Original Article

Incidence and Risk Factors for Development of New-onset Diabetes after Kidney Transplantation

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Abstract

Introduction: New-onset diabetes after transplantation (NODAT) is an increasingly recognised metabolic complication of kidney transplantation that is associated with increased morbidity and mortality. This study aimed to determine the incidence of NODAT and identify risk factors for development of NODAT among kidney allograft recipients in a single centre. Materials and Methods: We retrospectively reviewed all kidney allograft recipients in our centre between 1998 and 2007. NODAT were determined using criteria as per American Diabetes Association guidelines. Logistic regression analyses were performed to identify predictors of NODAT. Results: Among 388 patients included in the analysis, NODAT was reported in 94 patients (24.2%) after a median follow-up time of 52.1 months. The cumulative incidence of NODAT was 15.8%, 22.8% and 24.5% at 1, 3, and 5 years following transplantation. Seven clinical factors were independent predictors of NODAT: older age, HLA B13 and B15 phenotypes, use of sirolimus, acute rejections, higher pre-transplant and post-transplant (day 1) plasma glucose levels. Patients with NODAT had poorer outcomes in both graft and patient survival. Conclusion: Our study demonstrates a significant risk and burden of NODAT in an Asian transplant population. Risk stratification and aggressive monitoring of blood glucose early post-transplantation is necessary to identify high-risk patients so that appropriate tailoring of immunosuppression and early institution of lifestyle modifications can be implemented.

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Key words: Diabetes mellitus, Immunosuppression, Kidney transplantation, Metabolic complication, Sirolimus

Introduction

The development of new-onset diabetes after transplantation (NODAT) is a serious metabolic complication of kidney transplantation that predisposes patients to graft dysfunction, cardiovascular disease and death.[1,2] Although NODAT has been recognised for many years, the true incidence has been difficult to establish due to inconsistencies in the definition of diabetes mellitus employed in clinical studies, and estimates vary widely from 2% to 50% in the first post-transplant year.[3] In recent years, clinicians have adopted the strict definitions of diabetes mellitus defined by American Diabetes Association (ADA) in an attempt to better define the incidence of this disorder.[4] Several risk factors have been shown to be independent predictors of NODAT. These include older age, higher body mass index, ethnicity, hepatitis C positive patients and the use of tacrolimus.[1] Identifying high-risk patients based on these factors may improve long-term outcome by allowing tailoring of immunosuppression and early institution of lifestyle modifications.

The first kidney transplant in Singapore took place in 1970 in our hospital.[5] Since then, more than 1000 patients have been successfully transplanted in our centre. However, local data on the incidence of NODAT remain unknown. The aim of this study was to determine the incidence of NODAT among kidney allograft recipients in our centre and to evaluate potential risk factors for the development of NODAT in an Asian transplant population.

Materials and Methods

This is a single centre retrospective review of solitary kidney allograft recipients transplanted in our hospital between 1 January 1998 and 31 December 2007. A total of 432 patients were transplanted during this 10-year period. Three hundred and eighty-eight patients were eligible for

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the study. Reasons for exclusion were pre-existing diabetes mellitus (n = 16), death within the first 2 weeks after transplantation (n = 3), graft loss within the first 2 weeks after transplantation (n = 10), and follow-up duration of less than 6 months (n = 15).

Data were collected retrospectively from transplant charts and electronic medical records (EMR) according to institutional ethical guidelines. Pre-transplant information obtained from the patients included age at transplantation, gender, ethnicity, height, weight, calculated body mass index, time in renal replacement therapy, type of renal replacement therapy, hepatitis C status at time of transplant, human leukocyte antigen (HLA) phenotype, total number of HLA mismatches, donor type, age and gender. Post-transplant information included type of immunosuppressive drugs that was started after transplantation (intention-to-treat), acute rejections, cytomegalovirus infection status, duration of follow-up and duration of graft and patient survival. We also collected data on the random plasma glucose (RPG) level 1 day prior to transplantation and fasting plasma glucose (FPG) levels 1 and 5 days post-transplantation.

A diagnosis of NODAT was made in patients who after the first 2 weeks post-transplant had at least 2 abnormal glucose levels (i.e. RPG levels ≥11.1 mmol/L and/or FPG levels ≥7.0 mmol/L) taken on separate occasions, as per published ADA guidelines. Chart and EMR review of all available plasma glucose levels were completed for purpose of diagnosing NODAT. The types of treatment administered for NODAT (at diagnosis and 6 months later) and the HbA1c measured upon the diagnosis of NODAT were also recorded.

All patients received corticosteroids, beginning with a single preoperative intravenous bolus of 1g hydrocortisone, followed by 30 mg/day of prednisolone per oral post-transplant, with gradual tapering to 10 to 15 mg/day prednisolone by the third month. Besides corticosteroids, standard immunosuppression consisted of a calcineurin inhibitor (e.g. cyclosporine or tacrolimus) and anti-proliferative agents (azathioprine or mycophenolate mofetil). Mammalian target of rapamycin (mTOR) inhibitor (e.g. sirolimus) was used selectively in patients with high immunologic risk. The local protocol for treating clinically suspected or biopsy proven acute rejection was 3 pulses of 500 mg intravenous methylprednisolone.

Statistical Analysis

Results were expressed as mean ± standard deviation or median and range. Categorical variables were compared using chi-squared test. Continuous variables were compared using Students t-test or Mann-Whitney U-test. Predictors of NODAT were determined by logistic regression analysis. The results were expressed as hazard ratios (HR), 95% confidence intervals (CI) and P values. After a number of univariate prognostic factors had been determined, forward stepwise selection was carried out to determine the appropriate multivariate model. Factors selected for the multivariate model were those found significant in the univariate model (P <0.05). Graft and patient survival were calculated using Kaplan-Meier survival curves after censoring for patient death and graft loss respectively and log rank test was used to compare survival curves. All statistical analyses were carried out using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). Results were considered statistically significant for P <0.05.

Results

Patient Characteristics

Three hundred and eighty-eight kidney allograft recipients were included in the analysis. The mean age at transplantation was 43.2 years and 50.3% of the patients were male. The percentage of patients in the 3 major ethnic groups was as follow: 82.7% Chinese, 12.9% Malay and 3.1% Indian. Of the 388 patients, 76.5% received their kidney allograft from a deceased donor and 7 patients (1.8%) were second transplants. The median time in renal replacement therapy was 84.8 months (range, 0 to 488.2), with 95.4% of patients receiving haemodialysis. Only 5 (1.3%) patients had pre-emptive kidney transplants.

Incidence of NODAT

NODAT was reported in 94 of 388 recipients (24.2%) after a median follow up time of 52.1 months. The cumulative incidences of NODAT after 1, 3, and 5 years post-transplantation were 15.8%, 22.8% and 24.5%, respectively. The median time to diagnosis of NODAT was 4.3 months (range, 0.5 to 112.5 months). Table 1 compared patients who developed NODAT with those who did not. There were no statistically significant differences in the incidence of NODAT between the ethnic groups. Patients who developed NODAT were significantly older, more likely to have HLA B13, B15 and DR5 phenotypes and more likely to have received kidney allografts from deceased and male donors. They also had higher RPG levels 1 day prior to transplantation and higher FPG levels 1 and 5 days post-transplantation.

In our cohort, 9.0% of patients received tacrolimus as the calcineurin inhibitor of choice as compared with 86.3% who received cyclosporine. NODAT was reported in 37.1% of patients treated with tacrolimus compared to 23.0% of cyclosporine-treated patients, although this did not reach statistical significance (P = 0.06). Sirolimus

Table 1. Comparison of Patients with Developed NODAT to Those without NODAT

	NODAT	No NODAT	*P* value
Number	94	294	
Age (years)	46.8 ± 7.5	42.0 ± 9.7	<0.001
Gender (% male)	45.7	51.7	0.32
Weight (kg)	57.2 ± 12.0	56.9 ± 12.6	0.85
BMI (kg/m^2)	22.2 ± 4.2	21.8 ± 4.2	0.47
Race (%)			
Chinese	83.0	82.7	0.79
Malay	12.8	12.9	
Indian	2.1	3.4	
Others	2.1	1.0	
Pre-transplant characteristics			
Renal replacement therapy			
Haemodialysis	94.7	95.6	0.22
Peritoneal dialysis	5.3	2.7	
Pre-emptive	0	1.7	
Duration of renal replacement therapy (mths)	88.7 ± 62.6	81.4 ± 61.2	0.33
HLA phenotypes (%)			
HLA B13	20.4	12.3	0.05
HLA B15	30.1	16.0	0.003
HLA DR5	45.2	30.0	0.007
HLA mismatches	2.8 ± 1.2	2.6 ± 1.4	0.21
Positive hepatitis C status (%)	4.3	3.4	0.75
Type of transplant (%)			
Live	14.9	26.2	0.02
Deceased	85.1	73.8	
Donor age (years)	42.2 ± 11.7	42.1 ± 11.6	0.98
Donor gender (% male)	72.0	56.5	0.008
Post-transplant characteristics			
Cyclosporin (%)	81.9	87.8	0.15
Tacrolimus (%)	13.8	7.5	0.06
Sirolimus (%)	14.9	7.5	0.03
Azathioprine (%)	35.1	37.8	0.64
Mycophenolate (%)	52.1	52.7	0.92
Acute rejection (%)	44.1	31.6	0.03
Positive CMV infection (%)	51.2	37.3	0.02
Plasma glucose (mmol/L)			
Day -1 (random)	5.8 ± 1.4	5.5 ± 1.2	0.04
Day 1 (fasting)	8.1 ± 1.6	7.3 ± 1.2	<0.001
Day 5 (fasting)	5.6 ± 1.1	5.2 ± 1.3	0.01

NODAT: new onset diabetes after transplant; BMI: body mass index; HLA: human leukocyte antigen; CMV: Cytomegalovirus.

was used in 36 (9.3%) patients, out of which 17 patients received cyclosporine-sirolimus combination. Significantly more patients who were treated with sirolimus developed NODAT (38.9%) compared to those not given this immunosuppressant (22.7%) ($P = 0.03$). In addition, the use of cyclosporine-sirolimus combination resulted in 52.9% of patients developing NODAT (52.9%) compared to 21.4% of those receiving a cyclosporine-only regimen (21.4%)

($P = 0.003$). Pulsed methylprednisolone was administered at least once to 34.5% of patients for clinically suspected or biopsy proven acute rejections. Patients who had acute rejections were more likely to develop NODAT compared to those without acute rejections ($P = 0.03$).

Of the 94 patients with NODAT, 54.2% required treatment with either oral hypoglycemic agents (40.4%) or insulin (13.8%) at diagnosis. Hence the incidence of treatment-requiring NODAT in this cohort was 13.1%. There was no difference in age, gender, ethnicity, BMI and pre- and post-transplant glucose levels of patients who required medications compared with those who required diet only. However, the HbA1c in those treated with medications was significantly higher than those treated with diet only (10.3% vs 6.2%, $P < 0.001$). The median HbA1c after diagnosis of NODAT was 8.2% (range, 4.8% to 17.5%). The percentage of patients with NODAT still requiring medications at 6 months after diagnosis dropped to 47.3%.

Risk Factors for NODAT

Table 2 shows the factors associated with the development of NODAT according to univariate logistic regression analysis. Factors that proved to be significant by univariate analysis were entered into a multivariate model. FPG day 1 post-transplant was used instead of day 5 as this was a stronger predictor by univariate analysis. Multivariate analysis demonstrated seven factors as independent predictors of NODAT (Table 3). These factors were older age, having HLA B13 or B15 phenotypes, use of sirolimus, acute rejections, higher RPG pre-transplant and higher FPG day 1 post-transplant.

Figure 1 shows the effect of age and FPG day 1 post-transplant on the incidence of NODAT. NODAT developed in 12.8% of patients <45 years with FPG day 1 <7.0 mmol/L compared to 41.8% of patients ≥45 years with FPG day 1 ≥7.8 mmol/L.

Graft and Patient Survival

Overall graft survival (censored for death) at 1-, 5- and 10-year post-transplant was 97.2%, 92.9% and 84.3%, respectively. Figure 2 shows the graft survival rates (censored for death) according to diabetes status. There

Table 2. Predictors of NODAT Defined by Univariate Analysis

Variable	Hazard ratio	95% CI	*P* value
Age (year)	1.06	1.03 – 1.09	<0.001
BMI at transplant (≥23 vs <23)	1.71	1.03 – 2.84	0.04
Type of transplants (deceased vs live)	2.03	1.09 – 3.79	0.03
HLA B13 (yes vs no)	1.83	0.99 – 3.38	0.05
HLA B15 (yes vs no)	2.26	1.31 – 3.88	0.003
HLA DR5 (yes vs no)	1.92	1.19 – 3.10	0.008
Sirolimus (yes vs no)	2.16	1.06 – 4.42	0.03
Acute rejection (yes vs no)	1.70	1.06 – 2.75	0.03
CMV infection (yes vs no)	1.76	1.08 – 2.87	0.03
RPG day -1 (pre-transplant) (mmol/L)	1.21	1.01 – 1.45	0.04
FPG day 1 post-transplant (mmol/L)	1.55	1.29 – 1.85	<0.001
FPG day 5 post-transplant (mmol/L)	1.24	1.04 – 1.49	0.02

BMI: body mass index; HLA: human leukocyte antigen; CMV: cytomegalovirus; RPG: random plasma glucose; FPG: fasting plasma glucose; CI: confidence interval

Table 3. Independent Predictors of NODAT Defined by Multivariate Analysis

Variable	Hazard ratio	95% CI	*P* value
Age (year)	1.05	1.02 – 1.09	0.002
HLA B13 (yes vs no)	2.38	1.20 – 4.72	0.02
HLA B15 (yes vs no)	2.48	1.33 – 4.61	0.004
Sirolimus (yes vs no)	2.36	1.04 – 5.39	0.04
Acute rejection (yes vs no)	2.17	1.24 – 3.83	0.007
RPG day -1 (pre-transplant) (mmol/L)	1.37	1.11 – 1.68	0.003
FPG day 1 post-transplant (mmol/L)	1.46	1.19 – 1.79	< 0.001

HLA: human leukocyte antigen; RPG: random plasma glucose; FPG: fasting plasma glucose; CI: confidence interval

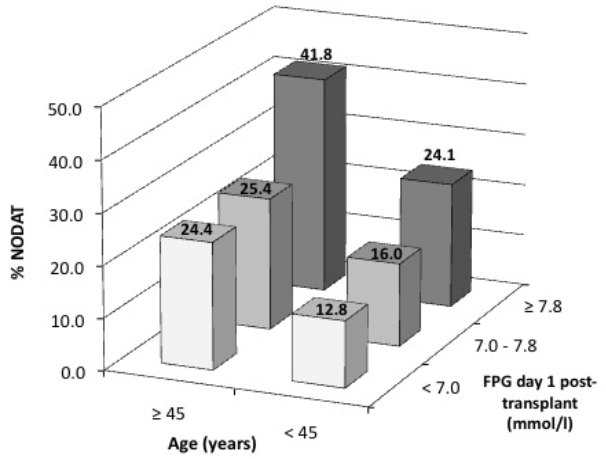

Fig. 1. Incidence of NODAT according to age and fasting plasma glucose (FPG) day 1 post-transplant.

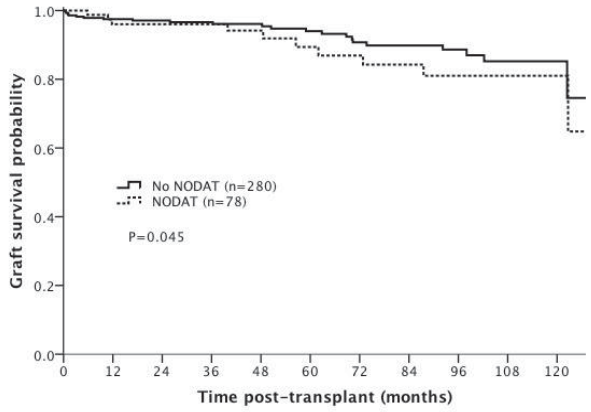

Fig. 2. Graft survival (censored for death) according to diabetes status.

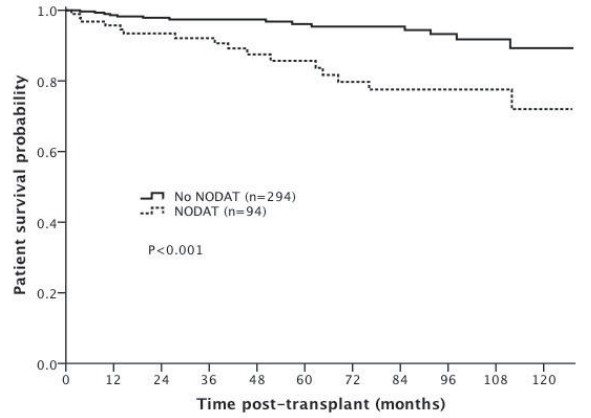

Fig. 3. Patient survival according to diabetes status.

was a significant difference in graft survival ($P = 0.045$) between those with NODAT and those without. One-, 5- and 10-year graft survival was 96.0%, 89.4% and 81.0% for those with NODAT compared to 97.5%, 94.0% and 85.2% for those without diabetes.

Overall patient survival at 1-, 5-, and 10-year post-transplant was 97.9%, 93.4% and 84.7%, respectively. Figure 3 shows patient survival rates according to diabetes status. Similarly, there was a significant difference in patient survival between the 2 groups ($P < 0.001$). One-, 5- and 10-year patient survival was 95.7%, 85.7% and 72.0% for those with NODAT compared to 98.6%, 96.1% and 89.3% for those without diabetes. Among the patients with NODAT, there was no difference in graft and patient survival between those patients treated with medications and those on dietary control.

Discussion

In our study of kidney transplant recipients over a 10-year period, NODAT was found in 94 (24.2%) patients and the 1-year cumulative incidence was 15.8%. Among the potential risk factors, older age, HLA B13 and B15 phenotypes, use of sirolimus, acute rejections, higher pre-transplant and post-transplant (day 1) plasma glucose levels were independent predictors of NODAT. We also showed that patients who developed NODAT had increased graft failure and mortality compared to those who did not have NODAT.

In recent years, increasing attention has been drawn to the importance of NODAT as a disease entity in kidney allograft recipients. A meta-analysis of studies showed that the cumulative incidence of NODAT at 1 year post-transplantation varied from 2% to 50%.[3] This wide estimate was largely due to the various definitions of NODAT used in the studies. Some studies relied solely on the use of hypoglycemic agents as diagnostic criteria for NODAT and we have shown that this is inaccurate as 45.8% of our patients with NODAT did not receive hypoglycemia agents. More recently, studies using uniform criteria for diagnosing NODAT as per ADA guidelines showed that the cumulative incidence of NODAT at 1 year ranged from 7.0% to 19.0%.[6-9] In our study, the 15.8% cumulative incidence at 1 year is thus comparable to other transplant centres.

NODAT was particularly accelerated in the first few post-transplant months as shown by the median time to diagnosis of 4.3 months in this study. Thereafter, the number of patients developing NODAT increased progressively over time. This is consistent with other published reports.[8,10] Collectively, these results showed that there are 2 distinct periods of development of NODAT. The first (high-risk) period comprises the first 6 months post-transplant, reflecting

acute superimposition of transplant-associated factors on the underlying baseline risk. The second comprises the rest of the post-transplant time when there is a continuous increase in the number of patients with NODAT.

Old age has consistently been shown to be an important contributing factor to the development of NODAT,[10-13] particularly in patients over the age of 40. This is perhaps not surprising considering the influence of age on the incidence of diabetes mellitus in the general population.[14] We have observed a similar relationship between age and NODAT in our cohort. Hjelmesaeth el al[15] reported that older age is an important determinant of β-cell dysfunction after renal transplantation. They showed that increasing age was strongly and independently associated with a blunted insulin secretory response. It is also plausible that older patients are likely to be more susceptible than younger patients to equal doses of immunosuppressive agents.

A higher incidence of NODAT has been associated with certain HLA phenotypes including HLA A28,[16] A30, B42,[12] B8,[17] and B27.[18] However, these associations were not seen in our study. Furthermore, we found no increased frequency of HLA DR3 or DR4, which is known to confer susceptibility for type 1 diabetes mellitus, nor decreased frequency of the protective HLA DR2 phenotype. Instead, HLA B13 and HLA B15 phenotypes were found to be independent predictors of NODAT. We did not detect any significant difference in the prevalence of these 2 phenotypes among the 3 ethnic groups. These 2 HLA phenotypes have not previously been shown to be associated with NODAT and warrant further investigation in a larger cohort. However, we do recognise the possibility that the high numbers of HLA phenotypes investigated in a relatively small population may have resulted in statistical significance merely by chance.

Evidence from systematic review suggests that immunosuppressive medications account for 74% of the variability in the incidence of NODAT.[3] Corticosteroids and calcineurin inhibitors have both been well elucidated as contributory to development of NODAT whereas azathioprine and mycophenolate mofetil do not seem to influence glucose control. Recently, the formerly assumed beneficial impact of mTOR inhibitors on glucose metabolism has been questioned.[19] Our data showed that the use of sirolimus independently predicted NODAT. Several studies supported our finding. Using the United States Renal Data System (USRDS) database, sirolimus was found to be independently associated with NODAT among 20,124 adult kidney transplant recipients.[20] Romagnoli et al[21] reported in their retrospective study that patients treated with a combination of sirolimus and cyclosporine had a significantly higher incidence of NODAT compared with patients treated with cyclosporine alone. Hence, individualisation of immunosuppressive therapy is an important modifiable risk factor for NODAT.

Previous studies have shown that acute rejections were independently predictive of NODAT development and this is likely due to the inherent nature of relationship between corticosteroids and hyperglycaemia.[8,22] We have shown a similar relationship in our cohort. The principal mechanisms of corticosteroid-induced new-onset diabetes are widely believed to be increased insulin resistance and increased hepatic gluconeogenesis.[23] Furthermore, the diabetogenic effects of corticosteroids are known to be dose-related.[18] It is likely that the short-term high dose corticosteroids given to these patients during episodes of acute rejection precipitates hyperglycaemia and increase their risk of developing NODAT.

We found fasting plasma glucose levels at day 1 post-transplant predicted NODAT development. This is consistent with many other studies that reported the predictive value of plasma glucose levels in the first week post-transplant for NODAT. Cosio et al[2] analysed a database of 490 adult kidney transplant recipients from the USA and showed that development of hyperglycaemia during the first week post-transplant was statistically the strongest predictor of NODAT at one year. Joss et al[24] showed that RPG level at day 7 independently predicted development of NODAT. We recognised that plasma glucose at day 1 is likely to be influenced by the use of high dose corticosteroids and stress of surgery. However, it provides a very early indication of possible defects in glucose tolerance and should alert the physician that the patient is at high-risk of NODAT.

Notably, several well-established risk factors were found not be associated with NODAT in our study. We did not find weight or BMI to be predictors of NODAT in multivariate analysis, unlike previous studies which have shown an association of obesity with NODAT.[1,24] This is likely due to the low obesity rate in our cohort. The mean BMI in our study was 22.0 kg/m^2 and only 4.6% of patients had BMI $\geq$30 kg/m^2. The association of hepatitis C infection and NODAT was demonstrated in several studies.[1,25,26] Postulated pathophysiologic mechanisms include direct cytopathic effect of the virus on beta cells, decreased hepatic glycogenesis and insulin resistance mediated by a post-receptor signaling defect.[27] We did not find such an association in our study. This may be due to the relatively small number of patients with hepatitis C infection (3.6%) in our cohort.

Our study lends support to the strong evidence on the contribution of NODAT to reduced patient survival post-transplantation. Cosio et al[28] analysed the data from 1811 adult renal allograft recipients transplanted between 1983 and 1998 and showed that NODAT is an independent predictor of reduced patient survival. In another study, data from USRDS demonstrated that in comparison of

patients with no diabetes, NODAT was associated with an 87% increased risk of mortality (P <0.001).[1] On the contrary, the evidence on the effect of NODAT on graft survival has been conflicting. Our study, in accordance with some studies, showed a reduction in graft survival in patients with NODAT.[1,29] In particular, Kasiske et al[1] reported a 63% increased risk of graft failure (P <0.0001) and 46% increased risk of death-censored graft failure (P <0.0001) in patient with NODAT. Other studies failed to find a difference.[8,30]

This study has some limitations that have to be acknowledged. This is a retrospective analysis that is subject to reporting bias or error inherent in registry database, including the non-random assignment of patients to different immunosuppression protocols. Pre-existing glucose intolerance was not systematically assessed in this study cohort by performing pre-transplantation oral glucose tolerance test (OGTT), partly because of organisational reasons. It is possible that some of the patients who developed NODAT had pre-transplant impaired glucose tolerance. Post-transplant OGTT was not performed routinely in this study cohort to formally assess glucose tolerance, thus possibly underestimating the true incidence of NODAT.[31] Nevertheless, our analysis is based on a close follow-up of a cohort within a single transplant centre and the charts and electronic medical records were reviewed individually.

Conclusion

In conclusion, this study shows that there is a significant risk of NODAT in an Asian kidney transplant population and it is associated with worse outcomes in both graft and patient survival. NODAT is associated with risk factors present before and after kidney transplantation. Notably, the predictive value of plasma glucose levels day 1 post-transplant for NODAT highlights the importance of aggressive monitoring of blood glucose early post-transplantation so that high-risk patients can be identified. In addition, appropriate tailoring of immunosuppression and early lifestyle modifications for high-risk patients should be implemented to prevent development of NODAT.

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