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ORIGINAL ARTICLE

Risk factors and long-term consequences of new-onset diabetes after renal transplantation

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Abstract

Background New-onset diabetes after transplant (NODAT) confers risk of diabetes-related complications as well as a threat to graft function and overall patient survival. The reported incidence of NODAT varies from 14 to 37% in renal transplant recipients worldwide; however, NODAT is yet to be studied in the Irish renal transplant population.

Aims Primary aims of this project were to estimate the incidence, to determine associated risk factors and to assess the long-term consequences of NODAT on graft survival and patient survival in the Irish renal transplant population.

Methods Retrospective data collection of 415 renal transplant recipients over a 12-year period was performed to record presence of NODAT, patient characteristics and perioperative management. Preoperative screening was reviewed in a subgroup of patients to determine concordance with the International Consensus Guidelines. Statistical analysis was performed using Kaplan-Meier survival functions estimating NODAT detection over time, graft and patient survival. Risk factor association was determined using Cox proportional-hazards models.

Results NODAT incidence was 10.2% in the first 5 years of post-transplant. Risk factors for developing NODAT were recipient age and body weight. Risk of NODAT was highest in the first year of post-transplant and conferred decreased patient survival; however, it did not significantly affect graft survival. Only seven patients of a subgroup of 21 patients who developed NODAT had preoperative testing for diabetes.

Conclusions NODAT incidence in the Irish renal transplant population is slightly below international figures. This project has highlighted current deficits in the national transplant guidelines for the detection of NODAT and NODAT-related risk factors.

Keywords Diabetes mellitus · NODAT · Post-transplant complications · Renal transplant

Background

Renal transplant is the preferred method of renal replacement therapy in end-stage renal disease, offering improved survival, quality of life and cost-effectiveness when compared to dialysis [1]. In Ireland, kidneys are the most commonly transplanted solid organ [2], with 167 renal transplants performed in 2018 [3].

New-onset diabetes after transplant (NODAT) is a frequent metabolic complication of renal transplantation and confers risk of diabetes-related complications as well as a threat to graft function and overall patient survival [4]. Importantly, NODAT increases the risk of cardiovascular events and infection, both major contributors to morbidity and mortality in the transplant population [5]. Diabetic complications occur at an accelerated rate in patients with NODAT compared to non-transplant patients with type 2 diabetes mellitus, with a median of 1.8 years to first-reported complication and a 31% incidence rate of diabetic nephropathy 3 years of post-transplant [6].

International Consensus Guidelines, published in 2003 and updated in 2014, clearly define the diagnostic criteria and management of NODAT [7]. Using these guidelines, the reported incidence of NODAT varies from 14 to 37% in renal transplant recipients [8, 9], but in Ireland, the incidence and perioperative management of NODAT is not known.

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NODAT may occur in transplant recipients any time after transplantation; however, the incidence peaks in the first 3–6 months of post-transplant [10]. It is diagnosed using the World Health Organization and American Diabetes Association (WHO/ADA) criteria for the diagnosis of diabetes mellitus which are shown in Table 1 [11, 12].

Current guidelines as per the International Consensus Meeting on post-transplant diabetes (2014) recommend OGTT as the gold standard for diagnosis of NODAT due to improved detection, identification of impaired glucose tolerance and lack of reliability of HbA1c particularly in the early post-transplant period [7].

These guidelines also stress the importance of preoperative screening in renal transplant recipients with evidence of pre-transplant metabolic syndrome and insulin resistance predicting development of NODAT. The International Consensus Guideline recommends pre-transplant screening with dedicated risk factor assessment and fasting plasma glucose. In addition, an oral glucose tolerance test (OGTT) should be performed if the fasting plasma glucose (FPG) is normal. Pre-transplant NODAT risk factors and cardiovascular comorbidities, such as dyslipidaemia, hypertension and smoking, should also be addressed and optimised prior to transplantation [13].

Aims

The primary aims of this project were to estimate the incidence, to determine associated risk factors and to assess the long-term consequences of NODAT on graft survival and patient survival in the Irish renal transplant population.

Standards and methodology

Inclusion criteria for this analysis were patients who underwent renal transplant between 2006 and 2017, inclusive, whose follow-up was entirely in our centre, Beaumont Hospital, Dublin. This ensured consistency and availability of data. Electronic records were reviewed and patients were stratified into those who developed NODAT and those who did not. Patients who developed NODAT were defined as those who met WHO/ADA diagnostic criteria for diabetes mellitus [11, 12] in the postoperative period, those who were prescribed anti-diabetic treatment in the postoperative period or those with a documented diagnosis of diabetes mellitus in the postoperative period only. Patients who had evidence of diabetes mellitus preoperatively were excluded.

The National Kidney Transplant Service (NKTS) registry provided baseline demographic information pertaining to gender, age at transplant, transplant type (cadaveric/living), donor age, cause of end-stage renal failure, cause of death, cause of graft failure, weight at transplant, smoking status and type of immunosuppression.

Statistical analysis was performed using Kaplan-Meier survivor functions to estimate percentage of NODAT over time in the post-transplant period within the study population. Univariate analysis of baseline characteristics followed by multivariable analysis was performed using Cox proportional-hazards models. A subgroup of patients who developed NODAT within 5 years of transplant were categorised to assess patient and clinical features associated with NODAT. Finally, graft and patient survival from a 1 year of post-transplant was performed for patients who developed NODAT and those who did not within the first year of post-transplant. All of the analysis was conducted using Stata SE (version 13, College Station, Texas), and significance was assumed for p values less than 0.05.

Preoperative risk factor analysis was also assessed in a subgroup of patients who developed NODAT to determine concordance with International Consensus Guidelines [7].

Table 1 WHO/ADA diagnostic criteria for the diagnosis of new-onset diabetes after transplant

Test	Diabetes criteria
Random plasma glucose (RPG)	≥ 11.1 mmol/L
	with symptoms of diabetes mellitus (polyuria, polydipsia, unexplained weight loss)
Fasting plasma glucose (FPG)	≥ 7.0 mmol/L
	Should be confirmed on another day
Oral glucose tolerance test (OGTT)	Two-hour plasma glucose ≥ 11.1 mmol/L
	Following administration of 75 g anhydrous glucose dissolved in water
Haemoglobin A1c (HbA1c)	≥ 48 mmol/L
	Can be used 3 months of post-transplant.
	Within 3 months of transplantation, HbA1c is less reliable and not recommended for diagnostic use, as haemoglobin synthesis is disrupted in the immediate post-transplant period [11, 12]

Results

Four hundred and twelve patients followed in our centre received a kidney transplant from January 2006 to December 2017 inclusive; 61 patients were excluded from our analysis due to a preoperative diagnosis of diabetes mellitus. A further 4 patients had graft failure within 1 month which was deemed to be insufficient for analysis purposes. On analysing the data of the remaining 347 patients, NODAT was evidenced in 38 cases, or 10.9% of assessed patients (Fig. 1). Baseline demographics of the two groups are shown in Table 2.

Time to event analysis shown in Fig. 2 illustrates the development of NODAT over time with the highest risk of developing NODAT within the first year of post-transplant of 5.2%, rising to 10.2% at 5 years and 15.8% at 10 years of post-transplant.

Univariate and multivariable analysis of baseline characteristics between the two groups are shown in Tables 3 and 4. Risk factors for developing NODAT were identified as recipient age at transplant (HR 1.044; p 0.007) and recipient weight at transplant (HR 1.036; p 0.008). Low magnesium (median serum magnesium < 0.66 mmol/L in the first postoperative month) also correlated with NODAT risk; however, this was not statistically significant. These findings were consistent on a further subgroup analysis of patients who developed NODAT within 5 years of transplant (Table 5). Median follow-up was 5 years with interquartile range of 3–8 years.

The majority of patients (336 of 347, 97%) were taking an immunosuppression regimen of tacrolimus, mycophenolate and prednisolone. The remaining 11 patients' immunosuppressive regimens were mycophenolate and tacrolimus in 4 cases, tacrolimus, azathioprine and prednisolone in 4 cases, azathioprine and tacrolimus in one case, azathioprine and prednisolone in one case and tacrolimus and prednisolone in one case. Higher tacrolimus levels did not significantly confer greater risk of NODAT (Fig. 3).

Patient and graft survival between groups who developed NODAT within the first year of transplant and those who did not is depicted in Figs. 4 and 5. Those who developed NODAT within the first year of transplant demonstrated higher mortality than those who did not with an unadjusted hazard ratio of 4.04 (p 0.013), however with adjustment for confounding, this effect was less significant (HR 2.24; p 0.178) (Fig. 4). There was no significant decrease in graft survival observed in patients who developed NODAT within 1 year of transplant.

A subgroup of patients were assessed for presence of preoperative screening for NODAT-related risk factors. Twenty-one medical records were reviewed. All 21 developed NODAT. Biochemical testing did not meet International Consensus Guideline recommendations [7]. Only two patients had a fasting plasma glucose, one had an oral glucose tolerance test and four had HbA1c tested preoperatively. All patients underwent clinical history and physical examination which were tailored to identify NODAT-related and cardiometabolic risk factors prior to transplantation (Table 6). This information was available in a tailored proforma which was present in the medical records. Moreover, evidence of risk factor optimisation was present, with use of dietetics and smoking cessation initiatives, where appropriate.

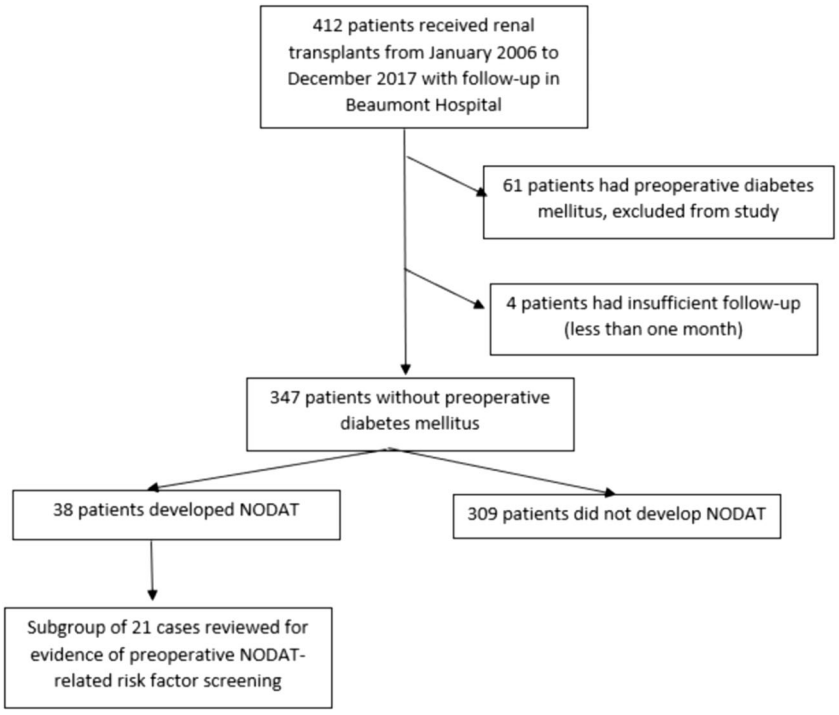


Fig. 1 Study design

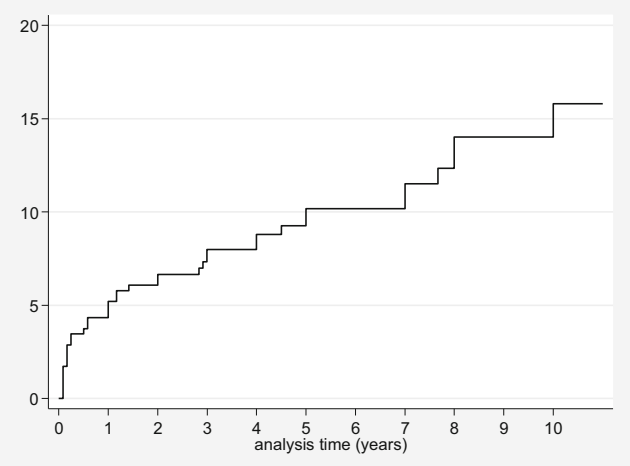
Table 2 Baseline demographics

Demographics	Developed NODAT $n = 38$	Did not develop NODAT $n = 309$
Gender		
Male	31 (82%)	211 (68%)
Female	7 (18%)	98 (32%)
Median age at time of transplant (± IQR)	57 (± 15) years	43 (± 22) years
Type of transplant		
Cadaveric donor	30	238
Living related donor	8	69
Living unrelated donor	0	2
Median weight at transplant	80 kg	70 kg
Mean HbA1c (± SD)	56.7 (± 14.7) mmol/mol	36 (± 4.9) mmol/mol
Smoking status		
Current smoker	4	34
Non-smoker	34	275

IQR, interquartile range; SD, standard deviation

Discussion

Our audit, the first of its kind in an Irish renal transplant population, showed an incidence rate of NODAT in 10.73% of transplanted patients, below the international average. A recent Portuguese study reported a NODAT incidence rate of 24.8% in the first year of post-transplant, in subjects with a similar demographic profile to our audit population [8]. However, our analysis found an incidence rate of only 5.2% in the first year. Ireland lacks epidemiological data surrounding diabetes incidence and prevalence due to the absence of a national diabetes registry. The International Diabetes Federation Atlas (2017) estimates that Ireland has a diabetes prevalence rate 4.3%, which is similar to our European counterparts; therefore, it is unlikely that NODAT is less common in Ireland [14]. A more reasonable interpretation of our low NODAT incidence rate may reflect under-reporting and under-investigation of NODAT in the renal transplant population. Given the lack of pre-transplant biochemical screening for diabetes in this audit, it is possible that patients with undiagnosed diabetes mellitus prior to transplant were not identified during this retrospective analysis. This limitation of our



Time (years)	Failure function	Standard error	95% Confidence interval
1	0.0521	0.0120	0.0332 - 0.0814
2	0.0668	0.0135	0.0449 - 0.0988
3	0.0801	0.0148	0.0556 - 0.1147
4	0.0882	0.0158	0.0620 - 0.1247
5	0.1020	0.0174	0.0728 - 0.1420
8	0.1404	0.0238	0.1004 - 0.1946
10	0.1583	0.0292	0.1096 - 0.2258

Fig. 2 Onset of NODAT. DM, diabetes mellitus. A 5-year NODAT incidence rate of 10.2% (95% confidence interval 7.3–14.2%)

Table 3 Univariate analysis of baseline characteristics

Variable	Hazard ratio	95% confidence interval		*P* value
Recipient age	1.059	1.031	1.087	< 0.001
Recipient sex	2.211	0.973	5.022	0.058
Recipient weight	1.038	1.017	1.058	< 0.001
Transplant number	0.934	0.485	1.799	0.838
Delayed graft function	0.966	0.342	2.726	0.948
Time on dialysis	1.008	0.998	1.017	0.103
% PRA	1.046	0.785	1.393	0.761
HLA mismatch	1.023	0.841	1.244	0.823
Acute rejection	1.278	0.533	3.064	0.582
Donor age	1.046	1.019	1.074	0.001
Donor sex	0.730	0.386	1.379	0.332
Living donor transplant	0.969	0.444	2.116	0.937
Smoker	1.400	0.431	4.553	0.576
Cause of ESRD (GN)	0.642	0.294	1.400	0.265
Magnesium < 0.66 mmol/L	1.445	0.591	3.538	0.420

ESRD, end-stage renal disease; GN, glomerulonephritis

Table 4 Multivariable model demonstrating that recipient age and weight at transplant are associated with NODAT

Variable	Hazard ratio	95% confidence interval		*P* value
Age at transplant	1.044	1.012	1.077	0.007
Recipient sex	1.501	0.609	3.701	0.378
Recipient weight	1.036	1.009	1.063	0.008
Donor age	1.026	0.994	1.059	0.117
Donor sex	0.633	0.332	1.208	0.165

analysis may have led to over-reporting of NODAT in the post-transplant period in patients who in fact had preoperative unidentified diabetes mellitus. Therefore, the actual reported incidence of NODAT may be even lower than identified in this study. Of concern, it is possible that post-transplant screening for diabetes mellitus is also underperformed and therefore NODAT may be under-diagnosed in the postoperative period. There is an obvious need for clear communication via a national diabetes registry and national guidelines for identification and screening of NODAT.

The time of onset of NODAT was similar to other reports, with greatest risk of NODAT in the first year; however, the risk of developing NODAT continues over time following transplant. A large US cohort of 11,659 patient's incidence rates were 9.1%, 16% and 24% at 3, 12 and 36 months of post-transplant respectively [15]. Our Irish cohort shows a similar distribution in relation to the incidence of NODAT over time (Fig. 2).

On reviewing the data of the renal transplant population of Ireland, patient weight and age pre-transplant were significantly associated with development of NODAT. Magnesium levels and tacrolimus were not significantly correlated with risk of NODAT in our cohort. Immunosuppressive therapy was consistent across the cohort with the majority of patients exposed to tacrolimus and glucocorticoids. Modification of pre-transplant risk factors, where possible, and interventions

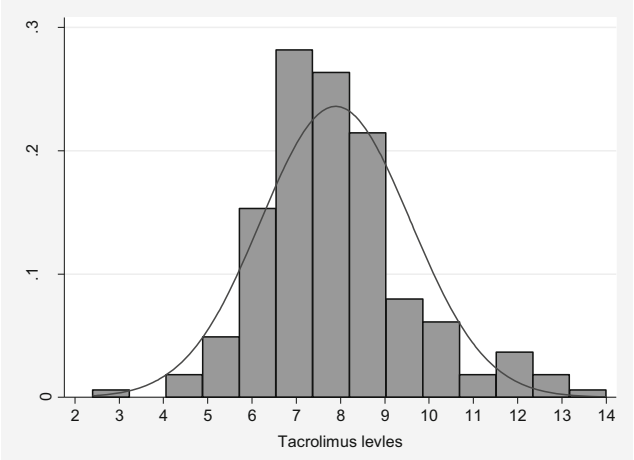


Fig. 3 Tacrolimus levels and risk of NODAT univariate test for median tacrolimus levels for first transplant and outcome of NODAT HR 1.159 (*p* 0.186, 95% confidence interval 0.93–1.44)

to improve glucose tolerance may reduce the risk of progression of NODAT [16]. The Diabetes Prevention Program has demonstrated that physical activity and structured diet, with modest weight loss, in patients who are overweight or have impaired glucose tolerance significantly reduces the development of diabetes, a result which is sustained for up to 15 years [17]. Similar lifestyle interventions as well as treatment of hepatitis C virus and individualisation of immunosuppressive therapies in renal transplant recipients will collectively reduce the risk of NODAT and therefore improve renal allograft survival and patient mortality and morbidity [18, 19].

A major concern of NODAT is the effect on patient and graft survival. This audit is consistent with previous international studies showing an associated mortality risk in patients who develop NODAT versus those who do not [4, 15]. This again, stresses the importance of preoperative optimisation in mitigating postoperative NODAT risk. Graft survival was not affected in this analysis. In comparison to other population-based studies, our population size and duration of follow-up

Table 5 Characteristics of patients 5 years of post-transplant

Variable	NODAT post 5 years (*N* = 32)	No NODAT post 5 years (*N* = 199)	*P* value
Recipient age at transplant (mean [SD])	54.8 [12.0]	41.8 [14.3]	< 0.001
Donor age at transplant (mean [SD])	49.3 [11.2]	40.7 [14.6]	0.002
Recipient weight at transplant (mean [SD])	79.1 [13.8]	69.4 [16.3]	0.002
Time on dialysis in months (median [IQR])	37.8 [23.3–49.2]	26.4 [15.9–39.6]	0.013
Recipient sex (% M/F)	78.1/21.9	68.3/31.7	0.306
Donor sex (% M/F)	50.0/50.0	58.4/41.6	0.442
ESRD GN (%)	18.8	28.6	0.290
PRA groups % 0–10/11–49/5–84/85–100	34/22/25/19	38/26/21/15	0.847
Living donor transplant (%)	18.8	21.6	0.819
Transplant number (% 2nd or more)	18.8	19.1	1.000

SD, standard deviation; M, male; F, female

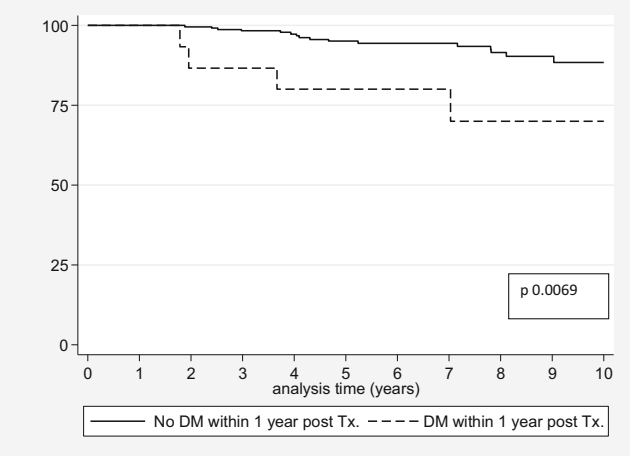


Fig. 4 Patient survival. DM, diabetes mellitus

was modest which may explain the survival results. Detriment to patient and graft survival has been shown in larger population-based studies. For example, in the USA, NODAT was associated with higher rates of graft failure and mortality, independent of NODAT-related risk factors and other risk factors of graft failure [15]. Similarly, in a prospective Norwegian study, patients with NODAT had an increased risk of death compared to nondiabetic patients, as well as higher cumulative incidence of cardiovascular and infection-related death. Specifically, NODAT was associated with an up to three-fold increased risk of myocardial infarction, ischaemic heart disease or cardiovascular disease, within 7 years of renal transplantation [4].

From the data gathered in this audit, preoperative assessment of NODAT risk is poor in Ireland and fails to meet the recommendations of the International Consensus Guidelines [7]. There is a discrepancy in the number of patients biochemically tested for diabetes mellitus or impaired glucose tolerance pre-transplant. Of the 21 patients reviewed in the subgroup analysis, only seven had any preoperative biochemical diabetes testing, with HbA1c used in four of these seven which is known to be inappropriate in end-stage renal failure

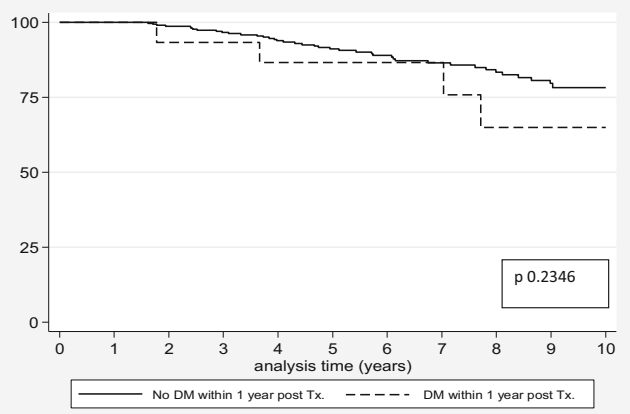


Fig. 5 Graft survival. DM, diabetes mellitus

Table 6 Preoperative NODAT-related risk factor screening

Pre-transplant risk factor assessment	Testing performed in:
Biochemical testing	
Fasting plasma glucose	2/21 (10%)
Oral glucose tolerance test	1/21 (5%)
Haemoglobin A1c	4/21 (19%)
Random plasma glucose	10/21 (48%)
Cardiac risks	
Hypertension	21/21 (100%)
Dyslipidaemia	21/21 (100%)
Smoking status	21/21 (100%)
NODAT risk factors	
BMI	14/21 (67%)
Family history of DM	21/21 (100%)
Previous gestational DM (females)	3/3 (100%)
Hepatitis C virus status	21/21 (100%)
CMV status	21/21 (100%)

BMI, body mass index; DM, diabetes mellitus; CMV, cytomegalovirus

[12]. We fail to meet the International Consensus Guidelines recommendation to perform FPG in all patients and, when this is normal, to proceed to OGTT [7]. Preoperative screening provides clinicians with the opportunity to improve quality of life, morbidity, healthcare costs and, of critical concern, patient and graft survival [16], and so it is disappointing that we are missing an opportunity to intervene at an earlier stage in patients listed for renal transplantation. Risk stratification and early intervention should be integral to the management of prospective transplant recipients. Currently, the Irish National Transplant Centre guidelines do not recommend measurement of preoperative fasting plasma glucose pre-transplant but propose measurement of random plasma glucose only. Due to this, a large number of patients appear not to have had any testing for preoperative diabetes performed, a change to national guidelines to reflect current International Consensus Guidelines could potentially improve preoperative screening rates.

Conclusion

Survival following renal transplantation in Ireland has shown steady improvement since the 1980s, with overall median survival for deceased donors 13.7 years as per Organ Donation and Transplant Ireland Annual Report 2017 [2]. Clinicians must be cognizant therefore of factors, such as NODAT, which impede survival and graft function in renal transplant recipients, and where possible must mitigate this risk [4, 12]. This audit demonstrates the deficits in preoperative NODAT-related risk factor screening in our transplant population

which, if rectified, may significantly enhance the postoperative course for the transplanted patient.

Author contribution Material preparation, data collection and analysis were performed by Maria Tomkins, Patrick O'Kelly, Yvonne Williams, Kevin Cronin and Roxana Tudor. The first draft of the manuscript was written by Maria Tomkins and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval For the purpose of this audit, ethical approval was not required. All procedures performed were in accordance with the standards of the institutional audit committee of Beaumont Hospital.

Consent Informed consent was not required for the purposes of this audit.

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