Original Research Article

New onset diabetes after renal transplantation: An experience from a developing country – India

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International Archives of Integrated Medicine, Vol. 4, Issue 7, July, 2017.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 19-06-2017 **Accepted on:** 25-06-2017
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: G. Swarnalatha, K.R. Karthik, N. Bharathi, S. Raghavendra, K. Siva Parvathi, A. Deepti, T. Gangadhar. New onset diabetes after renal transplantation: An experience from a developing country – India. IAIM, 2017; 4(7): 74-82.

Abstract

New onset diabetes after transplantation (NODAT) is one of the serious side effects of immunosuppressive medications used in renal transplant recipients. Diabetes in transplantation increases the risk of cardiovascular disease and has adverse outcome on graft and patient survival. The aim of this study was to evaluate the incidence of NODAT in renal transplant recipients, the risk factors for the development of NODAT and its effect on graft and patient survival. Total 210 patients underwent renal transplantation from Jan 2010 to June 2016. Mean follow-up period after renal transplantation was 38.14 $\pm$ 20.12 months. NODAT was defined as two consecutive fasting blood glucose determinations above 126 mg/dL. Thirty five (16.66%) recipients developed NODAT, the duration of onset of NODAT was 4.22 months (range 1 month to 30 months) after transplantation. All of them required insulin treatment. NODAT disappeared in 3(8.57%) recipients with reduction in tacrolimus dose and conversion to everolimus. Cox-Regression analysis was done to estimate the hazard ratio at confidence interval to assess whether the age more than 50 years, deceased donor, induction therapy, graft dysfunction, graft rejection, tacrolimus toxicity, everolimus based immunosuppression, HCV and CMV infection were risk factors for the development of NODAT. Induction therapy and graft dysfunction had 2 fold increased risk of development of NODAT and tacrolimus toxicity had 4 fold increased risk of development of NODAT. Fungal infection (17.14% Vs 2.28%, P value 0.00) was significantly higher in NODAT group compared to recipients without

NODAT. There was no significant difference in 6 months, 1, 2, 3 and 5 years patient survival or the death censored graft survival of recipients with NODAT compared to patients without NODAT.

Key words

Diabetes, Transplantation, India.

Introduction

Renal transplantation is the treatment modality of choice for patients with end-stage renal disease (ESRD). However, the immunosuppressive drugs used in renal transplantation are associated with serious side effects like new onset diabetes after transplantation (NODAT) [1]. It is often under diagnosed due to lack of uniform screening methods and diagnostic criteria [2]. Diabetes in transplantation increases the risk of cardiovascular disease and has adverse outcome on graft and patient survival [3]. There is sparse published data on NODAT from developing country like India.

The aim of this study was to evaluate the incidence of NODAT in renal transplant recipients, the effect of immunosuppressive in the development of NODAT, the duration of onset of NODAT after renal transplantation, the risk factors for the development of NODAT in renal transplant recipients and to know the effect of NODAT on the graft survival and patient survival.

Materials and methods

This was a retrospective, observational study of patients who underwent renal transplantation from January 2010 to June 2016 at Nizams Institute of Medical Sciences, Hyderabad. Patient who were on regular follow up with minimum of 6 months were included in the study. Recipients who were lost to follow up and whose complete data was not available were excluded from the study.

All patients received 3 consecutive doses of 1 gram Intravenous Methylprednisolone (IVMP) and maintenance triple immunosuppression with Tacrolimus (0.1 mg/kg/day and if induction was given @0.08 mg/kg/d), Mycophenolate Mofetil (MMF) (600 mg/m^2/dose twice a day) and Prednisolone 20mg a day. Tacrolimus dose was tapered according to serum drug levels which were monitored on a monthly basis for 1st 6 months and as and when required subsequently. Dose of steroid was tapered from 20mg/day to 10 mg/day at end of 6 months and continued thereafter.

Induction therapy was given in spousal and deceased donor transplantation with Basiliximab (20 mg in two doses on day 0 and day 4). Patients who were given induction and anti-rejection therapy were given prophylaxis with Valgancyclovir 450 mg orally on alternate days, Fluconazole 150 mg daily and Cotrimoxazole once daily for 3 months. All the patients were followed regularly, with monthly investigations of Fasting blood sugars (FBS), post prandial bloods sugars, complete blood picture, complete urine examination, liver function test, renal function tests, lipid profile, urine culture and sensitivity, 24 hour urine proteins, hepatitis B virus (HBV) and hepatitis C virus (HCV) antibodies, renal graft doppler and DTPA renogram. Cytomegalovirus (CMV) PCR was done when patients had clinical suspicion of disease like leukopenia, pneumonia, hepatitis etc. HCV PCR was done in recipients who had hepatitis. HBA1C was done if FBS was more than 126 mg/dL.

Renal biopsy was done in patients with graft dysfunction in whom pre and post renal causes of were excluded. Findings of biopsy were documented and treated accordingly. Rejection was, defined as per Banff criteria and was treated with escalation of baseline immunosuppression and 3 doses of 1 gram IVMP. In steroid resistant cellular rejection ATG for 3-5 days @1mg/kg/d

was given. And in steroid resistant humoral rejection 5 to 6 plasmapheresis sessions and/or Rituximab (375 mg/m2) was considered.

Data of recipients who developed NODAT was collected and analyzed. The incidence of NODAT and the duration of onset of NODAT were evaluated. Data on recipient blood group, age, gender, native kidney disease, duration of dialysis, mode of dialysis, CMV status, HCV, donor details, immunosuppression protocol, change in immunosuppression prior to development of NODAT, lipid profile, graft dysfunction episodes, rejection episodes, therapy & response to rejection and infections were analyzed and compared to recipients without NODAT. The patient survival and death censored graft at 6 months, 1, 2, 3 and 5 years were analyzed and compared in both the groups.

Definitions

NODAT was defined as per ADA criteria [2] - Fasting blood glucose (FBG) ≥126 mg/dL two times; or glucose ≥200 mg/dL one time; or HbA1c ≥6.5% two times; or glucose ≥126 mg/dL and HbA1c ≥6.5% simultaneously one time.

Acute graft dysfunction: Defined as an elevation in the level of serum creatinine by more than 0.3 mg/dl or increase by 50% from the baseline.

Rejection, both cellular and antibody mediated were defined according to Banff 2013 criteria [4].

Patient survival was calculated from date of transplantation to date of death or date of last follow up. Graft survival censored for death with a functioning graft (death-censored graft survival) was calculated from the date of transplantation to the date of irreversible graft failure signified by return to long term dialysis or retransplantation.

Statistical analysis

SPSS 17 Software was used for statistical analysis. Continuous variables were expressed as mean± SD (standard deviation). Categorical variables were expressed as proportions. Cox-Regression analysis was done to estimate the hazard risk at 95% Confidence interval was done to assess the influence of various risk factors on development of NODT and patient survival and death censored graft survival. P-value < 0.05 was considered as statistically significant. Kaplan-Meier survival analysis was done to estimate graft and patient survival at, 5 years.

Results

A total of 240 patients underwent renal transplantation during this period, out of which 210 renal transplant recipients were included in the study with mean follow up period of 38.14± 20.12 months (range 6-79 months) . Others were either lost to follow up or complete data was not available. Of 210 recipients, 35 (16.66%) recipients developed NODAT with mean duration of onset of NODAT of 4.22 months (range 1month to 30 months) after transplantation. The mean age was 34.65± 10.24 years with male predominance (M: F- 1:0.34) which was not different from either the total recipient data or the recipient group without NODAT. Other baseline characteristics of recipients with NODAT and without NODAT are shown in **Table - 1**. There was no statistical difference in the baseline characteristic features in both the groups. Cox regression analysis was done to estimate the hazard ratio of the risk factors for the development of NODAT. Parameters like recipient age more than 50 years, deceased donor, induction therapy, graft dysfunction, graft rejection, tacrolimus toxicity, everolimus based immunosuppression, HCV and CMV infection were taken to analyse hazard ratio. It was found that induction therapy [HR: 2.54(0.23-28.00) P value 0.44] and graft dysfunction [HR: 2.80 (0.88-8.90) P value 0.08] had 2 fold increased risk of development of NODAT, and tacrolimus toxicity [HR : 4.35 (0.69-27.30) P value 0.11] had 4 fold increased risk of development of NODAT (**Table - 2**). Among infective complication, though sepsis, tuberculosis (TB), and fungal infection rates were higher in recipients with NODAT, it was

statistically significant only in fungal infection (17.14% Vs 2.28%, p value-0.00) compared to recipients without NODAT (**Table - 3**).

Table - 1: Base line characteristics of recipients with NODAT Vs without NODAT.

Parameter	Total (n-210)	NODAT (n=35)	Without NODAT (n=175)	P value
Mean±SD age of recipient (years)	32.56± 10.68	34.65± 10.24	31.26± 10.36	0.75
Mean±SD age of donor(years)	44.68± 10.28	45.88± 9.79	42.97± 10.31	0.13
Gender of recipient (M:F)	1:0.33	1:0.34	1:0.33	0.94
Gender of donor (F:M)	1: 0.60	1:0.75	1:0.52	0.33
Mode of RRT:HD CAPD: Preemptive (%)	192(94.5%) 11(5.41%)	30(85.71%) 3(8.5%) 2(5.7%)	162(92.5%) 9(5.14%) 4(2.28%)	0.32
Mean±SD duration of dialysis (months)	12.59± 17.68	15.11± 10.47	12.27± 16.68	0.34
Blood group -0:B:A:AB (%)	41.9:33.8:20:4.2	51.42:27.75:14.42:8.5	40:35.42:21.11:3.4	0.24
Commonest Etiology of ESRD –CGN	144(68.57%)	23(65.71%)	121(69.14%)	0.23
Donor (Live related: deceased)	176(83.80%) 34(16.19%)	28(79.95%) 7(20%)	148(84.57%) 27(15.42%)	0.50
Mean±SD duration of follow up in months	38.14 ± 20.12	35.05±19.39	38.76±21.5	0.34
Mean±SD serum creatinine (mg/dL)	1.26(0.7 to 4.8)	1.459±1.000	1.22 ±0.53	0.08

Table - 2: Risk factors for the development NODAT.

Parameter	NODAT	Without NODAT	P Value	Hazard ratio (HR)	95%-confidence Interval (CI) for HR	
					Lower	Upper
Age >50 years	3(8.57%)	7(4.0%)	0.18	0.35	0.77	1.61
Female sex	9(25.71%)	44(25.14%)	0.93	1.04	0.37	2.91
Deceased donor	7(20%)	27(15.42%)	0.56	0.50	0.52	4.97
Induction	12(34.28%)	63(36%)	0.44	2.54	0.23	28.00
Graft dysfunction	23(65.72%)	44(25.14%	0.08	2.80	0.88	8.90
Graft Rejection	7(20%)	36(20.57%)	0.35	0.40	0.60	2.75
Tacrolimus toxicity	3(8.57%)	10(5.71%)	0.11	4.35	0.69	27.30
HCV	1(2.85%)	9(5.14%)	0.90	0.87	0.09	8.01
CMV	6 (17.14%)	19(10.85)	0.79	0.86	0.29	2.54
Everolimus based immunosuppression	11(31.42%)	59(33.71%)	0.45	1.47	0.53	4.03

Table - 3: Comparison of Infection rate in recipient with NODAT Vs without NODAT.

Infections	NODAT	Without NODAT	P value
Urinary Tract Infection	9(25.71%)	53(30.28%	0.58
Fungal Infection	6(17.14%)	4(2.28%)	0.00
Respiratory infection	6(17.14%)	27(15.45%)	0.73
TB	3(8.57%)	8(4.57%)	0.33
Sepsis	6(17.14%)	12(6.85%)	0.29

Table - 4: Patient survival rates of recipients with NODAT Vs without NODAT.

Follow up period	NODAT	Without NODAT	P value	HR	95% CI for HR	
					Lower	Upper
6 months	88.57%	96.52%	0.53	0.66	0.18	2.4
1 year	87.87%	93.56%	0.29	0.58	0.21	1.60
2 year	79.31%	89.61%	0.53	0.73	0.27	1.9
3 year	72.72%	84.03%	0.29	0.63	0.27	1.4
5 year	61.11%	74.44%	0.32	0.65	0.28	1.5

Table - 5: Death censored graft survival rates of recipients with NODAT Vs without NODAT.

Follow up period	NODAT	Without NODAT	P value	HR	95% CI for HR	
					Lower	Upper
6 months	100%	88.57%	0.69	26.6	.00	2
1year	100%	87.87%	0.97	0.96	0.11	8.23
2 year	100%	79.31%	0.83	0.85	0.18	3.9
3 year	95.45%	72.72%	0.95	1.04	0.23	4.72
5 year	94.44%	61.11%	0.80	1.20	0.27	5.35

Figure - 1: Kaplan meier patient survival rate curves of recipients with NODAT compared to without NODAT.

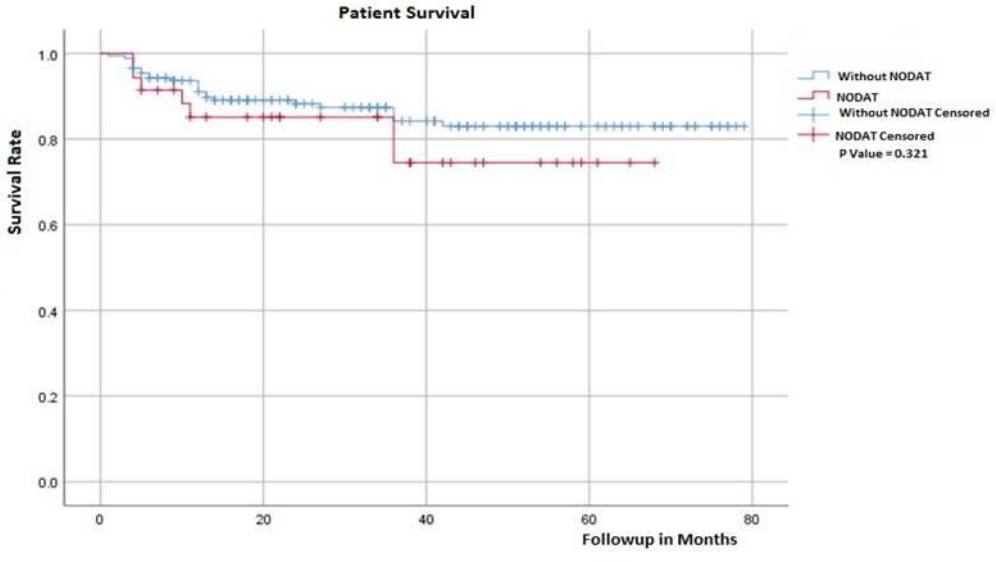
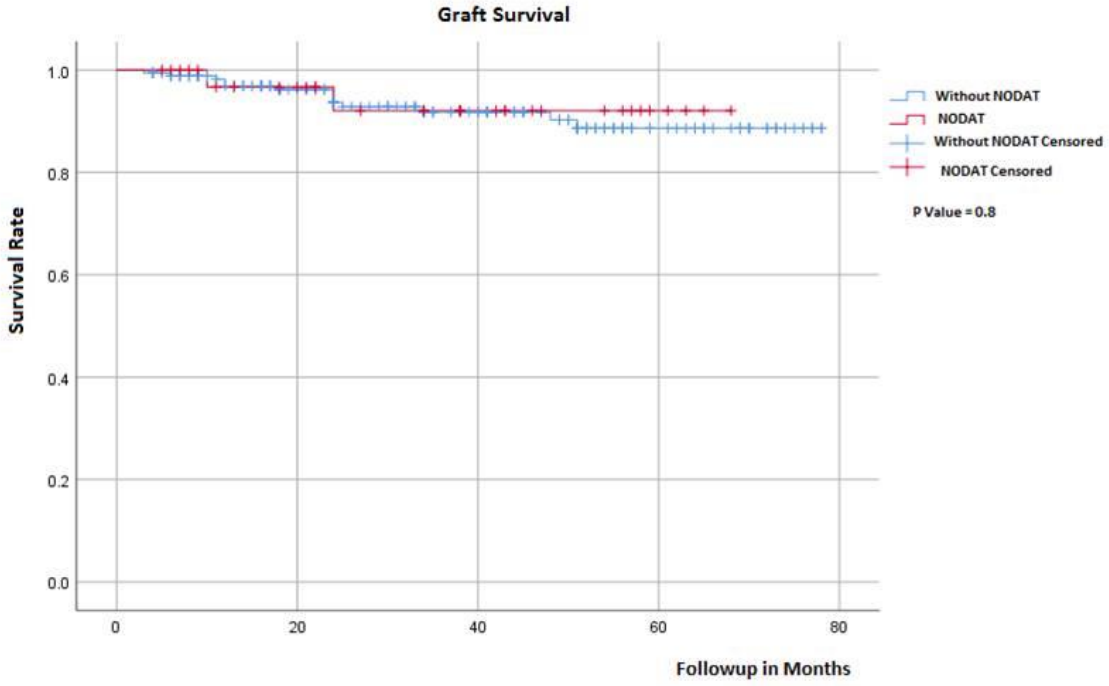


Figure - 2: Kaplan meier death censored graft survival rate curves of recipients with NODAT compared to without NODAT.



There was no significant difference in the 6 months, 1, 2, 3, and 5 years patient survival rate in recipients with NODAT (88.57%, 87.87%, 79.31%, 72.72 and 61.11% respectively) compared to recipients without NODAT (96.57%, 93.56%, 89.61%, 84.03% and 74.44% respectively) P value 0.321 (**Table – 4** and **Figure - 1**).

There was no significant difference in 6 months 1, 2, 3 and 5 years graft survival rate in recipients with NODAT (100%, 100%, 100%, 95.45% and 94.44% respectively) compared to recipients without NODAT (100%, 98.2%, 96.10%, 90.75% and 86.66% respectively) P value 0.8 (**Table - 5**, **Figure - 2**).

Mortality rate was high in recipients with NODAT 7(20%) compared to recipients without NODAT; 24(13.71%). More than 50% of mortality in NODAT group occurred within 6 months post-transplant and mean duration of onset of NODAT in those patients was 52.5 days. However, the most common cause of mortality was sepsis in both the groups.

Discussion

The incidence for NODAT in our study was 16.66 % with mean follow by period of 38.14 ± 20.12 months. Using the USRDS registry, the cumulative incidences were 9.1, 16, and 24% at 3, 12, and 36 months, respectively [5]. In a European study [6], the incidence of NODAT was 8.2% in the first year, 10.3% at 3 years, 11.5% at 5 years and 15.0% at 10 years after transplantation. It rose to 18.4% and 22.0% at 15 and 20 years, respectively. In another study [7], the overall incidence of NODAT was 10% during the mean follow-up of 10 months. The incidence of NODAT in the first year after kidney transplantation varied from 2 to 50% [8]. Vide range in the incidence of NODAT is due to variation in the definition of NODAT, different immunosuppressant protocol and screening methods used in different transplant centers.

In our study, Cox-Regression analysis used to estimate the hazard ratio for age more than 50 years, female sex, deceased donor, induction therapy, graft dysfunction, graft rejection, tacrolimus toxicity, everolimus based immunosuppression, HCV and CMV infection as

risk factors for the development of NODAT showed that induction therapy [HR :2.54 (0.23-28.00) P value 0.44] and graft dysfunction [HR : 2.80 (0.88-8.90) P value 0.08] had 2 fold increased risk of development of NODAT, and tacrolimus toxicity [HR : 4.35 (0.69-27.30) P value 0.11] had 4 fold increased risk of development of NODAT. Previous study [6] showed age, body mass index (BMI), glucose (all P < 0.0001) and triglycerides [hazard ratio (HR) per 1 mmol/l: 1.44 (1.17–1.77), P - 0.0006] use of sirolimus and tacrolimus were independent risk factors for development for NODAT.

Factors that highly correlated with the development of NODAT included older age (P - 0.001), hypertension prior to transplant (P - 0.001), black race (P - 0.001), BMI 30 (P - 0.001), HCV antibody positivity in the recipient (P - 0.001), tacrolimus use vs. other immunosuppressant (P - 0.001) [7]. The type of transplant was shown to be a risk factor in univariate analysis but was not an independent risk factor in the multivariate analysis. The relative risk of NODAT was 49% greater in patients treated with tacrolimus compared those who were not discharged with tacrolimus [7].

Alemtuzumab was associated with a 48% lower relative risk of NODAT compared to no induction explanation was that the use of alemtuzumab induction was more common use in calcineurin inhibitor or steroid minimization regimens, which may in turn, resulted in a lower risk of NODAT [7, 9]. A randomized controlled trial [10], showed that the incidence of NODAT was consistently higher among patients treated with tacrolimus compared to cyclosporine.

In a recent study [11], old age, high body weight and high body mass index (BMI) before transplantation, Afro- American or Hispanic ethnicity, HCV infection, and impaired fasting glucose level before transplantation, male donor, acute rejection episodes, CMV infection and the immunosuppressive regimen, especially the use of tacrolimus, steroids, or mammalian target for rapamycin inhibitors were risk factors for development of NODAT.

In our study, though sepsis, tuberculosis, and fungal infection rates were higher in recipients with NODAT, it was statistically significant only in fungal infection (17.14% Vs 2.28%, P value-0.00) compared to recipients without NODAT.

In our study, there was no significant difference in the 6 months, 1, 2, 3, and 5 years patient survival rate in recipients with NODAT (88.57%, 87.87%, 79.31%, 72.72 and 61.11% respectively) compared to recipients without NODAT (96.57%, 93.56%, 89.61%, 84.03% and 74.44% respectively) P value 0.32. There was also no significant difference in 6 months 1, 2, 3 and 5 years graft survival rate in recipients with NODAT (100%, 100%, 100%, 95.45% and 94.44% respectively) compared to recipients without NODAT (100%, 98.2%,96.10%, 90.75% and 86.66% respectively) P value 0.8.

Unlike our study, several previous studies [3, 5, 12-14], NODAT has been strongly associated with inferior graft and patient outcomes in adult renal transplant recipients. An outcome-based study [15] of 27,707 adult recipients of first kidney transplants, with graft survival of at least 1 year, performed between 1995 and 2002, showed that the new-onset diabetes was not associated with death-censored graft loss but with an increased risk for death with a functioning graft. An analysis of OPTN/UNOS database [16] showed that the unadjusted graft survival rates at subsequent 12 and 24 months were 100% and 91.7% respectively for recipients with NODAT and 95.7% and 91.1% respectively for recipients without NODAT (P - 0.91). The development of NODAT within first year of transplant was not associated with inferior graft survival during subsequent 24 months.

Conclusion

The incidence for NODAT in our study was 16.66 % with mean follow up period of 38.14 ±

20.12 months. Cox-Regression analysis showed 2 fold higher risk in the development of NODAT with induction therapy and graft dysfunction and 4 fold increased risk of development of NODAT with tacrolimus toxicity, however, it was not statistically significant. The fungal infection rate was significantly higher in recipient with NODAT compared to recipient without NODAT. The development of NODAT was not associated with inferior graft survival or patient survival rates at 6 months, 1, 2, 3 and 5 years

Acknowledgement

We are thankful to Dr. Radhika, Associate Professor, Department of Clinical Pharmacology, NIMS, Hyderabad for helping in statistical analysis.

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