Original Article

Prevalence and Predictors of "New-onset Diabetes after Transplantation" (NODAT) in Renal Transplant Recipients: An Observational Study

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Abstract

Objective: New-onset diabetes after transplantation (NODAT) develops frequently after renal transplant. The study aims at the prevalence of NODAT , predictors for developing it and therapeutic glycemic responses in NODAT. **Materials and Methods:** Consecutive renal transplant recipients excluding Diabetic Kidney Disease (DKD) or pretransplant diabetes were evaluated. Forty-three out of 250 persons were found to have NODAT. Ninety age-matched transplant recipients from the rest were recruited as control. Fasting blood sugar (FBS), HbA1c, lipid profile, and trough tacrolimus level (T_0) were examined in all. HOMA IR C-peptide and HOMA-beta C-peptide were calculated. **Results:** Prevalence of NODAT in renal transplant recipients was 17.2% (43/250). Twenty-four (55.8%) developed early NODAT (<1 year) and 19 (44.2%) developed late NODAT (>1 year). Significantly higher pretransplant body mass index (BMI) (kg/m^2) ($P < 0.001$), waist circumference (WC) (cm) ($P < 0.001$), pretransplant cholesterol (mg%) ($P = 0.04$), triglyceride (mg%) ($P < 0.001$), and FBS (mg%) ($P < 0.001$) were found in NODAT compared with non-NODAT. Trough tacrolimus (ng/mL) was found to be higher in NODAT (10.2 vs. 5.37, $P < 0.001$). Though HOMA IR was not found to be different between groups, HOMA-beta C-peptide was low in NODAT compared with non-NODAT ($P = 0.03$). Predictors of NODAT were WC [odds ratio (OR) = 01.15] and trough tacrolimus level (OR = 1.316). Best cut-off of WC for predicting NODAT was 87.5 cm for male and 83.5 cm for female. Best cut-off of T_0 was 8.5 ng/mL. In NODAT, 9.3% were treated by lifestyle modification, 67.4% by oral hypoglycemic agents, 11.6% by insulin, and 11.6% by combined insulin and oral antidiabetic agents with HbA1c <7%. **Conclusion:** NODAT in renal transplant recipients is more common in those with higher pretransplant BMI, WC, pretransplant total cholesterol, triglyceride, and FBS. Beta-cell secretory defect is more relevant as etiological factor rather than insulin resistance. Higher WC and trough tacrolimus level above 8.5 ng/mL may be important factors for predicting NODAT.

Keywords: HOMA-beta C-peptide, new-onset diabetes after transplantation, renal transplant, tacrolimus

Introduction

Renal replacement therapy is considered to be the definitive therapy for patients with end-stage renal disease. This is the most common solid-organ transplant worldwide. However, the posttransplant complications especially "new-onset diabetes after transplantation" (NODAT) have shown to increase the risk of morbidity and mortality among these patients.[1] In fact, NODAT is now considered to be a major determinant of loss of renal allograft, development of infections, and increased risk of cardiovascular morbidity and mortality,[1] and thus it can significantly affect the clinical outcome of the transplant recipients.

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NODAT is defined as development of diabetes for the first time after transplantation in previously nondiabetic transplant recipients Prevalence of NODAT may vary from 2% to 53%. A recent Indian study showed prevalence of NODAT to be 26.7%.[2] Etiology and risk factors for NODAT are manifold. Apart from the general risk factors, unique

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contribution by immune-suppression regimen may play a distinct role. Tacrolimus or FK-506 is now commonly used in the immune-suppression regimen along with mycophenolate mofetil and prednisolone. Not only prednisolone is known to be a potent diabetogenic agent but also induction with an FK-506-based immunosuppressive regimen resulted in a high incidence of glucose metabolism disorders in renal transplantation recipients. Higher trough levels of FK-506 during the first month, acute rejections, and higher body mass index (BMI) are the most obvious risk factors for development of posttransplant diabetes in a study[3] done by Maes *et al*.

In this multiobservational study, we evaluated a cohort of renal transplant patients attending Post Transplant Clinic to evaluate its prevalence, to look at the variables which might be associated with the development of NODAT, and to find out predictors of development of NODAT based on several factors. We also evaluated different forms of therapy and their response in patients diagnosed with NODAT.

Materials and Methods

In all, 286 consecutive transplant recipients attending "Post Transplant Clinic" of IPGME and R, Kolkata, during the study period were initially screened for the study. Indication of transplant was hypertensive kidney disease in 152 subjects, different variety of glomerulonephritis in 83 subjects, polycystic kidney disease in 5 subjects, nephrolithiasis in 11 subjects, unknown native kidney disease in 16 subjects, and diabetic kidney disease in 19 subjects. Diagnosis of NODAT was done as per "International consensus guidelines of NODAT (2003)" which recommended that it should be based on the criteria of the American Diabetes Association. Renal transplant recipients less than 18 years of age were excluded from this study. The pretransplant records of all posttransplant patients were evaluated from their clinical documents and investigations and those found to have documented diabetes from pretransplant stage (19 DKD subjects and 17 subjects having diabetes associated with other diagnosis of chronic kidney disease) were also excluded. All persons included in the cohort were evaluated several times during the study period. In general, they were evaluated weekly for the next 4 weeks after transplant, followed by a monthly visit for the next 3 months. After that, they were followed up at every 3 months for clinical and biochemical assessment. Diagnosis of NODAT was established in those with an HbA1c of more than 6.5% or having increased venous fasting blood glucose ≥126 mg% on more than one occasion during their follow-up after 3 months of transplant. Those having hyperglycemia till 1 month but resolved spontaneously were evaluated again at 3 months, and if found to fulfil the criteria of diabetes were included with a diagnosis of NODAT. Those not fulfilling such criteria were diagnosed as transient posttransplant diabetes and were not counted as NODAT. A total of 250 consecutive transplant recipients after appropriate exclusion, as described above, during the study period were thus actually evaluated for the study. Forty-three patients were found to have NODAT. All of them either had fasting venous plasma glucose above 126 mg% on at least two occasions or were on antidiabetic therapy. Forty-one of them had HbA1c more than 6.5% at the time of initiation of treatment. Out of the remaining transplant recipients who were not suffering from NODAT, 90 age-matched patients were recruited in the study as controls. All subjects were evaluated for clinical parameters, for example, age, sex, BMI, waist circumference (WC), history of hypertension, family history of diabetes mellitus, hypertension, history of addiction, and time elapsed after transplantation till development of NODAT. Records of immunosuppressive treatment received by all transplant recipients and antidiabetic treatment received for NODAT were also analyzed.

Fasting blood samples were obtained in all for biochemical analysis, for example, fasting blood sugar (FBS), HbA1c, C-peptide, and trough tacrolimus level (T_0). FBS was measured by Glucose Oxidase (GOD)-Peroxidase (POD) method. HbA1c was measured by high-performance liquid chromatography (D-10; Bio-Rad, US) method. C-peptide was estimated by chemiluminiscent immunometric assay by Immulite-1000 (Siemans Healthcare Diagnostics, Germany). HOMA IR C-peptide was calculated as a measure of insulin resistance replacing serum insulin with C-peptide in the standard formula. Insulin secretory defect was expressed as HOMA-beta C-peptide using the formula as follows: 0.27 × fasting C-peptide)/(FBS − 3.5). In both, the formula glucose was expressed in mmol/L.

Monitoring of trough level tacrolimus is now a standard practice in postrenal transplant patients.[4] Achieving early adequate tacrolimus exposure significantly reduces the risk for acute rejection. Patients with a tacrolimus Area under Curve (AUC) >200 ng/h/mL had a markedly lower risk for acute rejection, regardless of whether they received Mycophenolate mofetil (MMF).[4] The threshold value of 200 ng/h/mL is correlated to a tacrolimus trough of 10 ng/mL.[5] Tacrolimus assay was done from an NABL accredited laboratory using EDTA whole blood with measuring range of 0.5–40 ng/mL by COBAS e 411 analyzer (Roche Diagnostics, Switzerland) with a imprecision of 2.1%–14.2%.

Statistical Package for the Social Sciences (version 21.0; SPSS Inc., Chicago, US) was used for data analysis. Continuous variables were presented as mean ± standard deviation, and categorical variables were presented in number and percentage. Mann–Whitney *U*-test and Student's unpaired *t*-test were used for comparison as appropriate. Binary logistic regression was used to predict development of NODAT from various categorical and continuous covariates as mentioned above. Receiver operating characteristic (ROC) curve analysis was used to find best cut-off with sensitivity and specificity for relevant variables as necessary.

Results

Forty-three out of 250 (17.2%) renal transplant recipients were detected to have NODAT. Thirty-three out of these 43 NODAT

subjects (76.74%) were male. There was no significant sex difference in NODAT when compared with non-NODAT subjects, where 75.56% (68/90) were male. Twenty-four of 43 subjects (55.8%) developed NODAT in less than 1 year after transplantation (early NODAT) and the remaining 19 subjects (44.2%) developed NODAT more than 1 year after transplantation (late NODAT). Twenty-out of 24 early NODAT developed it within 6 months after transplantation. Table 1 represents the baseline demographic, clinical, and biochemical characteristics of NODAT compared with non-NODAT subjects.

Trough tacrolimus level (ng/mL) was found to be significantly higher in NODAT subjects compared with non-NODAT subjects ($P = 0.04$). HOMA IR C-peptide was not different between the groups, but HOMA-beta C-peptide was significantly worse in NODAT subjects compared with non-NODAT ($P = 0.03$). There were no statistical difference in the proportion of subjects using tacrolimus, mycophenolate mofetil, and prednisolone as immunosuppressant (NODAT 88.4% vs. non-NODAT 96.7%, P = NS by Chi-square test).

Binary logistic regression was done to identify independent predictors of NODAT. It was found that WC [odds ratio (OR) = 01.15, 95% confidence interval (CI) = 1.07–1.19, $P < 0.001$] and trough tacrolimus level (OR = 1.316, 95% CI = 1.119–4.796) were independent predictors of NODAT. In ROC curve analysis, the best cut-off of WC for independently predicting occurrence of NODAT in female was found to be 83.5 cm (sensitivity 90%, specificity 86.4%, and AUC 0.934; $P < 0.05$) and that in male was found to be 87.5 cm (sensitivity 75.8%, specificity 82.4%, AUC 0.816; $P < 0.05$). The best cut-off of T_0 to predict NODAT was found to be 8.5 ng/mL with a sensitivity of 86.8%, specificity of 98.9%, and positive predictive value of 96.97% (AUC 0.934, $P < 0.05$), classifying it as a good to excellent predictor for the diagnosis of NODAT in terms of differentiating from non-NODAT group.

Table 1: Demographic, clinical, and biochemical characteristics of NODAT and non-NODAT patients

Characteristics	NODAT ($n=43$)	Non-NODAT ($n=90$)	*P*
Age (years)	37.4±10.4	35.87±9.1	0.381
Sex (male:female)	33:10	68:22	0.881
Pretransplant BMI (kg/m^2)	22.4±2.8	20.3±2.01	<0.001
Waist circumference (cm)	91.77±7.47	82.58±6.37	<0.001
Pretransplant FBS (mg/dL)	109±18	85±11.5	<0.001
Hypertension (%)	76.7	63.3	0.175
Family h/o diabetes mellitus (%)	27.9	18.9	0.239
Family h/o hypertension (%)	39.5	27.8	0.172
Smoking (%)	18.6	17.8	0.908
Alcoholism (%)	4.7	3.3	0.709
Total cholesterol (mg/dL)	244.8±46	230±34.1	0.04
Triglyceride (mg/dL)	209±62.5	168.9±32.8	<0.001
T_0 (ng/mL)	10.2±2.28	5.37±1.19	<0.001
HOMA IR C-peptide	1.02±0.70	1.06±0.80	0.817
HOMA-beta C-peptide	0.62±0.89	1.29±1.44	0.03

NODAT: New-onset diabetes mellitus after transplantation; BMI: Body mass index; FBS: Fasting blood sugar. Comparison of mean was done by Student's unpaired *t*-test for continuous variables and comparison of proportions (expressed as percentage) was done by Chi-square test

Among 43 NODAT patients, a majority of the subjects, that is, 29 (67.4%) were treated by oral antidiabetic agent (OAD), 4 (11.6%) subjects received lifestyle modification only as treatment, 5 patients (11.6%) were managed by insulin only, while the rest 5 (11.6%) patients were treated by combined insulin and OAD with a HbA1c of less than 7%. The mean HbA1c in NODAT patients was 6.1% ± 0.87%.

Discussion

Diabetes occurring as a complication of solid-organ transplantation is recognized for decades. The incidence for NODAT, as reported in world literature, is between 2% and 53%. Unfortunately, the condition is often underestimated. However, the development of NODAT has serious consequences for the patient and threatens the long-term outcome of transplantation and increases the possibility of cardiovascular risks. Over the past decade, there has been a gradual rise in the number of patients seeking renal transplantation and is now the most common form of solid-organ transplant. Hence, there is also a large kidney transplant recipient population who are at risk of NODAT. In a recent Indian study, the prevalence of NODAT was found to be 26.7%.[2] Patel *et al.* found a prevalence of NODAT to be 33.89%.[6] In the study by Kasiske *et al.*, the prevalence of NODAT was shown to be 20%–50%.[7] However in our study, we found a prevalence of NODAT to be 17.2%. The moderately high prevalence of NODAT in our study could be attributable to the fact that almost all kidney transplant recipients received steroids and tacrolimus as part of immunosuppressive regimen. Also, population in the Indian subcontinent are more prone to develop diabetes.

Early NODAT and late NODAT are defined as occurrence of NODAT less than 1 year and more than 1 year after renal transplantation, respectively. A study by Woodward *et al.* showed that most of the cases of NODAT occurred within the first year after renal transplantation, more commonly within the first 6 months.[8] Another Indian study by Lakshminaryana *et al.* showed that a majority of NODAT occurred within the first 6 months of transplantation.[9] In our study, among 43 patients with NODAT, 24 (55.8%) had early NODAT and the rest 19 patients (44.2%) had late NODAT. Moreover, among those having early NODAT, most of the patients [46.5% (20/24)] developed NODAT within 6 months after renal transplantation.

The incidence of NODAT appears to be more in elderly and the risk of developing NODAT appears to increase in patients over 40 years.[10,11] In the study by Lakshminaryana *et al.*, males formed majority (86.20%) of subjects with NODAT.[9] However, we could not establish any significant difference in age of the renal transplant recipients. Though males were more commonly affected with NODAT, the sex difference was not significantly different between the groups. Bonato *et al.* showed[12] that overweight or obese patients were more

prone to develop NODAT with a Relative Risk (RR) of 1.4 for patients with BMI between 25 and 30 kg/m^2 and an RR of 1.7–1.8 for those with BMI >30 kg/m^2. In our study, the mean pretransplant BMI was more in NODAT subjects compared with non-NODAT subjects. WC, pretransplant total cholesterol, triglyceride, and FBS were other notable variables which were significantly worse in NODAT subjects. The proportion of subjects using tacrolimus, mycophenolate mofetil, and prednisolone as immunosuppressant was also not significantly different in between the groups.

A study by Sinangil *et al.*[13] also found pretransplant triglyceride as a risk factor of NODAT as was shown by Porrini *et al.*[14] also. Among the several variables examined in this study, independent predictors of NODAT were WC (best cut-off in male was 87.5 cm and in female was 83.5 cm) and T_0 (best cut-off was 8.5 ng/mL). The significantly higher mean trough tacrolimus level (T_0) in NODAT subjects when compared with non-NODAT subjects could be explained by the fact that T_0 is primarily determined by individual variation in pharmacokinetics of tacrolimus *in vivo* as well as by the mode of titration of dose by nephrologist for the sake of prevention of graft rejection. In a study by Maes *et al.*,[3] high trough tacrolimus level above 15 ng/mL in the first month after transplantation was also shown as an important risk factor for NODAT.

Glucocorticoids were noted for reduced insulin-dependent glucose uptake in peripheral tissues and increased gluconeogenesis in liver. The study by Hjelmesaeth *et al.* opined that a rise in prednisolone dose by 0.01 mg/kg/day was associated with a 5% risk of developing NODAT.[15] In our study, HOMA IR (C-peptide) was not significantly different between the NODAT group and the non-NODAT group showing that insulin resistance might not be the contributory cause of NODAT. This also was corroborated with the fact that low-dose glucocorticoid was used as immunosuppressant in our study. However, HOMA-beta (C-peptide) was found to be significantly reduced in NODAT group when compared with the non-NODAT group showing a secretory defect of insulin from beta cells of pancreas in NODAT patients. This could be attributed to tacrolimus (a calcineurin inhibitor) which is noted for inducing reversible suppression of insulin secretion. Calcineurin inhibitor interferes with nuclear factor of activated T-cell signalling in beta cells of pancreas.[16] It suppresses insulin mRNA transcription by binding to FK 506 binding protein 12 followed by inhibition of calcineurin in beta cells.[17]

With regard to the management of NODAT, Lakshminaryana *et al.*[9] showed that a majority (58.62%) of subjects responded adequately to oral hypoglycemic agents (metformin, glibenclamide, gliclazide, glimepiride) along with diet and lifestyle modification. About 20.69% of subjects needed combination of insulin and oral hypoglycemic agent, and additional 20.69% were managed with insulin alone. Around 10.34% of subjects responded to only diet and lifestyle modification.[5] Most of the NODAT subjects in our study (67.4%) were managed by OAD (metformin, gliclazide, glimepiride, voglibose), whereas only 9.3% were treated solely by lifestyle modification. About 11.6% of subjects received insulin therapy and the rest 11.7% were treated by combined insulin and OAD. All subjects on therapeutic lifestyle modification were also doing well. Almost all patients were well within the target of an HbA1c of less than 7%.

Conclusion

NODAT in renal transplant recipients is a common complication. Prevalence of NODAT appears to be higher in subjects with higher pretransplant BMI, WC, pretransplant total cholesterol, triglyceride, and FBS. Beta-cell secretory defect is more relevant as etiological factor rather than insulin resistance. Higher WC and trough tacrolimus level (above 8.5 ng/mL) appears to be important factors for predicting NODAT.

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Conflicts of interest

There are no conflicts of interest.

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