Original Article

An observational Prospective Study to Evaluate the Preoperative Risk Factors of New-onset Diabetes Mellitus after Renal Transplantation in a Tertiary Care Centre in Eastern India

Santosh Kumar, Debmalya Sanyal[1], Pratik Das, Kingshuk Bhattacharjee[2], Rohit Rungta

Department of Nephrology, Rabindranath Tagore International Institute of Cardiac Sciences, EM Bypass, [1]Department of Endocrinology, KPC Medical College, Jadavpur, Kolkata, West Bengal, [2]JJT University, Rajasthan, India

Abstract

Objectives: This study aimed to determine the pre-transplant risk factors as independent predictors on the new-onset of diabetes mellitus after renal transplants (NODATs). **Materials and Methods:** A single-centred prospective real-world observational study of 100 subjects who underwent renal transplantation over a period of 2 years. All known patients with diabetes were excluded from the study. NODAT was defined according to the American Diabetes Association definition. In addition to pre-transplant workup 2 days prior to transplant, post-transplant follow-up done on weekly basis for 1st month, every 15th day from 1st month to 3rd month, monthly from 3rd month to 12th month. Each transplant patient followed up for 1 year post-transplant or for 6 months post-development of NODAT, whichever was later. All the pre-transplant variables namely body mass index (BMI), family history of diabetes mellitus (DM), HbA1c, fasting insulin level, fasting c-peptide level, serology for hepatitis B, C, serum magnesium level and pre-operative insulin ressistance were further compared between NODAT and non-NODAT groups at the end of the study to assess their strength of associations. **Results:** Among the 100 subjects included in the study, 24 developed NODAT. Risk factors namely age, family history of DM, BMI, hepatitis B and C infection, total cholesterol, triglyceride level, pre-operative HbA1c, pre-operative insulin resistance and pre-diabetes were significantly higher, whereas beta-cell function, ABO compatibility and magnesium levels being significantly lower in NODAT cohort. **Conclusion:** The incidence of NODAT is quite high (24%). Risk of development of NODAT was related to traditional as well as novel risk factors. Key aspects lies in identifying patients at risk of developing NODAT, using traditional risk factors for early diagnosis and introducing interventions on modifiable risk factors for prevention and timely intervention.

Keywords: Incidence, new-onset of diabetes mellitus after renal transplants, prospective study, risk factors

Introduction

New-onset diabetes after transplantation (NODAT) refers to diabetes that occurs in previously non-diabetic persons after solid-organ transplantation. International consensus guidelines regarding the definition of NODAT were published in 2003.[1,2]

There are many risk factors of NODAT. Some risk factors are same as in general risk factors for diabetes mellitus (DM), while some are specific to transplantation. Many of the same risk factors that predispose non-transplant patients to DM have been identified as risk factors for its development after transplantation. Such common risk factors include age, obesity, African–American and Hispanic. Obesity independently correlates with the development of NODAT.[3–5] It is one of the important modifiable risk factor. Increasing age is associated with increasing risk for NODAT.[6] In addition, some risk factors are unique to the transplant population. These include specific agents used for immunosuppression, human leukocyte antigen mismatch, donor sex and type of underlying renal disease.[7] Impaired glucose tolerance prior to transplant[8] and hyperglycaemia in the immediate perioperative period[9,10] may identify patients at higher risk for the development of NODAT. As there is a paucity of data from prospective studies with regards to risk factors of NODAT, we carried out the present study to shed some light on this area.

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Address for correspondence: Dr. Debmalya Sanyal, 36 Block H New Alipore Kolkata, West Bengal - 700 053, India. E-mail: drdebmalyasanyal@gmail.com

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Materials and Methods

This was a single-centred prospective real-world observational study of 100 subjects who underwent renal transplantation over a period of 2 years in a tertiary care centre in eastern India. The scheme of selecting the study participants in depicted in Figure 1.

The inclusion criteria comprised of adult subjects with end stage renal disease who underwent live donor kidney transplantation, absence of diabetes prior to kidney transplantation, defined according to the American Diabetes Association (ADA) guideline (not on oral hypoglycemic agents or insulin with fasting glucose <126 mg/dL) and those who received immunosuppressive medications that included triple immunosuppressive medications namely tacrolimus, mycophenolate mofetil or mycophenolate sodium and steroids with or without induction (ATG). Subjects who were capable of understanding the study and gave informed written consent for study participation were only included. Patients with a diagnosis of DM prior to kidney transplantation based on ADA criteria, for diagnosis of DM,[12] or those receiving anti-diabetic medications or those who were not capable of providing consent were excluded from the study.

'Prediabetes' in our study was defined according to ADA 2016 guidelines as HbA1c value 5.7–6.4%.

Those who are non-diabetic and underwent renal transplantation are further evaluated for the development of NODAT during 1-year post-transplantation follow-up. Post-transplant follow-up done on weekly basis for 1st month, every 15th day from 1st month to 3rd month, monthly from 3rd month to 12th month. Each transplant patient was followed up for 1 year post-transplant or for 6 months post-development of NODAT, whichever is later.

In addition to pre-transplant workup, BMI, family history of DM, HbA1c, fasting insulin level, fasting c-peptide level, serology for hepatitis B, C and serum magnesium level were evaluated in all patients 2 days prior to transplant. Pre-operative insulin resistance (HOMA-IR), insulin sensitivity (HOMA-S) beta-cell function (HOMA-B and c-peptide levels) were assessed. All the above pre-transplant variables were further compared between NODAT and non-NODAT subjects at the end of the study to assess their strength of association.

Statistical analysis

Descriptive statistics analyzed with SPSS version 17.0 software for windows. Continuous variables will be presented as mean ± SD and analyzed by unpaired *t* test. Categorical variables expressed as frequencies and percentages. Nominal categorical data between the groups will be compared using Chi-square test or Fisher's exact test as appropriate. A *P* value of <0.05 considered to be statistically significant. Univariate analysis done to evaluate odds ratio of various parameters associated with increased risk of NODAT among study population.

Ethical considerations

The study was approved by the Institutional Ethics Committee of the institute.

Results

Among the 100 subjects included in the analysis, 24 patients (19 males and 5 females) developed NODAT during 1 year of follow-up after transplantation. The study has a slight male preponderance with only 30 (30%) of subjects were females and the rest 70 (70%) were males. Mean age of the subjects was 45.2 ± 10.93 years and 36.04 ± 10.96 years in NODAT (n = 24) and non-NODAT (n = 76) cohort, respectively. There was a statistically significant difference between two groups with respect to age, P = 0.0004. In the present study, 16 (66.7%) NODAT subjects had family history of DM while 9 (11.8%) non-NODAT subjects had family history of DM, P < 0.001. Mean BMI of subjects was 25.09 ± 4.44 and 20.53 ± 3.33 in NODAT and non-NODAT, respectively, P < 0.001 [Table 1].

With respect to ABO compatibility transplant and NODAT, four (16.67%) NODAT subjects had ABO incompatibility transplant and two (2.63%) non-NODAT subjects had ABO incompatibility transplant. Fisher's exact test was applied for the above data and P value = 0.0282 was obtained. Therefore, statistically significant difference exists between two groups [Table 1].

Mean magnesium levels of subjects was 1.66 ± 0.27 mEq/L and 1.94 ± 0.46 mEq/L in NODAT and non-NODAT, respectively, P = 0.005 [Table 1]. In the present study, four (16.67%) NODAT subjects had hepatitis infection (hepatitis B infection – 2, hepatitis C infection – 2) and two (2.63%) non-NODAT subjects had hepatitis infection (hepatitis B infection – 1, hepatitis C infection – 1), P = 0.0282 [Table 1].

Also two subjects each in NODAT and non-NODAT had autosomal dominant polycystic kidney disease (ADPKD). Fisher exact test was applied and P value of 0.242 was obtained. Therefore, no statistically significant difference between two groups [Table 1].

With regards to lipid parameters, mean total cholesterol levels of subjects was 147.75 ± 21.33 mg/dL and 136.78 ± 37.74 mg/dL in NODAT and non-NODAT, respectively, P = 0.020. Mean total triglyceride levels of subjects was 117.38 ± 97.71 mg/dL and 73.49 ± 45.52 mg/dL in NODAT and non-NODAT, respectively, P = 0.016 [Table 1].

Mean pre-operative HbA1c levels of subjects was 5.58 ± 0.58% and 4.89 ± 0.59% in NODAT and non-NODAT, respectively, P < 0.001 [Table 1]. Twelve (50%) of NODAT subjects had HbA1c in the pre-diabetes range compared to 2.63% (2) non-NODAT subjects, P < 0.0001.

HOMA-beta and c-peptide was significantly lower in the NODAT cohort being 41.67 ± 24.42 and 9.75 ± 4.84 versus 71.25 ± 37.12 and 12.21 ± 5.98, respectively in

Table 1: Comparison of variables between subjects who developed NODAT and without NODAT

	Overall cohort, *n*=100	NODAT, *n*=24	Non-NODAT, *n*=76	OR, 95%CI	*P*
Age (in years), mean±SD	38.24±11.3	45.2 (10.93)	36.04 (10.56)	1.084, 1.033-1.138	0.0004
Family h/o diabetes mellitus, *n* (%)	25 (25%)	16 (66.67%)	9 (11.84%)	1.133, 1.013-1.89	<0.001
BMI (in kg/m^2), mean±SD	21.62 (4.03)	25.09 (4.44)	20.53 (3.33)	1.363, 1.178-1.577	<0.001
Hepatitis B infection, *n* (%)	3 (3%)	2 (8.33%)	1 (1.32%)	7.4, 0.638-85.81	0.028
Hepatitis C infection, *n* (%)	3 (3%)	2 (8.33%)	1 (1.32%)	7.4, 0.638-85.81	
Autosomal dominant polycystic kidney disease, *n* (%)	4 (4%)	2 (8.33%)	2 (2.64%)	1.001, 0.856-1.087	0.242
Mean magnesium levels (mEq/L), mean±SD	1.84±0.51	1.66±0.27	1.94±0.46	0.780, 0.3151.930	0.005
Mean total cholesterol levels (mg/dL), mean±SD	139.41±35.01	147.75±21.33	136.78±37.74	1.015, 0.997-1.032	0.02
Mean triglyceride levels (mg/dL), mean±SD	84.02±64.52	117.38±97.71	73.49±45.52	1.008, 0.998-1.018	0.016
Pre-operative HbA1c >5.7%, *n* (%)	14 (14%)	12 (50%)	2 (2.64%)	2.315, 1.389-2.561	<0.001
Pre-operative HbA1c (%), mean (SD)	5.34±0.086	5.58±0.58	4.89±0.59	1.057, 1.029-1.085	<0.001
ABO compatibility transplant, *n* (%)	94 (94%)	20 (83.33)	74 (97.37)	0.135, 0.023-0.792	<0.001
HOMA-IR	1.87±1.08	2.79±1.10	1.58±0.89	0.987, 0.932-0.998	<0.001
HOMA-S	79.35±48.07	44±29	90.51±47.61	0.957, 0.921-0.997	<0.001
HOMA-beta-cell function	64.14±3.64	41.68±24.42	71.25±37.12	0.956, 0.901-0.978	<0.001
c-peptide level	11.06±5.09	9.75±4.84	12.21±5.98	1.057, 0.943-1.184	<0.001

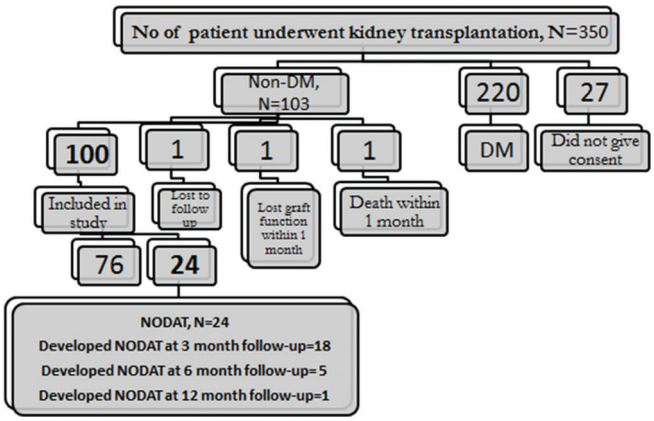

Figure 1: Flow diagram for selection our study subjects from total number of transplants done during study period

the non-NODAT cohort, $P < 0.001$. Insulin sensitivity in NODAT cohort was significantly lower with 44 ± 29 versus 90.51 ± 47.61 in non-NODATs. Mean HOMA-IR in NODAT subjects was 2.79 ± 1.10 versus 1.58 ± 0.89 in non-NODAT subjects, $P < 0.001$ [Table 1]. Also, in the present study among non-NODAT subjects, 26 (34.2%) had HOMA-IR levels in the lowest tertile (<1), 36 (47.4%) had HOMA-IR levels between 1 and 1.9, while 14 (18.4%) had HOMA-IR levels in the highest tertile (≥2) 2. In NODAT subjects, 1 (4.2%) had HOMA-IR levels in the lowest tertile (<1), 2 (8.3%) had HOMA-IR levels between 1 and 1.9 while 21 (87.5%) had HOMA-IR levels in the highest tertile (≥2), *P* value < 0.00001.

Discussion

In our study, among 100 non-diabetic patients who underwent renal transplantation, 24% patient developed NODAT during 1 year of follow-up after transplantation. In a meta-analysis of 19 studies, Montori *et al*.[11] reported that the incidence of NODAT in patients after any solid organ transplant, except pancreas or islet cell transplants, ranged from 2 to 50% at 1-year post-transplantation.[12] The varying prevalence are due to the lack of consensus in the definition and confusion between NODAT and post-transplant DM (PTDM). PTDM is newly diagnosed diabetes in post-transplant setting (irrespective of timing or whether it was present but undetected prior to transplantation or not). The term PTDM should be utilized for clinically stable patients who have developed persistent post-transplantation hyperglycaemia. This was done, because adequately excluding diabetes/pre-diabetes pre-transplantation is often impractical and also accounting for early transient hyperglycaemic period which often resolves (included in NODAT). Valderhaug *et al*.[13] in his study found PTDM in 14% patients. From Indian studies the incidences of NODAT were 19.12% by Prakash *et al*.,[14] while Sharma *et al*.[15] and Bora *et al*.[16] found incidence of NODAT was 16.75% and 54.5%, respectively.

An analysis of US Medicare kidney transplant recipients found that age ≥60 years was associated with a relative risk (RR) of 2.6 for the development of NODAT versus that observed with younger patients [3]. In Indian study by Prakash *et al*.[14] mean age of NODAT was 40.4 and in non-NODAT it was 31.13. The mean age of our subjects was 45.2 ± 10.93 years and 36.04 ± 10.56 years in NODAT and non-NODAT groups, respectively. There was statistically significant difference in mean age between two groups highlighting the fact that with increasing age there is more chance of developing NODAT.

Obesity independently correlates with the development of NODAT.[3,4] An analysis of 15,309 patients using the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database found that the risk of NODAT increased 1.4-fold for those with a BMI of 25–30 and nearly doubled if the BMI was >30.[17] Though in our

study most of the patients had lower BMI probably due to the poor socioeconomic status, but mean BMI was significantly higher in NODAT than in non-NODAT group. Higher BMI is an important modifiable risk factor for the development of NODAT.[18]

A family history of diabetes has been identified as an independent risk factor for the development of NODAT as shown in many studies.[19,20] In the present study, NODAT subjects had a significantly higher (66.67%) family history of diabetes compared to non-NODAT (11.84%) subjects. Similarly Prakash *et al*.[14] found positive family history was strongly associated with NODAT occurrence (*P* value 0.009, odds ratio 5.96, 95% CI,1.6–2.91).

Most studies have shown that hepatitis C virus (HCV) infection correlates with both pre- and post-transplant diabetes.[21–24] A 2005 meta-analysis of 10 studies of 2502 patients found that anti-HCV-positive patients were nearly four times more likely to develop NODAT, compared with uninfected individuals.[23] In our study both hepatitis B and C are associated with significantly increased incidence of NODAT. Contrary to our study most of the previous studies have shown no association of hepatitis B with NODAT. This may be due to high incidence of hepatitis B infection in our society.

Polycystic kidney disease may confer an increased risk of NODAT, although this has not been consistently observed.[24,25] Two matched historical cohort studies have suggested that ADPKD may be a risk factor for NODAT.[26,27] Also, the incidence of NODAT in ADPKD patients increased in a retrospective study comparing ADPKD and non-ADPKD groups (13.4% vs. 5.2%, respectively). deMattos *et al*.[25] concluded that ADPKD were at a three-fold increased risk for development of PTDM within the first year following renal transplantation. In our study there was no significant difference in ADPKD between NODAT and non-NODAT groups probably because of very small number (two in each group) of patients with ADPKD. Van Laecke *et al*.[27] demonstrated that patients with NODAT ($n = 75$; 29.5%) versus non-NODAT had lower magnesium levels ($P < 0.001$). Patients with magnesium level <1.9 mg/dL showed a faster development of NODAT (log-rank $P < 0.001$). Cheungpasitporn *et al*.[28] in his meta-analysis concluded that there is risk of NODAT in patients with hypomagnesaemia. The pooled RR of NODAT in patients with hypomagnesaemia was 1.25 (95% CI, 1.08–1.45). In our study, mean magnesium levels were significantly lower in NODAT (1.66 ± 0.27 mEq/L) subjects versus non-NODAT (1.94 ± 0.46 mEq/L) subjects. No Indian study has been done on serum magnesium level and its correlation with development of NODAT.

In ABO incompatible transplant stronger immunosuppression is used, so there is a chance of higher incidence of NODAT in comparison to ABO compatible transplant. In our study, NODAT (16.67%) subjects had significantly higher ABO incompatible transplants versus non-NODAT (0.026%) subjects.

With regards to pre-transplant cholesterol and triglyceride level, Prakash *et al*.[14] found pre-transplant hypercholesterolaemia (*P* value 0.029, odds ratio 4.38, 95% CI, 1.19–16.13), and pre-transplant hypertriglyceridemia (*P* value 0.023, odds ratio 5.03, 95% CI, 1.36–18.63), significantly associated with increased risk of post-transplant diabetes. In the current study, pre-transplant mean total cholesterol and total triglyceride levels were significantly higher in NODAT subjects compared to non-NODAT subjects. Pre-operative impaired glucose tolerance generally identifies those transplant candidates who are at higher risk for the development of NODAT. Caillard *et al*.[8] in his study found that among 31 patients who developed NODAT after transplantation, 16 (52%) had impaired glucose tolerance pre-transplant. In multivariate analysis, pre-transplant impaired glucose tolerance was associated with the development of NODAT (RR 2.4, 95% CI, 1.1–5.3). In our study, NODAT subjects had significantly higher mean pre-operative HbA1c levels compared to non-NODAT subjects. Significantly higher percentage of our NODAT (50%) subjects had HbA1c in the pre-diabetes range compared to non-NODAT (2.6%) subjects. Thus pre-transplant HbA1c and pre-diabetes may predict increased risk of development of NODAT after renal transplant.

In study done by Bayés *et al*.[29] NODAT patients showed higher pre-transplant plasma insulin concentrations [NODAT, 13.4 (11–22.7) microIU/mL; non-NODAT, 10.05 (7.45–18.4) microIU/mL; $P = 0.049$], HOMA-IR index [NODAT, 4.18 (2.49–5.75); non-NODAT, 2.63 (1.52–4.68); $P = 0.043$]. On contrary study done by Nagaraja *et al*.[30] found insulin indices calculated pre-transplantation using HOMA and McAuley's index did not predict NODAT. In our study, indices of beta-cell function like HOMA-beta and c-peptide was significantly lower in the NODAT cohort than in the non-NODAT cohort. Insulin sensitivity in NODAT cohort was also significantly lower versus non-NODATs. Markers of insulin resistance like HOMA-IR was significantly higher in NODAT subjects compared to non-NODAT subjects. Moreover, 87.5% of our NODAT subjects had HOMA-IR levels in the highest tertile (≥2) with 4.2% in the lowest tertile (<1), while 18.4% of non-NODAT subjects had HOMA-IR levels in the highest tertile, 47.4% had HOMA-IR between 1 and 1.9 and 34.2% of non-NODAT subjects were in the lowest tertile of HOMA-IR (<1). Significantly more number of NODAT subjects were in the highest tertile of HOMA-IR compared to non-NODAT subjects.

Thus, our NODAT subjects had significantly higher pre-operative insulin resistance levels (increased HOMA-IR) and lower insulin sensitivity (HOMA-S) coupled with reduced beta-cell function (HOMA-B and c-peptide levels) than non-NODAT subjects suggesting a strong association of development of NODAT in non-diabetic subjects with

high pre-transplant markers of insulin resistance and reduced insulin sensitivity and beta-cell function. These indices of insulin resistance, insulin sensitivity and beta-cell function like c-peptide may be helpful in predicting the development of NODAT in non-diabetic patients undergoing renal transplantation.

Strength of our study were prospective design, reasonable subject number and follow-up, pre-transplant assessment of risk factors and a standard fixed effective immunosuppressive regime as per recent recommendations of not compromising on immunosuppressive medications for NODAT prevention. Limitations of our study were additional risk factors including genetic factors were not evaluated and the causality of risk factors could not be established as it was not a randomized controlled trial. Thus future large-scale randomized controlled trials are necessary with addition risk factors for better management and establishment of causing.

Conclusion

One-year prospective study of 100 post-transplant patients showed 24% incidence of NODAT. Other than conventional risk factors like older age, high BMI, pre-diabetes, positive family history of diabetes, novel risk factors like hypomagnesaemia, pre-transplant dyslipidemia, indices of insulin resistance (HOMA-IR), insulin sensitivity (HOMA-S), beta-cell function (c-peptide, HOMA-B) may be helpful in predicting the development of NODAT in non-diabetic subjects undergoing renal transplantation. These risk factors may help in identifying subjects at risk of developing NODAT, facilitating early diagnosis and introducing interventions on modifiable risk factors for prevention and timely intervention.

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Conflicts of interest

There are no conflicts of interest.

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