-18.8% at 3 yr
Tillman *et al*[17]	oGTT	200	5% at 39 mo 30.5% dysglycemic
Bonet *et al*[18]	F BGL, R BGL, oGTT	138	13% at 6 mo
Cole *et al*[19]	Use of medications, F BGL, oGTT	49	4% at 6 mo
Nagaraja *et al*[20]	Use of medications, F BGL	118	21% at 3 mo, 37% at 1 yr
First *et al*[21]	Use of medications, F BGL, HbA1c	634	17.8%-36.5% at 1 yr
Nagaraja *et al*[22]	oGTT	76	13% at 5 yr, 24% at 11 yr 42% and 61% dysglycemic
Tokodai *et al*[23]	Use of medications, F BGL, R BGL	145	11.7% at 1 yr
Viecelli *et al*[24]	oGTT	83	17% at 3 mo, 15% at 15 mo 31% and 21% dysglycemic
Weng *et al*[25]	Use of medications, F BGL, R BGL	166	29.5%
Schweer *et al*[26]	R BGL, HbA1c	526	16.7%
Prasad *et al*[27]	oGTT	439	20% at 3 mo 33% dysglycemic
Silva *et al*[28]	HbA1c	638	21.3%-41.1% at 4 yr
Lv *et al*[29]	F BGL	428	20.3% at 5.7 yr

Definitions diabetes: F BGL ⩾ 7.0 mmol/L (126 mg/dL) or ⩾ 11.1 mmol/L (200 mg/dL) on oGTT or R BGL ⩾ 11.1 mmol/L (200 mg/dL) plus symptoms. Other dysglycemic states. IFG: ADA criteria 5.6-6.9 mmol/L (100-125 mg/dL); WHO criteria 6.1-6.9 mmol/dL (100-125 mg/dL); IGT: oGTT 7.8-11.0 mmol/L (140-199 mg/dL). F BGL: Fasting blood glucose level; R BGL: Random blood glucose level; oGTT: 2-h oral glucose tolerance test.

documented a small group of pre-transplant diabetic patients in whom the diabetic state remitted post-transplant.

The case finding described by table two highlights key differences in glucose homeostasis between end stage kidney disease (ESKD) uremic patients and the general population. Approximately 70% of general population patients can be diagnosed as diabetic *via* a F BGL[34], as compared to 22% in the Norwegian transplant wait listed cohort. Moreover, the incidence of new diagnosis of diabetes in wait listed patients on dialysis is approximately 5%-6% per year[33,35] (when using oGTT diagnostic criteria), compared with approximately 0.7%-1.3% per year in the general population[36]. These figures ought to give the reader cause to be cautious with regard to the interpretation of rates of post transplantation dysglycemia and diabetes. This is particularly the case when reviewing retrospective data, in which often only a pre-transplant F BGL is available and the time from glucose testing to transplantation may extend for many months. It may be that the denominator in the quoted rates of NODAT includes patients who were not normoglycemic at time of transplantation. This assessment is further complicated by the possibility that dysglycemia pre-transplant may not be a sufficient factor for dysglycemia post-transplant state (see below).

Further complicating the interpretation of incident rates of dysglycemia post-transplant is the spontaneous remission and normalisation of blood glucose levels observed in some patients. For example, early dysglycemia, such as in the period of hospitalisation post-transplant, is common and occurs in 75%-90% of patients within the first week[37-39]. Luan *et al*[8] in a prospective study of 203 non-diabetic patients showed the mean day 3 F BGL to be 124-134 mg/dL (6.9-7.4 mmol/L). Such dysglycemia should not be dismissed as due entirely to peri-operative factors, as some data suggests that day 7 F BGL may be predictive of NODAT at 1 year[40]. A recent clinical study measured continuous capillary blood glucose levels for the first 4 d post-transplant in 43 patients. There was a considerable

Table 2 The rates of unrecognized dysglycemia in patients on the transplant waiting list

Ref.	Unrecognised on waiting list - diabetes	Unrecognised on waiting list - dysglycemia
Ramesh Prasad *et al*[7]	-	15%
Hornum *et al*[33]	-	33%
Bergrem *et al*[30]	8.1%	45.2%
Iida *et al*[32]	4%	30.4%
Caillard *et al*[31]	3.3%	15.2%
Bonet *et al*[18]	< 0.1%	8.9%

burden on hyperglycemia with 43% having blood glucose above 7.7 mmol/L for more than 12 h per day. The incidence of NODAT at 72 mo was 18.6% and the authors suggested that the day 1 capillary blood glucose may identify those at risk[41]. Moreover, one study found that only 4% of patients normoglycemic early post-transplant later developed NODAT[42] and a normal oGTT within the first week has been shown to have a NPV of 97.6% for later NODAT development[43]. However, it is important to note that not all patients with early hyperglycemia develop permanent dysglycemic states, as there is a considerable degree of transience and variation in dysglycemic states[33]. For example, a Chinese study, employing F BGL for NODAT found an incident rate of 20.32% after a mean follow up of 5.65 years in patients who survived more than one year post transplantation. Of these, 65.5% developed NODAT within 1 year and 17.2% had transient NODAT[29]. Furthermore, such transience likely occurs within the first 3-6 mo. In an international trial comparing standard and reduced dose tacrolimus (Tac) the cumulative incidence at 6 mo of NODAT was 30.3%; however, the incidence in each group was lower at 6 mo compared to 3 mo (23.9% *vs* 28.4% and 13.2% *vs* 15.2%)[15].

Notwithstanding the notable degree of transient dysglycemia, persistent NODAT often develops within 3 to 6 mo following renal transplantation. A mean time to diagnosis of 4.3 mo has been reported[44]. This may help to determine the optimal time of testing. Using oGTT testing at 10 wk post transplantation, Valderhaug *et al*[11,45] reported an incidence of NODAT of 14%-17%. Most studies find that NODAT develops early and this is confirmed by analyses of large data sets. For instance, an analysis of the organ procurement and transplantation network (OPTN) registry data has found a cumulative incidence of NODAT of only 16.2% at 3 years (registry data is limited by the nature of reporting of outcomes), the majority had developed within the first year post transplantation[46]. Similar results have been reported in a United Sates cohort of 640 patients with a mean F BGL of less than 100 mg/dL (5.6 mmol/L) at time of transplantation. NODAT occurred in 31.4% of patients over 1 year, the majority of which had occurred within the first 6 mo (26.4% of total population by 6 mo). By 5 years post transplantation, 46.3% of previously believed to be non-diabetic patients had a diagnosis of NODAT[9].

With regard to any dysglycemia (IGT/IFG or NODAT), a moderate sized (n = 203) prospective study of the risk of developing dysglycemia post transplantation, documented a rate of 47.8% when tested at 10 wk with an oGTT and applying WHO/ADA diagnostic criteria[8]. Retrospective data has found rates of 39.7% who remained normoglycemic throughout the first year post-transplant[47]. A study specifically designed to determine the rates of pre-diabetic dysglycemia found 30.5% of patients met accepted criteria using an oGTT at a median of 39 mo post-transplant[17]. Similarly, in a large international study designed to determine the differences in diabetogenesis of cyclosporin (CsA) and Tac, at 6 mo post-transplant only 300 out of 587 patients (51.1%) remained normoglycemic[5]; however, the criteria for definition of NODAT was need for medications at greater than 30 d. A cross sectional study of multiple Spanish centres found a rate of dysglycemia of 31.8% at almost 4 years post-transplant, the majority detected by oGTT[6]. It is interesting to note that 58.8% of the dysglycemic patients had a simultaneous normal F BGL.

The above discussions reveal notable limitations when quoting rates of post-transplant dysglycemic states or NODAT alone. Whilst there is consensus with regard to blood glucose cut-off values, it is unclear which test should be employed and at which time post-transplant. Furthermore, the witnessed remission of some pre-transplant dysglycemia to normoglycemia post-transplant[19,37] (although this has not been commonly documented), further complicates analyses of rates of new-onset post-transplant dysglycemia.

RISK FACTORS

Multiple risk factors have been associated with the development of NODAT (Table 3) many of which are not modifiable. The most consistently found risk factor is advancing age appreciated since the recognition of NODAT in the early period of use of CsA[79] Increasing age has been found to be a risk factor in small and large retrospectively analysed and prospectively collected data sets, including registry datasets in which the prevalence of NODAT may have been underestimated[8,13,17,26,46,49,52-54]. Male gender, family history of diabetes and APCKD are documented as risk factors, but not consistently[46,49,54-57,61,62]. With regard to genetic risk multiple polymorphisms, including mitochondrial, have been described as contributing risk to the development of NODAT[53,54,63-67]. A closer analysis of genetic polymorphisms and their associated risk is beyond the scope of this review.

Transplant related factors: Calcineurin inhibitors

Potentially modifiable risk factors can be divided into transplant specific and generic. Of the generic, increasing body mass index (BMI) is associated with increased incidence of NODAT when categorised into intervals of 5 with < 20 as a reference, with increased

Table 3 Modifiable and non-modifiable risk factors associated with new-onset diabetes after transplantation or dysglycemic state

Variable	Ref.	Comment
ATG-divided dose	Stevens *et al*[48]	Increased dysglycemia compared to single dose in patients treated with Tac and sirolimus
African American	Kasiske *et al*[49]	OR = 1.68
	Shah *et al*[50]	RR = 1.38
	Johnston *et al*[51]	HR = 1.56
	Bayer *et al*[9]	HR = 1.35
Age	Kasiske *et al*[49]	Strong independent risk factor RR: 1.9-2.6
	Cole *et al*[52]	27707 registry patients OR: 1.33 If > 60 yr
	Ghisdal *et al*[53]	OR 1.03 of NODAT for each 6 mo of age
	Luan *et al*[8]	Increasing age associated with dysglycemia and new onset metabolic syndrome
	Luan *et al*[46]	Analysis of 25837 registry patients, increase in NODAT in each categorised group compared to reference 18-34 years old
	Israni *et al*[13]	HR: 1.33 of NODAT at 60 mo
	Tillmann *et al*[17]	Increase in dysglycemia at mean of 56 M post-transplant; RR of 1.28 for each 5 yr
	Mccaughan *et al*[54]	OR 1.4 per decade in 427 Northern Irish patients
	Schweer *et al*[26]	NODAT 56.1 yr *vs* 47.9 yr; $P < 0.01$
APCKD	de Mattos *et al*[55]	Increased 1 yr incidence in a matched cohort
	Hamer *et al*[56]	Multivariate analysis OR 2.4
	Johnston *et al*[51]	No increase found in 21564 USRDS patients
	Luan *et al*[46]	Multivariate analysis OR: 1.17
	Ruderman *et al*[57]	No increased risk found
Basiliximab	Aasebø *et al*[58]	Basilixmab (n = 134) *vs* no induction historical control; increased dysglycemic state $P = 0.017$
	Prasad *et al*[27]	In living recipients who elected to receive basiliximab OR 2.34 for NODAT at 3 mo
BMI	Kasiske *et al*[49]	Increased BMI, NODAT RR: 1.7
	Cole *et al*[52]	Multivariate analysis OR 1.76 for NODAT
	Luan *et al*[46]	Analysis of 25837 registry patients. increase in NODAT in each categorised group of BMI compared to reference < 20
	Israni *et al*[13]	BMI ⩾ 30, HR 1.69 for NODAT at 60 mo
CMV	Hjelmesaeth *et al*[59]	Asymptomatic infection OR: 4.0 for NODAT at 10 wk
CNI –	Chan *et al*[15]	NODAT 17% *vs* 31%, low dose *vs* standard dose Tac
Higher levels	Cole *et al*[19]	Single arm study of 49 patients with a 4% 6 mo incidence of NODAT. Early glucocorticoid reduction and low dose CsA
	Suszynski *et al*[60]	Higher Tac levels (plus sirolimus) compared to lower Tac (plus sirolimus) or CsA/MMF higher rates of NODAT with 10 yr FU
CNI –	Vincenti *et al*[5]	RCT. Dysglycemia at 6 mo higher in Tac/MMF *vs* CsA/MMF: $P = 0.05$
Tac *vs* CsA	Cole *et al*[52]	27707 registry patients OR 1.51 for NODAT
	Luan *et al*[46]	Analysis of 25837 registry patients. Increase in NODAT OR: 1.24
	Vacher-Coponat *et al*[16]	No difference in CsA/Aza *vs* Tac/MMF in RCT (n = 289)
	Cotovio *et al*[44]	Retrospective multivariate analysis higher Tac not CsA levels associated with NODAT
Family history of diabetes	Bora *et al*[61]	Recipients from living related donors
	Santos *et al*[62]	Retrospective (n = 303). RR: 3.6 for NODAT
Gender	Kasiske *et al*[49]	Greater risk in males in registry patients
	McCaughan *et al*[54]	OR 2.2 for male gender in 427 Northern Irish patients
Genetic polymorphisms	Ghisdal *et al*[53]	rs7903146 polymorphism of TCF7L2 OR 1.6 of NODAT at 6 mol/L, but not associated with IGT
	Ghisdal *et al*[63]	Summarises known associations
	Kurzawski *et al*[64]	Polish Caucasian patients. Increasing SNPs associated with increased risk, OR = 1.37
	Yao *et al*[65]	Fok1 vitamin D polymorphism associated with NODAT OR 11.8 $P = 0.012$
	McCaughan *et al*[54]	7 SNPs involved with β-cell apoptosis associated with NODAT
	Nicoletto *et al*[66]	Adiponectin gene polymorphism associated with NODAT
	Tavira *et al*[67]	Mitochondrial haplogroup H associated with NODAT in Tac treated patients
Glucocorticoids	Boots *et al*[68]	Early glucocorticoid withdrawal associated with reduced NODAT incidence in the first year
	Ghisdal *et al*[53]	OR 2.78 of NODAT at 6 mol/L if AR treated with glucocorticoids
	Luan *et al*[46]	Analysis of 25837 registry patients. OR 1.42 for NODAT if discharged on maintenance. Glucocorticoid only induction associated with increase in NODAT OR: 1.31
	Rizzari *et al*[69]	Significant reduction in NODAT compared with historical control when glucocorticoids rapidly tapered
	Cole *et al*[19]	Single arm study of 49 patients with a 4% 6 mo incidence of NODAT. Early glucocorticoid reduction and low dose CsA
	Schweer *et al*[26]	Pulse glucocorticoid for BPAR associated with increasing NODAT incidence
HCV +	Kasiske *et al*[49]	HCV+, NODAT RR: 1.3
	Cole *et al*[52]	27707 registry patients OR for NODAT 1.82
	Johnston *et al*[51]	21564 USRDS registry patients, HR: 1.7 for NODAT
	Baid-Agrawal *et al*[70]	14 HCV+ 24 HCV- patients. HCV+ increased insulin resistance; $P = 0.008$
	Luan *et al*[46]	Analysis of 25837 registry patients. Increase in NODAT OR: 1.43
	Lv *et al*[29]	Cohort of 428 Chinese patients. NODAT associated with HCV at mean 5.6 yr follow up, OR = 2.72
	Prasad *et al*[27]	439 Indian patients, OR = 6.37

Hyper-parathyroidism post transplant	Ivarsson *et al*[71]	PTH > 13.8 pmol/L associated with NODAT at 1 yr, OR = 4.25
Impaired glycemic state pre-transplant	Ramesh Prasad *et al*[7]	Higher within the normal range random BSL associated with NODAT
	Bora *et al*[61]	IGT at time of transplant associated with NODAT
	Hornum *et al*[33]	IGT NOT predictive of NODAT
	Cotovio *et al*[44]	Higher fasting BGL associated with NODAT
Magnesium post-transplant	Garg *et al*[72]	1 mol/L lower Mg associated with dysglycemia; no association with 1M CNI trough level
Magnesium pre-transplant	Augusto *et al*[73]	Lower magnesium immediately pre-transplant associated with NODAT; $P < 0.02$
Metabolic syndrome post-transplant	Israni *et al*[13]	MS in first 6-12 mo associated with NODAT by 60 mo, HR = 3.46
	Luan *et al*[8]	10 W dysglycemia associated with MS
	Nagaraja *et al*[22]	Development of MS predicts progressive dysglycemia
Metabolic syndrome pre-transplant	Bayer *et al*[9]	HR: 1.34 for NODAT at 1 yr
Sirolimus	Teutonico *et al*[74]	No improvement when changing from CNI to sirolimus
	Ekberg *et al*[75]	Low dose sirolimus may confer less risk than low dose Tac
	Johnston *et al*[51]	20124 registry patients. Compared to CsA + MMF/AZA: Sirolimus + CsA HR 1.61; Sirolimus + Tac HR 1.66; Sirolimus + MMF/AZA HR 1.36
	Guerra *et al*[76]	RCT (n = 150) Tac/sirolimus *vs* Tac/MMF *vs* CsA/sirolimus. No difference in NODAT
	Gyurus *et al*[77]	Retrospective (n = 514). Sirolimus HR 3.5 for NODAT over 10 yr
	Veroux *et al*[78]	21 NODAT converted to sirolimus, 80% remission of NODAT on basis of F BGL
	Suszynski *et al*[60]	Increased risk with high dose Tac/low dose sirolimus combination

F BGL: Fasting blood glucose level; oGTT: 2-h oral glucose tolerance test; NODAT: New-onset diabetes after transplantation; ATG: Antithymocyte globulin; USRDS: United States Renal Data System; BMI: Body mass index; CMV: Cytomegalovirus; CNI: Calcineurin inhibitors; Tac: Tacrolimus; MMF: Mycophenolate mofetil.

risk in the higher categories of BMI[47]. The most significant transplant specific modifiable risk factors are immunosuppressive medications specifically the use of calcineurin inhibitors (CNI - Tac and CsA) and glucocorticoids. The diabetogenic impact of CsA has been described since the early 1980s[79-82]. The introduction of Tac into clinical practice was associated with less acute rejection and improved graft function but at the expense of a greater incidence of NODAT[83]. The diabetes incidence after renal transplantation trial was first large randomised study (n = 682; not diabetic at baseline n = 567) designed primarily to investigate the increase risk posed by Tac use instead of CsA. The primary endpoint was a 6-mo composite endpoint of dysglycemia (NODAT or IFG) based on oGTT administered at 90 and 180 d. They found 6-mo cumulative incidence of 33.6% in Tac treated patients and 26% in CsA treated patients (P = 0.046). Furthermore, more patients required hypoglycemic treatment in the Tac treated group (P = 0.005) and more patients in the CsA treated group who were not treated with hypoglycemic agents had an improvement in their glycemic state by 6 mo (P = 0.067)[5]. This, however, was in the era of high trough Tac targets of approximately 10-15 in the first 3 mo.

Noting that over time target drug levels have decreased, the use of therapeutic drug monitoring may assist in the management of prevention of rejection and complications of immunosuppression. There is some evidence that dysglycemic states are related the degree of CNI exposure. For example, Chan *et al*[15] randomised 292 patients to low dose Tac (trough level 5-9 for first 3 mo then trough level 3-6 following 3 mo) or standard dose (trough level 10-15 for first 3 mo then trough level 8-12 following 3 mo). All patients received basiliximab, similar doses of MMF and glucocorticoids over the follow up period of 6 mo. Those in the low dose Tac group had significantly less NODAT incidence over 6 mo of follow up, with a tendency towards lower incidence rate of treated diabetes[15]. Similarly the dose response effect with respect to NODAT risk has also been described with the use of CsA with less dysglycemia post-transplant in those treated with low dose CsA (C2 600-800)[19]. Sub-analyses of data from larger trials, such as Efficacy Limiting Toxicity Elimination-SYMPHONY, have also suggested a dose-dependent relationship. SYMPHONY found significantly higher rates of NODAT in the low-dose Tac group, compared with low-dose CsA, low-dose sirolimus or standard dose CsA without induction agent (P = 0.02)[75]. Given the issues with choice of diagnostic test it is not surprising that when analysed according to F BGL there were no significant differences between the groups[84].

As age is commonly identified as a risk factor in univariate analysis, it is important to know if older age interacts with other risk factors. In a multivariate analysis of OPTN data there is a clear increase in risk with increasing age when grouped into age groups using 18-34 years old as a reference group[46]. Amongst the other identified risk factors use of Tac increased risk of NODAT. An analysis of the OPTN registry data compared rates of acute rejection and rates of NODAT and their impacts of graft survival. The rates of acute rejection were less in the older Tac treated patients, but the rates of NODAT were greater in the same older Tac treated group[51]. The authors comment that targeted and individualised use of immunosuppression based on the patient's risk profile may help to ameliorate worse outcomes. Part of this may be to reconsider the use of CNI, in particular Tac, in the older recipient in whom the

development of NODAT may precipitate morbidity and mortality. However, as outlined below, other strategies may be safer and more effective.

Transplant related factors: Glucocorticoids

Oral glucocorticoids form the backbone of many immunosuppressive regimens and the diabetogenic potential of these agents is well documented. The development of diabetes is related to the cumulative exposure to glucocorticoids. The data available on glucocorticoid withdrawal, glucocorticoid free or rapid glucocorticoid tapering suggests an incidence rate of 1%-22% over a 1-5 year follow-up period[12,19,26,46,60,69,85] which compares with rates of 15%-35% in regimens without glucocorticoid maintenance (Table 1). However, not all analyses find a benefit in glucocorticoids avoidance. For example, a meta-analysis of higher quality trials in which patients had glucocorticoid withdrawn within 14 d post-transplant and were treated with CNI/MMF did not find a reduction in NODAT[86]. However, the largest randomised placebo-controlled trial (n = 386) of early glucocorticoid withdrawal within 7 d of transplantation found no difference in the rate of NODAT, although fewer of the NODAT patients required insulin therapy in the early glucocorticoid withdrawal arm[83]. Furthermore, a matched cohort analysis of glucocorticoid free and maintenance therapy with glucocorticoid (n = 190 in each group) there were no differences in renal specific outcomes or any differences between F BGL or use of hypoglycemic agents. It is noteworthy that there was significantly more use of Tac and basixilimab in the glucocorticoid free group[85]. Nonetheless, many other studies do find an advantage to glucocorticoid avoidance. Analysis of United States Renal Data System (USRDS) data found that patients discharged on a glucocorticoid containing regimen had an OR of 1.42 for NODAT compared to those discharged on a glucocorticoid free regimen[46]. These results must be interpreted with caution, as it is not possible to capture the cumulative glucocorticoid exposure in the USRDS database. One small (n = 62) randomised prospective study in which glucocorticoids were ceased in one group by day 10 found a significant decrease in the incidence of NODAT when defined as used of hypoglycemic agents[68]. A more recent pilot study (n = 48) of thymoglobulin induction, MMF, low dose CsA and rapid glucocorticoid reduction in low immunological risk patients found that this protocol resulted in 42 of 48 patients being normoglycemic at 6 mo[19]. A larger single centre population (n = 1291) retrospectively analysed in which NODAT was defined as need for hypoglycemic agents found an incidence rate of only 2%-4% in the first year post transplantation in patients treated with glucocorticoid withdrawal after day 5 post-operative in combination with thymoglobulin induction, CNI plus sirolimus or MMF[69]. This was a significant improvement compared to a non-matched historical control group who received a glucocorticoid containing maintenance regimen. Despite the theoretical benefits of glucocorticoid withdrawal the studies referenced above demonstrate conflicting results[87]. The impact of glucocorticoid exposure of the development of NODAT may be answered by a current trial in which patients of low immunological risk will be randomised to one arm including thymoglobulin induction and glucocorticoid free CNI/MMF maintenance or basixilimab induction and ongoing glucocorticoid exposure[88].

The development of dysglycemia subsequent to the diagnosis and treatment of acute rejection may also disclose the risk of dysglycemia created by glucocorticoid exposure. A single centre review of 526 transplant recipients had a NODAT incidence of 16.7% when defined using ADA/WHO criteria for assessing random blood glucose or HbA1c. They found that there was a greater incidence of acute rejection in patients who developed NODAT and that intensified treatment with glucocorticoid and possible conversion to Tac was associated with increased risk of NODAT on multivariate analysis. However, the analysis did not treat rejection as a time varying co-variate[26].

Transplant related factors: Sirolimus

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, is an immunosuppressive agent used in conjunction with, or instead of, calcineurin inhibitors. Clinical data suggests that sirolimus use is not without risk for the development of NODAT[77]. Analysis of USRDS of 2598 patients recorded as having received sirolimus, found that the combination of sirolimus with a CNI created a higher HR for cumulative 1yr incidence of NODAT compared to CNI with mycophenolate/azathioprine (MMF/AZA) or sirolimus with MMF/AZA. A sub-group multivariate analysis of USRDS data of 16861 patients known to have remained on the same immunosuppressant regimen patients treated with the combination of sirolimus and a CNI remained at increased risk of 1 year NODAT[51]. In one study of non-NODAT renal transplant recipients who were switched from CNI to sirolimus there were no improvements noted in the glycemic state of the patients when studied robustly with oGTT. Indeed higher sirolimus levels in the absence of CNI may have increased the risk of NODAT[74].

However, just as with the data on CNI and glucocorticoids there are inconsistent findings in the literature on sirolimus. A recent large (n = 440) prospectively randomised trial found that higher dose Tac, but not high or standard dose sirolimus contributed to the NODAT[60]. A further example is a recent study of patients randomised to tacrolimus/mycophenolate, TAC/sirolimus or CsA/sirolimus. The median follow up was 8 years and the quoted cumulative incidence of NODAT was 19%-32%, with no significant differences between the groups based on the use of hypoglycemic agents[76]. Lastly, as with CNI, it is likely that there is an important interaction between modifiable and non-modifiable risk factors. For example, a multivariate

analysis has found that older age and higher sirolimus trough levels were associated with increased hazard for NODAT[77], once again suggesting that drug level targets in older recipients could be reviewed, for both effect and toxicity.

Transplant related factors: Other medications

Calcineurin inhibitors and glucocorticoids are the most well studied drugs in terms of impact upon glycemic control. There is no data on the contribution of MMF or AZA to the development of dysglycemia. In the transplant literature, there does not appear to be a signal that these drugs may be implicated. Recently, there has been interest in the possibility that basiliximab, a widely used induction agent particularly in the lower immunological risk patients, may be implicated in contributing to dysglycemia; although this is based on two data sets, neither of which were prospective or randomized[27,58]. There is also little data on the contribution of thymoglobulin to the development of NODAT. A study of single dose *vs* divided dose antithymocyte globulin (ATG) induction analysed dysglycemia as a secondary outcome. In this study, fasting blood sugar levels after 1 mo to 6 mo were significantly lower (P = 0.02) in patients who received single dose ATG induction[48].

PATHOGENESIS

The pathogenesis of dysglycemia post transplantation is complex and is widely assumed to be closely aligned to the pathogenesis of type 2 diabetes mellitus. However, this assumption underestimates that the impact of end stage renal failure and dialysis on glucose homeostasis. There is also little known about the histological changes in the graft over time when exposed to persistent NODAT. Small case series have found *de novo* diabetic nephropathy within 5-10 years of diagnosis of NODAT[89,90].

Changes in both insulin resistance and insulin secretion can be shown to underlie the development of the dysglycemia post transplantation. These changes are however dynamic and sometimes transient, particularly in the early post-transplant period. Lastly, the role of changes in incretin hormones remains to be elucidated, as does the impact of the severity of chronic kidney disease (CKD) pre- and post-transplant on insulin metabolism and resistance.

Pre-transplant factors

The dynamic nature of dysglycemic states has been documented by Hornum *et al*[33]. They followed 57 patients from pre- to 12 mo post-transplant. Importantly, none were diabetic on an oGTT pre-transplant, however only 67% were normoglycemic. At 3 mo only 46% were normoglycemic and this increased to 56% by 12 mo. Pre-transplant, patients were compared with uremic controls. The transplanted patients were significantly younger (39 *vs* 47 years old) with shorter period of time on dialysis (24 mo *vs* 45 mo); however, they did not differ in terms of measure of glycemic state. These measures included F BGL, oGTT and then specific validated measures of insulin resistance and secretion. It is noteworthy that both the uremic controls and transplant patients had a worse glycemic state than a small group of healthy controls - despite normal F BGL [5.1 mmol/L (all ESKD) *vs* 5.0 mmol/L]. The normal F BGL would suggest that hepatic gluconeogenesis was not impaired by the ESKD state; however, the ESKD patients had oGTT results of 7.4-7.5mmol/L (*vs* 5.4 mmol/L) and this seemed to be accounted for by increased peripheral insulin resistance. Interestingly, the increased resistance in ESKD patients was matched by increased insulin secretion compared to healthy controls (although not statistically significant). This may have been expected for two reasons. Firstly, ESKD patients will have reduced renal clearance of insulin[91]. Secondly, as insulin resistance and insulin secretion are described as being related in a hyperbolic fashion[92], such that changes in one parameter would be expected to drive compensator changes in the other parameter. Whilst there is evidence in these cohorts of compensatory increase in insulin secretion, it can be postulated that it was insufficient as the ESKD patients had markedly higher oGTT results and 33% were found to have IGT. At 12 mo, 14% of patients had developed NODAT and this was associated with increased insulin resistance and increased insulin secretion, which nonetheless, appeared not to be sufficient to maintain normoglycemia. The development of NODAT was not associated with pre-transplant IGT. However, those who developed dysglycemia tended to be older and have a higher pre-transplant BMI, which may co-vary (although not significant in multivariate analysis) with the noted increased pre-transplant insulin resistance and, again, higher compensatory pre-transplant insulin secretion.

Insulin resistance

Increasingly, understanding the factors responsible for insulin resistance and decreasing insulin secretion is being recognised as important for determining modifiable and treatable causes of NODAT. An increase in insulin resistance would be consistent with exposure to glucocorticoids. Glucocorticoids are believed to impair peripheral glucose uptake, impair hepatic glycogen synthesis and enhance gluconeogenesis. At higher doses they may induce β-cell apoptosis[93]. Furthermore, it has been proposed the diabetogenic risk is not restricted to higher dose of glucocorticoid but also occurs with chronic exposure to low doses[94]. In addition to duration and dose of glucocorticoid, older age and higher BMI also predispose to the development of diabetes in those receiving glucocorticoid treatment[95]. Perhaps it is less well recognised that CKD and uremia may also contribute to insulin resistance. It may be that the relief from uremia, but the nonetheless persistent state of CKD post-transplant contributes to the dynamic nature of post-

transplant dysglycemia. It may also be that whilst clearly the biological stress of transplantation and exposure to diabetogenic medications is crucial in the pathogenesis, the persistence of CKD in certain older and perhaps genetically predisposed patients forms a background milieu upon which the dysglycemia can develop. There has been renewed interest in the contribution of uremia or CKD to insulin resistance and the various mechanisms are beyond the scope of this article. However, when reading literature on post-transplant dysglycemia it is important to remember that transplant patients have had periods of severe CKD/ESKD requiring dialysis and, for the most part, remain a CKD patient[96,97]. One study of 27 diabetic and 35 non-diabetic EKSD patients using a homeostatic model assessment-insulin resistance model to assess insulin resistance found increased insulin resistance in the diabetic patients. The non-diabetic patients with increased insulin resistance had elevated C-peptide levels, indicating a compensatory response maintaining non-diabetic state[98].

Other factors that may increase insulin resistance post-transplant include hepatitis C virus (HCV) and metabolic syndrome. Two studies have found that HCV-positive patients have increased insulin resistance compared to non-HCV transplant patients. One of these studies found a compensatory increase in insulin secretion[99] and one did not find such compensation[70]. On the other hand, CMV, the other recognised diabetogenic virus, seems to be associated with impaired insulin secretion; although, the exact mechanism is not well studied[59]. Whilst metabolic syndrome has been described in the general population to be associated with insulin resistance, there is a paucity of data considering metabolic syndrome and insulin resistance in transplant recipients. A recent retrospective review of 76 patients with a mean 11.1 years post-transplant follow up found that even when adjusted for age, the presence of metabolic syndrome was associated with increased risk progression of dysglycemia[22]. In a larger cohort of patients (n = 640), the presence of metabolic syndrome pre-transplant remained a significant risk factor for developing NODAT even when adjusted for age[9]; however, there is no data available on insulin resistance in any significant cohort of transplant recipients who develop metabolic syndrome and NODAT.

Insulin secretion

It seems likely that as modifiable risk factors are altered, importantly including immunosuppressive agents, that the weights of forcing factors of NODAT will also be altered. As such, studies that repeatedly measure insulin indices throughout the post-transplant period, in particular in the higher risk first year post-transplant, are particularly valuable. Nagaraja *et al*[22] has recently described insulin indices pre- and 3 and 12 mo post-transplant in non-diabetic patients (n = 118) as defined by F BGL less than 7.0 mmol/L pre-transplant. The patients defined as NODAT had increased insulin resistance at 3 and 12 mo, although less resistance at 12 mo when compared to 3 mo. By 12 mo, insulin secretion had fallen in patients with NODAT; however, despite the fall in insulin resistance the levels of secretion failed to be compensatory, suggesting that even in the face of falling doses of glucocorticoid and improving peripheral insulin sensitivity, impaired insulin secretion increasingly threatens normoglycemia[20,100]. This data is supported by previous studies in which oGTT was used for diagnosis[101,102]. Nam *et al*[102] first demonstrated impairment in insulin secretion as a necessary component in the pathogenesis. They followed 144 patients pre- and post-transplant and noted that higher, although normal, oGTT results pre-transplant were associated with increased risk of dysglycemia post-transplant. They also noted that those who developed post-transplant dysglycemia 9-12 mo post-transplant had significantly lower insulin secretion in the face of improved insulin resistance. A long term study found similar results when using oGTT at 10 wk and 6 years post-transplant. Patients who were dysglycemic at 10 wk and became normoglycemic had improvement in insulin resistance and a non-significant impairment of insulin secretion, thus retaining a compensatory response. On the other hand, those who remained diabetic or became diabetic over the follow-up period had a non-significant deterioration in insulin resistance and a significant fall in insulin secretion[103].

The mechanism of impairment in insulin secretion post-transplant is thought to be related to CNI use. The mechanism of action is believed to be the impairment of pancreatic cell function due to the binding of CNI to calcineurin. Calcineurin is a systolic phosphatase that has two targets in the β-cell: the nuclear factor of activated T cells and cyclic-AMP-responsive element-binding protein transcriptional co-activator. In mice models, normal β-cell function has been shown to be dependent upon calcineurin[104]. Calcineurin may be important for the proper response to hyperglycemia and incretin activation. Human islet cells when treated with Tac increased β-cell apoptosis, possibly mediated by the above calcineurin targets and ameliorated by the administration of incretin analogues[105,106].

Incretins

Finally, there is no data on the impact of immunosuppression in renal transplant patients on incretin hormones. It is interesting to note that in healthy volunteers the administration of glucocorticoids in the setting of being sedentary and on a high calorie diet (not unlike the initial period of time post-transplant) have impaired responses to incretin hormones[107]. In dialysis dependent patients, those with IGT have been shown to have a reduced incretin effect[108], and even normoglycemic dialysis dependent patients have reduced insulin secretion with increased incretin secretion suggesting that uremia or CKD impacts upon the proper β-cell stimulation and response[109]. However,

Table 4 Risk of mortality, cardiovascular events and graft loss associated with new-onset diabetes after transplantation or dysglycemic state

	Mortality	CV event/death	Graft loss	Ref.
Diabetes at	3 mo: 37% at 8 yr (HR = 2.1)	20% (death) at 8 yr (HR = 3.5)		Hjelmesaeth *et al*[4]
	10 wk: 34% at 6.7 yr (HR = 2.0)			Valderhaug *et al*[11]
	1 yr: 44% at 11 yr (HR = 2.2)	Death HR: 2.72		Nagaraja *et al*[20]
Dysglycemia at	10 wk: 29% at 6.7 yr (HR = 1.78) each 1 mmol/L oGTT: 5% risk increase	Events increased with increased F BGL		Cosio *et al*[3]
	4 mo: 0.5 mmol/L increase F BGL: 4% risk increase	1 mmol/L oGTT: 6% risk increase in death		Valderhaug *et al*[11]
	12 mo: 0.5 mmol/L increase F BGL: 15% risk increase	12 mo: 0.5 mmol/L increase F BGL: 11% risk increase for event		Wauters *et al*[14]
			3 mo: RR 3.6 at 6 yr	Wojtusciszyn *et al*[41]

F BGL: Fasting blood glucose level; oGTT: 2-h oral glucose tolerance test.

the dynamics of incretin hormones are yet to be described in the post-transplant setting.

OUTCOMES

There is an urgent need to develop a consensus on the best test to detect and how to manage dysglycemic states post-transplant, as there is a direct correlation with the presence of dysglycemic states and mortality predominantly from cardiovascular causes (Table 4)[3,4,11,14,20]. An analysis of the USRDS database in which NODAT was defined according to Medicare claims analysed 27707 patients with data available greater than 1 year and not diabetic pre-transplant. Death censored graft loss was more likely in those who suffered acute rejection when compared to those who developed NODAT. Conversely, those who developed NODAT had a higher hazard ratio of death with a functioning graft compared to those with episodes of acute rejection (1.41 and 1.15 respectively) compared to patients with neither exposure[51]. Analysis of earlier data from the same database found the development of NODAT associated with increased risk for acute myocardial infarction after a minimum 3 year follow up[110]. Similarly, in an analysis on the International Collaborative Transplant Study database (n = 39251) with up to 10 years of follow up, Cox regression analysis of death with a functioning graft due to cardiovascular disease revealed an increased risk for NODAT (HR = 1.6, $P < 0.001$), which was greater than episodes of rejection within the first year (HR = 1.2, $P = 0.036$) but not as great as the risk associated with pre-transplant diabetes (HR = 2.5, $P < 0.001$)[111].

The above datasets are large and their analyses robust, but what is needed are large prospective datasets with well-defined populations and sufficient duration of follow up. Smaller studies have found significant risk for mortality from the development of NODAT, but these findings have disappeared when adjusted for confounding factors. In one such study, major cardiac events occurred in 20% of persistent NODAT patients compared to 7% without NODAT and 21% with pre-transplant diabetes over a 8 year follow up[4]. The outcomes of the largest prospectively followed well defined population was described by Valderhaug *et al*[112]. They followed 1410 patients for a mean of 6.7 years, of whom 55% were dysglycemic at 10 wk post-transplant of which 17% had NODAT. They reported a significant increase in the incidence of all cause mortality between the normoglycemic and dysglycemic groups, the rates being highest in those with NODAT. After adjusting for confounding traditional and transplant associated variables, the HR for all cause mortality was 1.54 was NODAT and 1.39 for IGT ($P < 0.05$). When analysed treating glucose as a continuous variable: on adjusted analysis, for every 1 mmol/L (18 mg/dL) increase in oGTT result there was a 5% increase risk in all cause mortality ($P < 0.05$). The main cause of death was cardiovascular disease, and those with NODAT by 10 wk were at significant increased risk on adjusted analysis (HR = 1.8 $P < 0.05$). For every 1mmol/L (18 mg/dL) increase in the oGTT result there was significant 6% increase risk in cardiovascular death ($P < 0.05$). Despite the findings of the continuous glucose analysis, other dysglycemic states were not associated with cardiovascular death. Further analysis of the same cohort found a graft failure rate of 28%, 60% of which was due to death. There was no association with death censored graft loss, but for every 1 mmol/L (18 mg/dL) increase in oGTT result there was a 3% increase risk in overall graft failure[110]. This suggests similar conclusions as the large registry analyses described above: NODAT may not be associated with increased graft loss, but is associated with increased mortality.

In another large single centre prospectively followed group an increase in risk of all cause mortality and cardiovascular death according to the presence of NODAT at 1 year post-transplant was reported[14]. The 12-mo rate of dysglycemia was 29.8% and NODAT 13.4%. Continuous analysis of the glucose levels revealed that for every 10 mg/dL (0.56 mmol/L) increase in F BGL there was an increase in all cause mortality censored at graft failure over a follow up period of 90.4 mo. At 12 mo, patients with IFG had a HR of 1.7 ($P = 0.009$) and those with NODAT a HR of 3.5 ($P < 0.0001$). Of note, in this study the patients on treatment for NODAT did not have a reduced mortality risk compared to the NODAT

patients not on treatment. Given the retrospective nature of the analysis it is not possible to conclude that treatment does not affect outcomes. However, such findings indicate the importance of well-defined prospectively followed transplant population analyses and potentially the need to identify early those patients at risk of dysglycemia so that directed interventions (be they aggressive glucose or metabolic risk factor control) may ameliorate the increased risk of mortality. Furthermore, such data highlights that in the transplant population clinicians do not have targets of glycemic control that can be achieved with treatment and are associated with improved outcomes. Even in the general population there is conflicting data concerning improved macrovascular outcomes achieved by treating to more intensive targets[113,114]; however, in the transplant population, it remains unknown if meeting these same targets may improve outcomes.

SCREENING AND DIAGNOSIS

Use of oGTT remains the gold standard for diagnosis of NODAT or dysglycemia. This test, however, is not an easily completed screening test. Simple office or laboratory based tests that may be used to adequately screen for NODAT, particularly in high risk patients, include F BGL, 4 pm capillary blood glucose or HbA1c. All of these parameters have limitations. For example, a Spanish study of 374 non-diabetic pre-transplant patients found that normal F BGL in 59% of patients with an abnormal oGTT over the first 12 mo post-transplant[6]. It is well known that changes in red cell viability, need for (due to for example, drug induced bone marrow suppression) and use of erythropoeitin stimulating agents, administration of red cell transfusions and changes in hemoglobin will impact upon HbA1c levels. Notwithstanding this issue more readily encountered in ESKD, some small studies (n = 71) have shown concordance between oGTT and an HbA1c cut-off of 6.2% for the diagnosis of NODAT[115]. It would be clinically more likely to find concordance between these tests after 2-3 mo post-transplant once there has been renal function recovery and the impact of uremia on erythropoiesis has resolved. However, analysis of a much larger cohort (n = 1571) found that using if HbA1c was used as a screening tool and oGTT as the gold standard test, then the cut-off should be 5.8%[44]. More recently, when using a combined test of HbA1c $\geqslant$ 6.5% and F BGL $\geqslant$ 7.0 a Norwegian group (n = 1619) have demonstrated a negative predictive value (NPV) of 97.4% for NODAT, using oGTT as gold standard test at 10 wk post transplantation[116]. Notably, the combination of the two tests had very little additive value (NPV F BGL alone 94.2%) and the lower the HbA1c cut-off value made little difference in exclusion of NODAT (*e.g.,* $\geqslant$ 5.5% NPV 97.5 compared with $\geqslant$ 6.5% NPV 93%). However, the positive predictive value of HbA1c $\geqslant$ 6.5% or 6.2% or in combination with F BGL $\geqslant$ 7.0 mmol/L was poor (53.4%, 42.1%, 69.4% and 50.9%, respectively). Thus, while HbA1c may be of use in screening for NODAT, current evidence does not support its use as a diagnostic test in transplant patients.

Determining the best test to use in transplant patients is complicated by the need to certain of the best time to administer the test. It has recently been shown that glucocorticoid administration in the morning leads to increased afternoon or evening blood glucose levels, at approximately 7-8 h after administration of glucocorticoid. Thus, reliance on F BGL may underestimate the incidence of dysglycemia. In fact, at six weeks post transplantation a 4 pm capillary blood glucose significantly outperformed oGTT, F BGL and HbA1c in detecting NODAT. Combining the tests done at 3 and 12 mo, the cumulative incidence of NODAT with oGTT was 14% and IGT 28%. Interestingly, using an HbA1c range of $\geqslant$ 5.7 and < 6.5 to detect IGT detected an incidence of 51%; but HbA1c did not perform as well as oGTT in detecting NODAT. Hence, the authors suggested using HbA1c as a screening test from 3 mo and using oGTT to determine the presence or absence of NODAT in patients detected to have dysglycemia by HbA1c. This strategy would avoid oGTT in 49% of patients and achieve a sensitivity of 94%[117]. As yet, this data and strategy has not been replicated. Furthermore, the results of these studies suggest that the cut-offs that have been applied in the general population may not apply in CKD, ESKD or post-transplant patients. The question of the cut-off levels for any of the possible tests will only be settled by long-term large prospectively collected data sets which permit determination of the risk for poorer clinical outcomes associated with different cut-off points. Some of this data has already been described, but it is worth emphasising that only oGTT results have been shown to be associated with poorer outcomes when analysed categorically (as distinct from continuous data) and not F BGL[11].

PREDICTING NODAT

If it is difficult to develop easy to administer diagnostic tests, it is even more challenging to develop to models that may predict the development of NODAT, based either on pre- or post- transplant data. There are very few studies able to draw conclusions about predicting NODAT using pre-transplant data. Post-transplant dysglycemia is dynamic phenomenon and there are multiple physiological changes post-transplant that may impact upon insulin and glucose handling. This is emphasised by the remarked upon cases of diabetic or dysglycemic pre-transplant patients resolving their dysglycemic state post-transplant. Hence, the pre-transplant prediction of those increasingly likely to have NODAT post-transplant is fraught with multiple difficult variables that need to be taken into account.

A range of pre-transplant variables has been described as predictors of NODAT. These include age, BMI, fasting and R BGL and metabolic syndrome. For example, one study of 139 non-diabetic patients

pre-transplant found that higher (albeit normal) pre-transplant R BGL were predictive (P = 0.011) of NODAT, although this data has not been replicated[7]. A matched cohort retrospective analysis of 47 patients who developed NODAT found that a higher, albeit normal range, F BGL was associated with the development of NODAT on multivariate analysis[44].

One reasonable sized study (n = 640) with a NODAT incidence at 1 year of 31.4% found an adjusted hazard for NODAT of 1.34 (1.00-1.79, P = 0.047) for pre-transplant metabolic syndrome. On multivariate analysis, only pre-transplant low HDL remained an independent predictor[9]. Other groups have attempted to apply scores that are predictive of type 2 diabetes mellitus in the general population. A retrospectively analysed cohort of 191 patients in which 41 developed NODAT, two general population risk scores were found to have AUC-ROC of 0.756-0.807 for NODAT at 1 year, but the PPV for each test was poor (24.5%-31.2%). However, the authors point out that the NPV were high (92.5%-93.7%) perhaps allowing the identification of high risk patients[118].

There is a small body of literature considering the development of predictive models that may be more unique to the transplant patient. Analyses in the general population of the patterns of oGTT results may be predictive of future type 2 diabetes[119]; similar analyses in renal transplant patients may be useful. An analysis of a 5 time point oGTT conducted pre-transplant in 145 patients found that whilst F BGL did not predict NODAT, the AUC of the oGTT and the glucose concentrations at each time point post glucose load could be used to predict NODAT[23]. Given the logistical difficulties in studying recipients of deceased donor organs, there is little data available that would enable us to reliably assess if pre-transplant markers for NODAT can be identified. For example, one study in which 120 transplanted patients were screened with oGTT pre-transplant found that pre-transplant IGT was significantly associated with NODAT; however, these patients were screened during the 3 mo prior to being waitlisted and there was no information provided regarding the time on the waiting list. This may introduce a potential bias in that some normoglycemic patients may have developed further dysglycemia pre-transplant[31].

Chakkera *et al*[120,121] have attempted to develop and validate a model of pre-transplant factors to predict the development of NODAT. On univariate analysis they described seven pre-transplant factors associated with increased risk of NODAT, which was defined by use of HbA1c, F BGL or requirement for treatment, including dietary changes. The seven factors were: age greater than 50 years old, use of maintenance glucocorticoids, use of gout therapies, BMI $\geqslant$ 30, F BGL $\geqslant$ 5.6 mmol/L, fasting triglycerides $\geqslant$ 2.24 mmol/L and a family history of type diabetes. Insulin indices were not measured and pre-transplant oGTT were not done pre- or post-transplantation, potentially treating pre-transplant diabetic patients as normoglycemic. Complex statistical methods, including bootstrapping were used. Within the limitations of this study, there were clear differences in the 1 year incidence of NODAT for those classified as low, moderate or high risk according to seven factor risk score. The results were similar in the initial and validation groups. In the higher risk group the incidence of NODAT was 44%-56% compared to the low risk group of 11%-13%. This was a first step in attempting to develop a risk score that may assist in identifying patients who could be targeted for trials of preventive therapies.

The analysis of the data from the 5 time point oGTT points towards the possibility of identifying higher risk patients by evaluating for impaired glucose and insulin regulation pre-transplant. A test that is helpful in this regard is known as the disposition index. This is a quantification of the hyperbolic balance between insulin secretion and insulin resistance. It can be measured either *via* oral or Ⅳ glucose loads and has been shown to be associated with increased risk for developing type 2 diabetes mellitus in the general population[122,123]. There is little literature using the disposition index as a predictive pre-transplant marker. However, there are some small studies measuring insulin resistance and secretion pre-transplant and testing their relationship with NODAT. Various models that utilise data derived from oGTT or Ⅳ GTT measure insulin resistance. The homeostasis model (HOMA) is widely used, and has been validated in studies of the general population. Variations of HOMA can be used to estimate insulin resistance and secretion. There is conflicting data on whether pre-transplant insulin indices may be predictive and most studies are small[124]. A study with the primary purpose of comparing Tac and CsA (n = 150) was used to retrospectively review the risk of NODAT from pre-, 3 and 12 mo indices of insulin resistance. Pre-transplant, there were no differences in insulin resistance or secretion found between those patients who developed NODAT at 3 or 12 mo[20]. This is in contrast to an earlier study (n = 57) in which those patients more resistant at baseline (and older) had an increased odds of a dysglycemic state after 1 year follow up[33]. However, as it appears increasingly more likely that falls in insulin secretion (and thus failing to compensate for insulin resistance) is crucial in the development of NODAT, it is interesting to note that measurements of insulin secretion in non-diabetic post-transplant patients can be used to predict the future development of NODAT[98].

MANAGEMENT

The principles of management of post-transplant dysglycemia are: (1) Pre-transplant risk assessment and development of amelioration strategies; (2) Early detection and monitoring for transient or permanent dysglycemia; and (3) Appropriate therapies that may reduce the poorer outcomes in those in whom post-transplant dysglycemia develops. The issues surrounding risk assessment and detection have been discussed

above. Current advice for glucose targets during post-transplant hospitalization suggest maintaining glucose levels below diabetic range; *i.e.*, F BGL 4-7 mmol/L (72-126 mg/dL)[125]. Following discharge, current guidelines recommend that patients be screened weekly for the first four weeks, and every 3 mo for the first year and yearly after the first year. Screening should also be commenced if there is commencement of, or substantial increase in dose of, CNI, mTOR inhibitor or glucocorticoids[126]. There is no consensus on the best screening test to utilise; however, a combination of tests as discussed above would appear to be of greatest clinical use. This may involve weekly F BGL or 4 pm capillary blood glucose (although this is not currently part of guidelines). Detection of IFG would then prompt oGTT assessment[125]. Perhaps use of HbA1c after the first 3 mo is warranted in stable patients. There are also few recommendations as to what the targets for blood glucose and HbA1c ought to be, as it is not known at what ranges there is substantial reduction in poorer outcomes. At present, guidelines give an ungraded suggestion to aim for an HbA1c of 7%-7.5% in United States[126] and < 7% in Scandanavia[125].

Adjusting immunosuppression

One approach to management is amelioration of risk. It remains difficult to identify patients at risk for dysglycemia with certainty; equally, it is challenging to know what may be done should they be identified. On the basis of data available concerning modifiable risks, physicians may wish to replace, minimise or withdraw one or more agents that form part of the maintenance immunosuppression; in particular CNI or glucocorticoids. For instance, perhaps older patients with a higher BMI and a worse (if still normal) pre-transplant oGTT may be judged to be at risk and as a result not exposed to maintenance glucocorticoids, or use of CsA in preference to Tac. This approach clearly needs to balance the immunological risk of reduced immunosuppressive exposure against the higher metabolic (and ultimately cardiovascular and infection) risk. Some authors have proposed protocols to assist in balancing the metabolic and rejection risk[61]; however, there are no well validated methods for reliably making such assessments in a broad transplant population. In addition, the clinician is also faced with the complicated issue of applying risk assessments to individual patients with varying degrees of co-morbidities.

One potentially helpful immunosuppressive agent that has not been discussed above is belatacept. This co-stimulatory blockade agent, which remains available in for off-label use in many countries, can be used as part of a maintenance regimen in place of CNI, in combination with MMF and glucocorticoids. The BENEFIT and BENEFIT-EXT (extended criteria donors) trials have reported up to 5 year results, comparing belatacept with MMF and glucocorticoids with CsA, MMF and glucocorticoids. There is a concern that there may be greater early acute rejection, however, over longer follow up there is no greater rejection rate. There has also been a concern about increased risk for EBV associated post transplant lymphoproliferative disease[127-130]. With regard to NODAT, results from 1 year follow-up of BENEFIT and BENEFIT-EXT have been published. There was a significant reduction in the 1 year cumulative incidence of NODAT in the belatacept arm, with rates of NODAT in the CsA arm being comparable to that found in other studies. This was in conjunction with clinically significant reductions in blood pressure, cholesterol and triglycerides, suggesting it may have a role in management of patients at higher risk of poorer cardiovascular and metabolic outcomes[131].

Lifestyle changes

Aside from altering immunosuppressive agents, other modifiable risk factors include reduced physical activity and poor diet. There is some data to suggest that low levels of physical activity post-transplant, particularly in patients whose appetite may now be improved, are at greater cardiovascular and all-cause mortality risk[132]. Improved diets, increased physical activity and weight loss has also been shown to improve dysglycemia in renal transplant patients[133]; however, this is not a well studied therapeutic approach.

Intensive and early glycemic control

As there are many obstacles to overcome should immunosuppression be tailored to meet metabolic and immunological risk, it may be that we require strategies to "rest" β-cells in patients without changing immunosuppression in those at higher risk of metabolic complications. Hecking *et al*[38] in a proof of concept trial (n = 50) randomised patients to (non-blinded) early basal insulin or standard therapy. NODAT was defined by oGTT or need for hypoglycemic agents at study visit. All patients received maintenance Tac, glucocorticoids and MMF. Patients were given isoprene insulin if their evening blood glucose was > 140 mg/dL (7.8 mmol/L) in the treatment group; the standard of care group received short acting insulin or oral agents if their blood glucose was 180-250 mg/dL (10-13.9 mmol/L), as directed by the treating clinician. All 25 patients in the treatment group received isoprene insulin on postoperative day 3, having had high evening blood glucose the day prior. By 12 mo, no patient in the treatment group required hypoglycemic agents compared to 8 in the control group. The majority of the patients in the treatment group did not receive any hypoglycemic agent after 120 d post-operative. All patients not on hypoglycemic agents had oGTT at 3, 6 and 12 mo. By 12 mo, 5 patients in the treatment group had NODAT on oGTT compared to 4 in the control group; thus, there was a reduction in NODAT from 12 to 5. More patients in the treatment group had IGT (8 *vs* 5); but, overall, more patients in the treatment group were normoglycemic (12 *vs* 8). Furthermore, consistent with the more

recent literature on insulin secretion as a significant contributor to the pathogenesis of post-transplant dysglycemia, measures of insulin resistance between the groups did not differ at 12 mo. There was, however, a significant difference in the insulinogenic index, an oGTT derived measure of β-cell function. There was also an improvement in the disposition index (although not significant). Together these results would indicate better or more preserved insulin secretion in those whose β-cells were "rested" at time of maximal stress. Should such results be achieved in a larger study population (perhaps of higher risk patients) who are studied for a longer period of time an found to have better metabolic and cardiovascular outcomes, then it may be that early basal insulin in those with elevated evening blood glucose may become a standard of care obviating any need to tailor immunosuppression.

Standard hypoglycemic agents

Nonetheless, currently patients receive care more like the standard care administered in Hecking *et al*[38]. If these patients then develop NODAT, they receive hypoglycemic agents. The choice of agent is mostly guided by opinion and knowledge of risks associated with administration of these agents in CKD. This is due to the paucity of trial data on use of hypoglycemic agents within this population. There is only one small study (n = 48) that compares potential therapies in which a DDP IV inhibitor, vildagliptin, was compared with pioglitazone or placebo in patients with IGT at more than 6 mo post renal transplantation. Both medications reduced oGTT blood glucose levels over 3 mo, with no differences between the treatment groups[134]. As there is concern that thiazolinediones may be associated with poorer cardiovascular outcomes, such medications may not be considered as first line therapy. The incretin analogues, remain the only other hypoglycemic agent studied in transplant patients. Vildagliptin has been studied as part of a randomised placebo controlled trial, in which patients with oGTT defined NODAT at least 6 mo post-transplant were recruited. Thirty-three patients were recruited, all of whom were on a similar maintenance regimen of CNI/MMF and glucocorticoids. The follow up period was short, however, vildagliptin did significantly reduce oGTT and HbA1c results at 3 mo with no hypoglycemic events[135]. Caution should be used with vildagliptin in conjunction with ACE inhibition as there is an increased risk of angiooedema (OR = 4.57), albeit on the basis of a small absolute risk[136]. Another small study (n = 19) has shown that sitagliptin can significantly increase insulin secretion in patients known to have NODAT[137]. Sitagliptin, saxagliptin and vildagliptin should be dose reduced in renal impairment, linagliptin is not renal excreted. It is unclear if incretin analogues are ameliorating an impact upon the incretin effect or assisting β-cell function in other ways. There is no data in the transplant population concerning the incretin effect. In healthy people administered glucocorticoids the incretin effect has been noted to be impaired[103]. In favour of incretin analogues, they do not tend to produce hypoglycemia or weight gain; but they have not been shown to reduced cardiovascular events, have been associated with pancreatitis and may theoretically increase cancer risk[138].

The incretin analogues are not widely used in the transplant population, with use of sulfonylureas and more common. Metformin may not be favoured as it can contribute to gastrointestinal side effects, potentially exacerbating the same caused by MMF use. Moreover, there is no also no data on its use in transplant patients with GFR < 30 mL/min and risks of lactic acidosis. However, its lack of contribution to weight gain, its association with reduced cardiovascular events in non-transplant patients and its role as an insulin sensitiser rather than stimulating further insulin secretion from "stressed" β-cells, may make metformin more favoured than sulfonylureas[139]. Sulfonylureas do not have the cardiovascular benefits and can contribute to weight gain. However, as long as dose adjusted to prevent hypoglycemia, their use is not associated with other serious adverse events. Nonetheless, it may be that some, if not most, transplant patients with develop dysglycemia have impaired β-cell function and that potentially a treatment strategy that induces more work from the β-cells may be counter-productive in terms of relieving dysglycemia and preventing worse cardiovascular outcomes[140]. Problematically, the paucity of data on treatment (including treatment targeted at the underlying pathology) in this area of transplantation means it is not possible to make any firm recommendations on the choice of oral hypoglycemic agents.

CONCLUSION

In summary, dysglycemic states, not limited to NODAT, are associated with increased risk of mortality, principally as a result of cardiovascular disease. NODAT is better studied than other dysglycemic states. The natural history of dysglycemic states is not well characterized, apart from the recognition of transient dysglycemia and NODAT within the first 3-6 mo post transplantation. The majority of persistent NODAT develops within one over the first year post transplant. Whilst the diagnosis is made using the WHO/ADA criteria accepted in the general population, there is no consensus on which test should be employed, either for screening or diagnosis. At present, oGTT remains the most reliable diagnostic test in the post-transplant setting. However, predicting the development of NODAT remains challenging. Possibly, the small group of patients who remain normoglycemic within the first week post-transplant are at very low risk of developing NODAT. There are a few studies that may assist in developing tools for identifying those at high risk.

There are multiple risk factors, some of which are modifiable. The most consistently found risk factor is increasing age and there is a growing body of liter-

ature documenting the genetic risk factors. The most well described modifiable risk factor is the use of immunosuppressive agents, in particular CNI (Tac more than CsA) and glucocorticoids. These agents likely contribute to the development of NODAT *via* different mechanisms – glucocorticoids encouraging insulin resistance and CNI *via* β - cell failure. It seems that reduction in insulin secretion is more important in the pathogenesis than insulin resistance.

Any attempt to balance the metabolic and immunological risks by adjusting immunosuppression is complicated. It may be better to identify higher risk patients and utilise a preventive strategy, such as described by Hecking *et al*[38]. As evidence emerges of the importance of β-cell failure as a major contributor to NODAT, such as strategy appears promising. In the absence of prevention, the management of NODAT in order to prevent the poorer outcomes is important. However, it is not clear which agent is most likely to successfully treat NODAT and ameliorate the poorer outcomes. A number of options exist, and it may be that metformin is the best option if insulin is not required.

Finally, further research is needed on pathogenesis, identification of higher risk patients and development of preventive and safe treatment options. Such research needs to take into account the caveats that are identified with respect to previous research: confirming normoglycemia pre-transplant, using oGTT as the primary diagnostic test (although there may be a role for capillary blood glucose early post-transplant), using WHO/ADA to define clinical states, testing regularly to detect transient and permanent states and having adequate follow up to detect the development of permanent dysglycemic states that impact upon poorer clinical outcomes. It would be ideal if future research could also map the changes in insulin secretion, resistance and the incretin effect pre- and post- transplantation in an effort to better understand the pathogenesis and further delineate targeted prevention and treatment options.

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