TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Role of insulin resistance indices in predicting new-onset diabetes after kidney transplantation

Pramod Nagaraja,[1] Vinod Ravindran,[1] Gareth Morris-Stiff[2] and Kesh Baboolal[1]

1 Nephrology and Transplantation Directorate, University Hospital of Wales, Cardiff, UK
2 Welsh Transplantation Research Group, University Hospital of Wales, Cardiff, UK

Keywords
homeostasis model assessment, insulin resistance, kidney transplantation, long-term survival, new-onset diabetes after transplantation.

Correspondence
Dr. Pramod Nagaraja, Directorate of Nephrology and Transplantation, University Hospital of Wales, Cardiff CF14 4XW, UK.
Tel.: 0044 2920748410;
fax: 0044 2920746661;
e-mail: npramod@doctors.net.uk

Conflicts of Interest
The authors have declared no conflict of interest.

Received: 8 July 2012
Revision requested: 8 August 2012
Accepted: 1 November 2012
Published online: 11 December 2012

doi:10.1111/tri.12026

Summary

New-onset diabetes mellitus (NODAT) is a serious complication following renal transplantation. In this cohort study, we studied 118 nondiabetic renal transplant recipients to examine whether indices of insulin resistance and secretion calculated before transplantation and at 3 months post-transplantation are associated with the development of NODAT within 1 year. We also analysed the long-term impact of early diagnosed NODAT. Insulin indices were calculated using homeostasis model assessment (HOMA) and McAuley's Index. NODAT was diagnosed using fasting plasma glucose. Median follow-up was 11 years. The cumulative incidence of NODAT at 1 year was 37%. By logistic regression, recipient age (per year) was the only significant pretransplant predictor of NODAT (OR 1.04, CI 1.009–1.072), while age (OR 1.04, CI 1.005–1.084) and impaired fasting glucose (OR 2.97, CI 1.009–8.733) were significant predictors at 3 months. Pretransplant and 3-month insulin resistance and secretion indices did not predict NODAT. All-cause mortality was significantly higher in recipients developing NODAT within 1 year compared with those remaining nondiabetic (44% vs. 22%, log-rank $P = 0.008$). By Cox's regression analysis, age (HR 1.075, CI 1.042–1.110), 1-year creatinine (HR 1.007, CI 1.004–1.010) and NODAT within 3 months (HR 2.4, CI 1.2–4.9) were independent predictors of death. In conclusion, NODAT developing early after renal transplantation was associated with poor long-term patient survival. Insulin indices calculated pretransplantation using HOMA and McAuley's Index did not predict NODAT.

Introduction

Post-transplant hyperglycaemia and new-onset diabetes after transplantation (NODAT) are common and important complications following organ transplantation [1]. In particular, NODAT has been shown to be associated with major cardiac events and increased mortality in kidney transplant recipients (KTRs) [1–3]. Certain traditional risk factors such as age, ethnicity and obesity, and transplant-specific risk factors such as steroids and calcineurin inhibitors (CNIs) are known to play a role in the causation of NODAT [4]. A few pretransplant risk factors have been used in attempts to predict the development of NODAT in KTRs, so that potential recipients at risk can be identified early and interventions started [5, 6]. Indeed, active lifestyle intervention with dietician advice and exercise programme has been shown to improve glucose metabolism in KTRs [7].

The pathophysiology of NODAT is similar to that of type 2 diabetes mellitus (DM). Defects in insulin secretion and insulin resistance both occur post-transplantation, but β-cell dysfunction seems to play the dominant role in causing NODAT [8, 9]. Insulin resistance and secretion can be estimated by the homeostasis model assessment (HOMA), which uses single fasting plasma glucose (FPG) and insulin measurements [10]. This model has been validated against gold-standard techniques for measuring insulin resistance and secretion. McAuley's Index is another equation which

estimates insulin sensitivity values that closely correlate with those obtained from gold-standard techniques [11]. These indices are simple and easy to calculate and hence are useful to estimate insulin resistance in large studies. In the general population, insulin resistance and secretion values estimated by HOMA have been used to predict the future development of type 2 DM [12,13]. While two studies found that HOMA was useful in predicting the development of type 2 DM [12, 13], one Korean study questioned the utility of HOMA in predicting DM [14].

Previous studies from our group and others have validated the HOMA model and McAuley's Index against more complex gold-standard methods in stable KTRs treated with tacrolimus and cyclosporin [15, 16]. HOMA has also been validated in patients with chronic kidney disease treated with dialysis [17, 18]. However, the utility of HOMA in predicting NODAT is unknown in the renal transplant population.

Previous studies on the impact of NODAT on patient survival have used indirect criteria such as insurance records, medication use or random blood glucose to diagnose diabetes. The long-term effect of NODAT diagnosed early after transplantation using FPG and WHO criteria is not clearly known.

The primary aim of this study was to determine whether insulin resistance indices calculated pretransplantation and early after transplantation can predict the development of NODAT in KTRs. We also sought to determine the effect of early-onset NODAT (diagnosed based on fasting glucose) on long-term patient survival.

Materials and methods

Study population

This was a single centre cohort study with a median follow-up of 11 years. Patients were derived from a larger group of 150 patients who received a deceased donor renal allograft as part of a randomized trial of tacrolimus versus cyclosporin undertaken between 1996 and 2001 at the University Hospital of Wales, Cardiff, UK. Patients were assigned randomly on a 1:1 basis to receive either tacrolimus- or cyclosporin-based triple therapy immunosuppression. The study obtained approval from the local research ethics committee. All 118 patients in this study met the following inclusion criteria: (i) age 18–80 years and (ii) no history of T2 DM and fasting glucose <7.0 mmol/l on at least two occasions in the year before transplantation.

Immunosuppression regimen

Patients randomized to cyclosporin were given Neoral® (Novartis Pharma AG, Basel, Switzerland) 8 mg/kg/day, in two divided doses to maintain trough drug levels of 150–250 ng/ml for the first postoperative month and 100–150 ng/ml thereafter. Individuals randomized to tacrolimus were prescribed Prograf® (Astellas Pharma, Tokyo, Japan) at a dose of 0.2 mg/kg/day, in two divided doses with target trough levels of 5–15 ng/ml for the first month and 5–10 ng/ml thereafter. In addition to the primary agents, both groups also received methylprednisolone (500 mg) intravenously per-operatively. Both groups received azathioprine (1.5 mg/kg/day) and prednisolone (20 mg/day). Prednisolone dose was tapered according to departmental protocol, so that all patients not experiencing an acute rejection (AR) episode were steroid free by 3 months, while individuals experiencing rejection continued taking 5 mg/day for at least 1 year.

Treatment of acute rejection episodes

All clinically suspected AR episodes were confirmed by an ultrasound-guided allograft biopsy, with histological classification carried out according to the Banff '97 criteria. All patients with histologically confirmed AR episodes were treated initially with intravenous steroid boluses (500 mg of methylprednisolone) on three consecutive days. For patients randomized to cyclosporin, in the presence of steroid resistant rejection, a switch from cyclosporin to tacrolimus was performed, and in the case of further rejection episodes, azathioprine was substituted by mycophenolate mofetil. In the presence of persisting rejection, anti-thymocyte globulin (ATG) was given. Patients in the tacrolimus arm of the study who experienced steroid resistant rejection were directly commenced on mycophenolate mofetil followed by ATG therapy if required.

Data collection

Follow-up data were obtained from the renal database (Proton) used at the University Hospital of Wales. Data were collected until 30 June 2010, loss of graft or death. Fasting metabolic parameters including plasma glucose, insulin and triglyceride levels were measured pretransplantation, and then at 3 and 12 months after transplantation. Fasting glucose tolerance was determined from FPG values according to the 1999 WHO classification [19] (NODAT diagnosed if FPG $\geq$ 7.0 mmol/l or pharmacological treatment for DM). Cardiovascular cause of death was defined as death because of myocardial infarction, cerebral haemorrhage, cerebral infarct or cardiac arrest because of unknown cause.

Insulin resistance indices

The following indices were calculated at baseline (pretransplantation), 3 months and 12 months after transplantation -

1. IR-HOMA [10] (homeostasis model assessment of insulin resistance) = FPG (mmol/l) × fasting plasma insulin (FPI) (mU/l)/22.5
2. McAuley's Index [11] = exp (2.63 − 0.28 ln[FPI {microunits/ml}] − 0.31 × ln[triglycerides {mmol/l}])
3. HOMA secretion index (HOMAsec) [10] = 20 × FPI (mU/l)/(FPG [mmol/l] − 3.5)

IR-HOMA is a surrogate marker for insulin resistance. A high value of IR-HOMA indicates a higher level of insulin resistance and lower level of insulin sensitivity [10]. McAuley's Index is a measure of insulin sensitivity [11]. HOMAsec indicates insulin secretion function for a given level of insulin resistance.

Statistical analysis

Continuous data were analysed using *t*-tests or appropriate nonparametric tests. Categorical data were analysed using Chi-squared test or Fisher's exact test as appropriate. Patient survival was analysed using Kaplan–Meier method and Cox's proportional hazards regression model. Risk factors for NODAT were identified using a logistic regression model. Factors with a *P*-value <0.1 for the odds ratio in univariate analysis were entered into the multivariate model. PASW18 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A *P*-value of <0.05 was used to determine significance.

Results

The cumulative incidence of NODAT at 3 months, 12 months and 10 years post-transplantation was 25 (21%), 44 (37%) and 48 (42%), respectively. Median follow-up was 11 years (range 10–15 years). Baseline characteristics of patients who developed NODAT in the first year and those who remained nondiabetic are shown in Table 1. Only two patients were non-Caucasian. Patients who developed NODAT were significantly older than those who remained nondiabetic (mean 52 ± 12 vs. 46 ± 14 years, $P = 0.01$). A numerically higher proportion of patients developing NODAT were on tacrolimus at baseline (59% vs. 43%, $P = 0.09$). Baseline BMI was similar in both groups.

Although the proportion of patients experiencing at least one AR episode in the first year was higher in patients developing NODAT than in nondiabetic patients, this was not statistically different [22 (50%) vs. 27 (37%), $P = 0.15$]. Nine recipients suffered two rejection episodes (6/44 in NODAT vs. 3/74 in nondiabetics) and one recipient suffered three rejection episodes (NODAT group). However, the mean number of AR episodes per patient in the first year was significantly higher amongst NODAT patients (0.7 vs. 0.4, $P = 0.04$). In 20 of 22 patients with NODAT and AR, the rejection episode occurred first. In general, recipients with AR by 3 months did not have a significantly higher insulin resistance at 3 months compared with those without AR (Table S1). Recipients who suffered AR and developed NODAT had an early increase in insulin resistance (by 3 months). In contrast, those recipients who did not suffer AR but still developed NODAT demonstrated a higher insulin resistance only by 12 months post-transplantation (Tables S2 and S3).

Table 1. Baseline characteristics of recipients who developed new-onset diabetes (NODAT) and those who remained nondiabetic in the first year after transplantation.

	NODAT ($n = 44$)	Non-NODAT ($n = 74$)	*P*
Age at transplant in years (mean ± 1SD)	52 ± 12	46 ± 14	0.01
Gender: male, *n* (%)	32 (73)	44 (60)	0.14
BMI in kg/m² (mean ± 1SD)	26.2 ± 4.5	26.1 ± 4.2	0.9
Fasting plasma glucose (mmol/l, mean ± 1SD)	5.4 ± 0.9	5.3 ± 0.7	0.55
Fasting plasma insulin in mU/l, median (range)	12 (3–41)	14 (3–43)	0.15
Fasting triglycerides in mmol/l, median (range)	1.8 (0.4–5.5)	1.7 (0.5–7.5)	0.85
Baseline CNI (*n*)			
Cyclosporin	18	42	0.09
Tacrolimus	26	32	

BMI, body mass index; SD, standard deviation; CNI, calcineurin inhibitor.

There was no difference in the number of patients receiving prednisolone at 3 months (NODAT 73% vs. nondiabetics 76%, $P = 0.7$) or 1 year (NODAT 56% vs. nondiabetics 49%, $P = 0.5$). Nine patients needed treatment with anti-diabetic medication; all nine patients were on tacrolimus at baseline and at follow-up.

Differences in insulin resistance and secretion indices between NODAT and nondiabetic patients

Table 2 shows the values for HOMAsec, IR-HOMA and McAuley's Index in patients who developed NODAT and those who remained nondiabetic in the first year after transplantation. There were no differences in pretransplant insulin resistance or secretion index between the two groups of patients. Median HOMAsec was significantly lower in patients with NODAT at 12 months compared with nondiabetics (88 vs. 125, $P = 0.05$). At 3 and 12 months after transplantation, patients who developed NODAT had a significantly higher IR-HOMA compared with nondiabetic patients (median 6.0 vs. 2.8, $P = 0.008$ and 4.8 vs. 2.6, $P = 0.01$ respectively).

In within group analyses, amongst NODAT patients, HOMAsec did not change significantly from baseline to 3

Table 2. Comparison of insulin parameters at baseline, 3 months and 12 months between recipients who developed new-onset diabetes (NODAT) and those who remained nondiabetic in the first year.

	Pretransplantation			3 months			12 months		
	NODAT $n = 44$	Non-NODAT $n = 74$	*P*	NODAT $n = 44$	Non-NODAT $n = 74$	*P*	NODAT $n = 40$	Non-NODAT $n = 74$	*P*
IR-HOMA	3.0 (0.6–11.0)	3.3 (0.8–10.7)	0.18	6.0 (1.0–40.0)	2.8 (1.1–13.1)	0.008	4.8 (0.6–32.0)	2.6 (0.7–9.5)	0.01
HOMAsec	131 (41–666)	166 (40–916)	0.18	136 (30–2340)	135 (31–896)	0.29	88 (23–500)	125 (36–1953)	0.05
McAuley's Index	5.6 (3.1–11.0)	5.4 (3.2–10.6)	0.50	4.7 (2.4–8.3)	5.8 (2.7–9.3)	0.05	5.8 (3.0–12.0)	6.0 (2.7–9.5)	0.40
Plasma glucose, mmol/l	5.6 ± 1.1	5.5 ± 1.0	0.70	6.9 ± 1.7	5.6 ± 0.7	<0.001	7.1 ± 1.9	5.5 ± 0.8	<0.001
Plasma insulin, mU/l	12 (3–41)	14 (3–43)	0.15	17 (3–87)	13 (5–161)	0.01	16 (3–154)	13 (4–122)	0.37
S. cholesterol, mmol/l	5.6 ± 1.5	5.4 ± 1.3	0.58	5.3 ± 1.5	5.7 ± 1.1	0.15	5.6 ± 1.4	5.5 ± 1.2	0.74
S. triglycerides, mmol/l	1.8 (0.4–5.5)	1.7 (0.5–7.5)	0.85	1.8 (0.8–5.4)	2.0 (0.8–6.4)	0.56	2.1 (0.7–5.2)	1.5 (0.5–13.2)	0.51
S. low density lipoprotein, mmol/l	3.3 ± 1.2	3.4 ± 1.1	0.74	3.2 ± 1.2	3.3 ± 1.0	0.62	3.1 ± 1.0	3.3 ± 1.0	0.52
Creatinine clearance, ml/min				57 ± 24	55 ± 17	0.54	60 ± 26	59 ± 19	0.90
Body mass index, kg/m^2	26.2 ± 4.5	26.1 ± 4.2	0.90	26.3 ± 4.3	26.2 ± 4.3	0.93	27.1 ± 4.7	26.9 ± 4.4	0.88
B. haemoglobin, g/dl	9.8 ± 1.8	10.1 ± 1.9	0.46	11.7 ± 1.6	11.7 ± 1.8	0.90	13.4 ± 1.8	13 ± 1.8	0.24

Values are expressed as median (range) or mean ± 1 standard deviation.
IR-HOMA, homeostasis model assessment of insulin resistance; HOMAsec, HOMA secretion index.

and 12 months (131 vs. 136, $P = 0.37$ and 131 vs. 88, $P = 0.85$ respectively). However, IR-HOMA at 3 and 12 months was significantly higher compared with baseline (median 6 vs. 3, $P = 0.001$ and 4.8 vs. 3, $P = 0.008$ respectively). In contrast, amongst the nondiabetic patients, neither HOMAsec nor IR-HOMA changed significantly by 3 and 12 months compared with baseline (HOMAsec 166, 135, 125 and IR-HOMA 3.3, 2.8, 2.6 at baseline, 3 months and 12 months respectively; P = NS for all comparisons with baseline).

Change in insulin parameters according to baseline CNI

HOMAsec and McAuley's Index at 3 and 12 months were not significantly different compared with pretransplant values in either CNI group (Table 3). In tacrolimus-treated patients, IR-HOMA was significantly higher at 3 and 12 months compared with baseline, whereas this was not the case in cyclosporin-treated patients. Furthermore, there was no difference in HOMAsec between tacrolimus and cyclosporin-treated patients at 3 (median 137 vs. 137, $P = 0.8$) or 12 months (115 vs. 125, $P = 0.5$).

Risk factors for developing NODAT

Logistic regression analysis was carried out to determine factors predicting NODAT. In the first model, the following pretransplant factors were included with NODAT in the first year ($n = 44$) as the dependent variable – age, gender, BMI, baseline CNI, fasting triglycerides, fasting glucose tolerance (NFG or IFG with FPG $\geq$ 5.6 mmol/l as cut-off), fasting insulin and baseline insulin indices (IR-HOMA, HOMAsec & McAuley's Index). On univariate analysis, age and baseline CNI were significant predictors of NODAT in the first year. On multivariate analysis, only age was a significant factor (OR 1.04, 95% CI 1.009–1.072).

In the second model, logistic regression analysis was carried out to see whether any factors at 3 months post-transplantation were associated with the development of NODAT after 3 months ($n = 23$). The following factors

Table 3. Differences in insulin parameters according to baseline calcineurin inhibitor (CNI)* (3- and 12-month median values were compared with baseline values for each CNI).

	IR-HOMA			HOMAsec			McAuley's Index		
	Baseline	3 months	12 months	Baseline	3 months	12 months	Baseline	3 months	12 months
Cyclosporin, $n = 43$	3.9	2.9†	3.5†	174	137†	125†	5.2	4.8†	5.6†
Tacrolimus, $n = 55$	2.6	3.5‡	4.1‡	133	137†	115†	5.8	5.5†	5.9†

IR-HOMA, homeostasis model of assessment insulin resistance; HOMAsec, HOMA secretion index.
*Recipients who had a switch of CNI within 12 months of transplantation are excluded from this analysis.
†$P > 0.05$ compared with baseline.
‡$P < 0.05$ compared with baseline.

Table 4. Causes of deaths.

	NODAT (n = 44)	Non-NODAT (n = 74)
Total deaths	19	16
Cardiovascular	3	6
Infection	5	5
Malignancy	5	2
Other	6	3

were included in the univariate analysis – age, gender, BMI, type of CNI, steroid use (yes or no), AR within 3 months, fasting triglycerides, fasting glucose tolerance (NFG or IFG), fasting insulin and insulin indices (IR-HOMA, HOMAsec & McAuley's Index). In both univariate and multivariate analysis, only age (OR 1.04, 95% CI 1.005–1.084) and IFG (OR 2.97, 95% CI 1.009–8.733) were significant predictors.

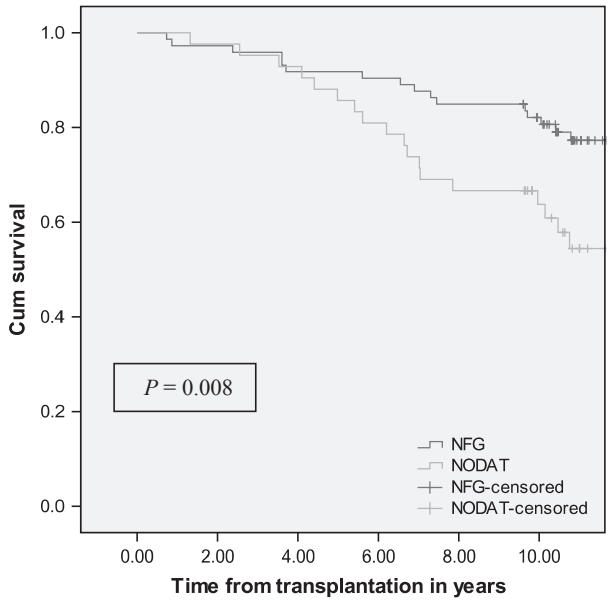

Figure 1 Kaplan–Meier estimates of patient survival in recipients with NODAT and those who remained nondiabetic in the first year after transplantation.

Survival analysis

During follow-up, 35 patients died (30%). All-cause mortality was higher in the NODAT group (44%) compared with that in the nondiabetic group (22%, P = 0.01). Causes of death were known in all patients and are shown in Table 4. There was no difference in death rates because of cardiovascular when compared with other causes (P = 0.3). There was also no difference in the proportion of cardiovascular deaths between the two groups (P = 0.4).

Figure 1 shows the Kaplan–Meier estimates for patient survival in patients with and without NODAT in the first year after transplantation. Patients with NODAT had significantly worse survival after a median follow-up of 11 years (log-rank test P = 0.008). It is worth noting that the survival curves in Fig. 1 start to diverge after only about 4 years post-transplantation.

Cox's proportional hazards regression analysis was performed to analyse variables correlated with decreased survival (Table 5). In univariate analysis, the following variables were associated with decreased survival: higher age at transplant, higher S. creatinine at 12 months, NODAT within 3 months and NODAT within 12 months. On multivariate analysis, age, S. creatinine at 12 months and NODAT within 3 months were significant factors. Other variables that did not correlate significantly with patient survival included gender, pretransplant FPG, FPG at 3 and 12 months, IR-HOMA at baseline or 3 months, BMI at baseline or 12 months, AR, prednisolone use at 3 or 12 months and cumulative methylprednisolone dose.

Discussion

Using simple and validated indices of insulin sensitivity and secretion, we have demonstrated increasing insulin resistance and a lack of compensatory increase in insulin secretion in patients who developed NODAT following renal transplantation. However, insulin indices calculated pretransplantation or early post-transplantation were not associated with the development of NODAT. We also found that NODAT developing within 1 year of transplantation decreased the probability of long-term patient survival.

Table 5. Cox's proportional hazards regression model for all-cause mortality.

	Univariate			Multivariate		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Recipient age (per year)	1.07	1.04–1.10	<0.001	1.06	1.02–1.09	0.001
NODAT in 3 months* (yes)	2.52	1.27–5.01	0.008	2.26	1.08–4.73	0.03
NODAT in 1 year (yes)	2.24	1.16–4.32	0.016	1.67	0.82–3.38	0.17
S. creatinine at 12 months (per μmol/l)	1.007	1.004–1.009	<0.001	1.007	1.004–1.01	<0.001

*Entered into multivariate model without "NODAT in 1 year".
CI, confidence interval.

Changes in insulin resistance and secretion that occur after renal transplantation have been previously described using complex techniques such as the short insulin tolerance test [8], clamp methods [9] and oral glucose tolerance test [20, 21]. These methods are time consuming, invasive and not practical for large-scale studies or routine clinical use. Using insulin indices such as those calculated from HOMA have an advantage of being simple and easy to use. Our findings on changes in insulin parameters detected using HOMA are consistent with other studies that have used gold-standard techniques to measure insulin resistance and secretion [21, 22]. Although a decline in insulin secretion has been shown consistently in patients developing NODAT, the evidence for increasing insulin resistance is conflicting. Nam *et al.*, using the insulin sensitivity index derived from the short insulin tolerance test, found that in comparison to pretransplantation, there was an improvement in insulin sensitivity 9 to 12 months after transplantation in patients who remained normoglycaemic as well as in those who developed NODAT [8]. Sato *et al.*, using a modified euglycaemic hyperinsulinaemic clamp technique, found no improvement in insulin sensitivity at 5 weeks after transplantation in patients treated with either cyclosporin or tacrolimus [23]. In contrast, Hornum *et al.* demonstrated deterioration in insulin sensitivity (calculated from an OGTT) by 12 months post-transplantation [24].

In this study, we found that in patients who maintained normoglycaemia, insulin resistance remained relatively stable, whereas in those who developed NODAT, insulin resistance increased in the first year compared with pretransplantation. As insulin resistance and secretion share a hyperbolic relationship with each other [25], a lack of increase in insulin secretion in patients with NODAT in the presence of increasing insulin resistance suggests pancreatic beta-cell deficiency. This is particularly evident by 12 months post-transplantation when HOMAsec is significantly lower in NODAT patients compared with those without NODAT (Table 2). We found an early increase in insulin resistance in KTRs with AR who developed NODAT, in contrast to a later increase in resistance in those without AR who developed NODAT (Tables S2 and S3). These results are interesting and support the hypothesis that AR and steroid treatment lead to an increase in insulin resistance and thus NODAT in the absence of a corresponding increase in insulin secretion. However, it has to be noted that this is based on a subgroup analysis and the results have to be interpreted with caution.

In the general population, insulin resistance and insulin secretion calculated by HOMA have been shown to predict the future development of type 2 DM [12, 13]. However, in one large epidemiological study in Korea, HOMA secretion index did not predict the development of diabetes [14]. In this study, pretransplant insulin resistance and secretion did not differ between the patients who went on to develop NODAT and those who remained nondiabetic. Also, a high IR-HOMA or low HOMAsec at either baseline or 3 months post-transplantation was not associated with the development of NODAT. There are a few possible explanations for this negative result. First, this study may have been underpowered to identify the indices as potential risk factors, but the lack of even a trend towards an association, and the fact that median pretransplant IR-HOMA was in fact numerically lower in the NODAT group, makes this less likely. Second, HOMA equation used to calculate IR-HOMA and HOMAsec contains plasma glucose and insulin. IR-HOMA and insulin level were almost perfectly correlated ($r = 0.98$). As the level of plasma glucose (as IFG) but not insulin was a significant factor associated with the development of NODAT, including IR-HOMA in the regression analysis only decreases the effect of glucose. Therefore, insulin resistance and secretion as estimated by HOMA may not predict NODAT. The effects of renal transplantation and immunosuppression on insulin resistance in individual patients are variable. In other words, insulin resistance might have changed after transplantation, thus modulating the risk of NODAT.

The incidence of NODAT was 37% in the first year post-transplantation. This incidence is higher compared with that reported by other studies randomizing KTRs to receive either cyclosporin or tacrolimus [26–28]. Disparities in CNI doses and methodological variations in diagnosing NODAT most likely account for the difference in the incidences of NODAT. We identified NODAT by using FPG measured in the outpatient clinic and by the use of pharmacological therapy (all patients on pharmacological therapy also had high fasting glucose levels). As a result, we labelled as diabetic even those patients who had a FPG $\geq$ 7.0 mmol/l but did not require pharmacological therapy for diabetes, unlike other studies. Furthermore, the mean age of recipients in this study (48 years) was higher than that reported in other studies (means ranging from 39 to 46.5), as was the BMI (mean 26.2 in this study compared to 23.5 to 25.6 in others) [26–28]. Higher age and BMI may account for the higher incidence of NODAT in this study.

Similar to the finding in the DIRECT study, we noticed that NODAT appeared to be more severe in patients treated with tacrolimus; all nine patients needing pharmacological therapy for NODAT were on tacrolimus. Although a higher proportion of patients randomized to tacrolimus compared with cyclosporin developed NODAT, this was not found to be statistically different. As development of NODAT was not an end-point in the original randomized study, this study may have been underpowered to detect differences in incidence of NODAT between tacrolimus and cyclosporin groups. In tacrolimus-treated patients, IR-HOMA was

significantly higher at 3 and 12 months compared with baseline, whereas this was not the case in cyclosporin-treated patients (Table 3). Despite this increase in IR-HOMA in tacrolimus-treated patients, there was no corresponding increase in HOMAsec. One would expect an increase in insulin secretion to compensate for an increase in insulin resistance. This lack of increase in HOMAsec suggests pancreatic beta-cell deficiency presumably as a result of the effect of tacrolimus on beta-cells. Hecking *et al.* have demonstrated that in tacrolimus-treated patients, basal insulin therapy may be a simple and safe intervention to confer beta-cell protection early after transplantation [29].

In this study, we have also demonstrated a worse long-term patient survival in KTRs who developed NODAT early after transplantation. After 11 years follow-up, recipients who remained normoglycaemic in the first year had much better survival rates than those who developed NODAT within this period. Using fasting glucose values to diagnose diabetes is important as our results indicate that even NODAT that may not require pharmacological therapy is detrimental to long-term patient survival. A study by Cosio *et al.* showed that a high plasma glucose level at 1 year after renal transplantation increased the risk of adverse cardiovascular events but was not related to long-term patient survival [30]. In this study, the presence of NODAT at 3 or 12 months but not FPG level itself was significantly associated with mortality. Because of small numbers, we were not able to demonstrate an association between NODAT and death because of cardiovascular causes. The mortality associated with early NODAT in this study could be speculated to be a reflection of over-immunosuppression, causing death by infection and malignancy in addition to CV causes. However, we did not see any association between mortality and AR, prednisolone use at 1 year or cumulative dose of methylprednisolone in the multivariate Cox analysis.

Our finding of a lack of association between NODAT and cardiovascular mortality is in contrast to that reported by Hjelmesaeth *et al.* [3]. In their study, cardiovascular mortality in KTRs with NODAT (20%) was higher than that in nondiabetic recipients (8%, $P = 0.058$). Although not statistically significant, there was a clear trend towards higher cardiovascular mortality in KTRs with NODAT. As they used OGTT in addition to fasting glucose to diagnose diabetes compared with only fasting glucose in this study, the difference in cardiovascular mortality in the two studies may be a reflection of the adverse effect of postprandial hyperglycaemia. Nevertheless, the factors we found significantly associated with death [increased age, chronic kidney disease (high creatinine level) and diabetes (NODAT)] are also the traditional CV risk factors.

The strengths of this study include the long duration of follow-up, use of fasting rather than random metabolic parameters and the use of WHO criteria for the diagnosis of diabetes. This study has certain limitations. First, OGTT was not performed prior to transplantation. This may have led to underestimation of the burden of type 2 DM at baseline and over-estimation of early NODAT because of unravelling of previously undiagnosed type 2 DM. A similar issue may have arisen post-transplantation by using FPG rather than an OGTT. Second, the relationship between GFR, glucose and insulin levels is complex [31]. HOMA equations contain FPG and insulin measurements. Therefore, using HOMA to estimate insulin resistance and secretion in patients with renal disease may be simplistic, but is the most practical method to avoid more invasive tests. However, these indices have been validated in dialysis patients and KTRs. Finally, homeostatic techniques such as HOMA may not accurately reflect the prevailing levels of insulin resistance and secretion. We speculate that dynamic methods such as the OGTT-derived Insulin Sensitivity Index may yield more accurate measurements of insulin sensitivity and thus give rise to differing results [32].

In conclusion, using validated indices, we have demonstrated a lack of an appropriate insulin secretory response in the face of increasing insulin resistance in patients developing NODAT in the first year after renal transplantation. However, these indices measured pretransplantation or 3 months after transplantation were not able to predict the development of NODAT. However, traditional risk factors for diabetes such as higher age and IFG remained significant risk factors for NODAT. Development of early NODAT was associated with decreased patient survival. These findings emphasize the importance of early and frequent screening to identify those at risk of progression to NODAT so that timely interventions can be initiated to reduce this risk.

Authors contributions

PN: designed the research, performed the research, analysed data and wrote paper; VR: analysed data and wrote paper; GM-S: designed the research, performed the research and analysed data; KB: designed the research, performed the research, analysed data and wrote paper.

Funding

The authors have declared no funding.

References

1. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; **3**: 178.

2. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM. Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. *Kidney Int* 2002; **62**: 1440.
3. Hjelmesaeth J, Hartmann A, Leivestad T, *et al.* The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. *Kidney Int* 2006; **69**: 588.
4. Sharif A, Baboolal K. Risk factors for new-onset diabetes after kidney transplantation. *Nat Rev Nephrol* 2010; **6**: 415.
5. Chakkera HA, Weil EJ, Swanson CM, *et al.* Pretransplant risk score for new-onset diabetes after kidney transplantation. *Diabetes Care* 2011; **34**: 2141.
6. Caillard S, Eprinchard L, Perrin P, *et al.* Incidence and risk factors of glucose metabolism disorders in kidney transplant recipients: role of systematic screening by oral glucose tolerance test. *Transplantation* 2011; **91**: 757.
7. Sharif A, Moore R, Baboolal K. Influence of lifestyle modification in renal transplant recipients with postprandial hyperglycemia. *Transplantation* 2008; **85**: 353.
8. Nam JH, Mun JI, Kim SI, *et al.* beta-Cell dysfunction rather than insulin resistance is the main contributing factor for the development of postrenal transplantation diabetes mellitus. *Transplantation* 2001; **71**: 1417.
9. Ekstrand AV, Eriksson JG, Gronhagen-Riska C, Ahonen PJ, Groop LC. Insulin resistance and insulin deficiency in the pathogenesis of posttransplantation diabetes in man. *Transplantation* 1992; **53**: 563.
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412.
11. McAuley KA, Williams SM, Mann JI, *et al.* Diagnosing insulin resistance in the general population. *Diabetes Care* 2001; **24**: 460.
12. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996; **19**: 1138.
13. Song Y, Manson JE, Tinker L, *et al.* Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. *Diabetes Care* 2007; **30**: 1747.
14. Sung KC, Reaven GM, Kim SH. Utility of homeostasis model assessment of beta-cell function in predicting diabetes in 12,924 healthy Koreans. *Diabetes Care* 2009; **33**: 200.
15. Sharif A, Ravindran V, Moore RH, *et al.* Insulin resistance indexes in renal transplant recipients maintained on tacrolimus immunosuppression. *Transplantation* 2010; **89**: 327.
16. Oterdoom LH, de Vries AP, van Son WJ, *et al.* Validation of insulin resistance indexes in a stable renal transplant population. *Diabetes Care* 2005; **28**: 2424.
17. Shoji T, Emoto M, Nishizawa Y. HOMA index to assess insulin resistance in renal failure patients. *Nephron* 2001; **89**: 348.
18. Crutchlow MF, Robinson B, Pappachen B, *et al.* Validation of steady-state insulin sensitivity indices in chronic kidney disease. *Diabetes Care* 2007; **30**: 1813.
19. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 1998; **15**: 539.
20. Bergrem HA, Valderhaug TG, Hartmann A, Bergrem H, Hjelmesaeth J, Jenssen T. Glucose tolerance before and after renal transplantation. *Nephrol Dial Transplant* 2009; **25**: 985.
21. Hjelmesaeth J, Hagen M, Hartmann A, Midtvedt K, Egeland T, Jenssen T. The impact of impaired insulin release and insulin resistance on glucose intolerance after renal transplantation. *Clin Transplant* 2002; **16**: 389.
22. Ravindran VK, Moore RH, Dunseath G, Luzio SD, Owens DR, Baboolal K. Insulin hyposecretion in nondiabetic, tacrolimus-treated renal transplant recipients more than 6 months posttransplantation. *Transplantation* 2009; **87**: 1870.
23. Sato T, Inagaki A, Uchida K, *et al.* Diabetes mellitus after transplant: relationship to pretransplant glucose metabolism and tacrolimus or cyclosporine A-based therapy. *Transplantation* 2003; **76**: 1320.
24. Hornum M, Jorgensen KA, Hansen JM, *et al.* New-onset diabetes mellitus after kidney transplantation in Denmark. *Clin J Am Soc Nephrol* 2010; **5**: 709.
25. Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes* 2002; **51**(Suppl. 1): S212.
26. van Duijnhoven EM, Christiaans MH, Boots JM, Nieman FH, Wolffenbuttel BH, van Hooff JP. Glucose metabolism in the first 3 years after renal transplantation in patients receiving tacrolimus versus cyclosporine-based immunosuppression. *J Am Soc Nephrol* 2002; **13**: 213.
27. Vincenti F, Friman S, Scheuermann E, *et al.* Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 2007; **7**: 1506.
28. David-Neto E, Lemos FC, Fadel LM, *et al.* The dynamics of glucose metabolism under calcineurin inhibitors in the first year after renal transplantation in nonobese patients. *Transplantation* 2007; **84**: 50.
29. Hecking M, Haidinger M, Doller D, *et al.* Early basal insulin therapy decreases new-onset diabetes after renal transplantation. *J Am Soc Nephrol* 2012; **23**: 739.
30. Cosio FG, Kudva Y, van der Velde M, *et al.* New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. *Kidney Int* 2005; **67**: 2415.
31. Sharif A, Ravindran V, Moore RH, *et al.* Complex interplay between insulinemia, glycemia, and glomerular filtration rate in nondiabetic renal transplant recipients. *Transplantation* 2009; **88**: 290.
32. Hjelmesaeth J, Midtvedt K, Jenssen T, Hartmann A. Insulin resistance after renal transplantation: impact of immunosuppressive and antihypertensive therapy. *Diabetes Care* 2001; **24**: 2121.