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# Study of Incidence of New Onset Diabetes After Transplant (NODAT) in Renal Transplant Recipients in a Hospital

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**ABSTRACT**

Diabetes mellitus occurs in a significant number of patients following renal transplantation. New-onset diabetes after transplant (NODAT) is associated with increased mortality and morbidity and, in particular, higher rates of cardiovascular disease and infection, which are the leading causes of death in renal transplant recipients. The study was conducted at Apollo hospital, Chennai from October 2015 to June 2017. All non-diabetic patients undergoing renal transplant were enrolled in study between October 2015 to December 2016 and these patients were followed till 6 months post-transplant period last follow-up, so the 6 month follow-up for last patient was in June 2017. Twenty seven (54%) patients were having Chronic glomerulonephritis (CGN) as underlying kidney disease, 8 (16%) patients were having Chronic interstitial nephritis (CIN), 6 (12%) patients were having Chronic pyelonephritis (CPN) and 2 (4%) were having Polycystic kidney disease, 6 (12%) were having hypertensive nephrosclerosis and 1 (2%) patient was having hereditery nephropathy as underlying disease. There is significant effect of pre and 1 month post-transplant GTT, pre-transplant HbA1c and pre-transplant serum triglyceride levels on the development of NODAT.

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**Key Words**
Diabetes, transplant, renal, NODAT, nephropathy

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## INTRODUCTION

Diabetes mellitus occurs in a significant number of patients following renal transplantation. New-onset diabetes after transplant (NODAT) is associated with increased mortality and morbidity and in particular, higher rates of cardiovascular disease and infection, which are the leading causes of death in renal transplant recipients. International consensus guidelines regarding the definition of new onset diabetes mellitus after transplantation were published in 2003[1,2]. The diagnostic clarification was important as the use of various definitions in prior publications made it difficult to assess the incidence of NODAT. Except for the HbA1c, which should not be used before three months post-transplantation, these guidelines use standard American Diabetes Association (ADA) criteria for the diagnosis of diabetes mellitus and impaired glucose tolerance[3]. Studies that were published prior to the development of the consensus definition reported rates of NODAT ranging from 7-46 %[4-7]. Several more recent studies have provided incidence rates of NODAT defined by the 2003 international consensus guidelines, including the use of the oral glucose tolerance test[8-10]. Overall, studies that use the current criteria for diagnosis suggest that approximately one-third of non-diabetic kidney transplant recipients develop persistently impaired glucose metabolism by six months post-transplantation[10]. The HbA1c is not recommended for diagnosis before three months following transplantation, because the test may not be valid until new haemoglobin has been synthesized and glycated for the appropriate period in the diabetogenic post-transplant setting[2].

Many of the same risk factors that predispose non-transplant patients to diabetes mellitus have been identified as risk factors for its development after transplantation. Such common risk factors include age, obesity, African race, family history and impaired glucose tolerance. Risk models for NODAT have been developed and validated using pre-transplant variables alone[11]. In addition, some risk factors are unique to the transplant population. These include specific agents used for immunosuppression, human leukocyte antigen (HLA) mismatch, infections (CMV/HCV), donor sex and type of underlying renal disease[12]. After three months post-transplant, a HbA1c = 6.5 percent can be used to diagnose diabetes by ADA criteria, with a HbA1c of 5.7-6.4% consistent with pre-diabetic state[13,14]. The above study was conducted to study the incidence of new onset diabetes after transplant (NODAT) in renal transplant recipients in a hospital.

## MATERIALS AND METHODS

**Study Place:** The study was conducted at the Apollo hospital, Chennai from October 2015 to June 2017.

**Study Design:** Prospective observational study.

**Inclusion Criteria:** All non-diabetic patients undergoing live related renal transplant in a hospital, non-diabetic patients undergoing deceased donor renal transplant in a hospital and patient willing to participate in study.

**Exclusion Criteria:** Patients diagnosed to have diabetes mellitus prior to renal transplant, unwilling to participate.

**Sample Size:** 44 patients.

**Data Analysis:** Data was processed and analyzed using the software SPSS ver16.0 (SPSS Inc, Chicago, IL). The continuous variables were expressed as mean+SD when the variables follow normal distribution, otherwise represented by median (Interquartile range). Data entry was done in MS-Excel spreadsheet. A two-tailed $p<0.05$ was considered as statistically significant.

**Ethical Considerations:** All the necessary permissions were obtained from the Institutional Ethical committee before beginning the study.

All the necessary details such as family history of diabetes, weight, height, BMI, waist circumference before transplant surgery were taken. Pre-transplant glucose tolerance test (75g of glucose), glycated Hb, fasting lipid profile and fasting c-peptide levels were done after enrolment. Pre-transplant Glucose tolerance test was not feasible in deceased donor renal transplant recipients and hence only in live renal transplant recipients pre-transplant GTT was done. Details of induction and maintenance immunosuppression, number of acute and treatment details of each rejection were noted. Post-transplant glucose tolerance test was done after 1 month of transplant surgery. After second month onwards, monthly FBS and PPBS was done till 6 months of post-transplant follow-up period. After second month onwards, monthly FBS and PPBS was done till 6 months of post-transplant follow-up period. Data was analyzed at the end of study i.e. at the end of 6 months follow up period for last patient enrolled in the study. The end point of the study was development of NODAT in renal transplant recipient or death of the patient.

## RESULT AND DISCUSSIONS

Above table shows mean standard deviation of different variables in two groups, 1) patients who developed diabetes (DM) and 2) Euglycemic patients or patients who were in pre-diabetic stage after 6 months of transplant surgery (Non DM). There was considerable difference observed between these two groups for all the variables. Except HDL cholesterol, all

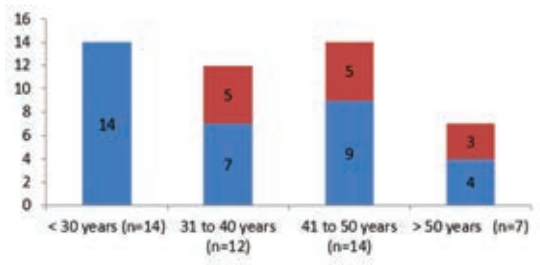


Fig. 1: Age distribution of study population

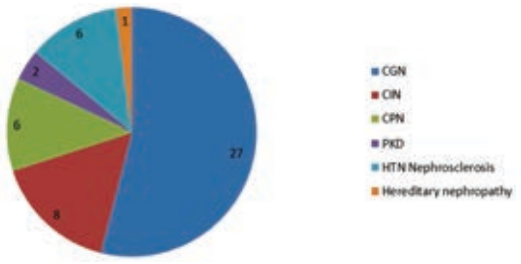


Fig. 2: Distribution of study population according to native kidney disease

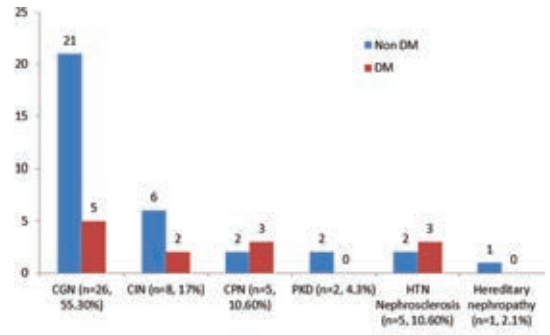


Fig. 3: Number of patients developing NODAT in each native kidney disease group

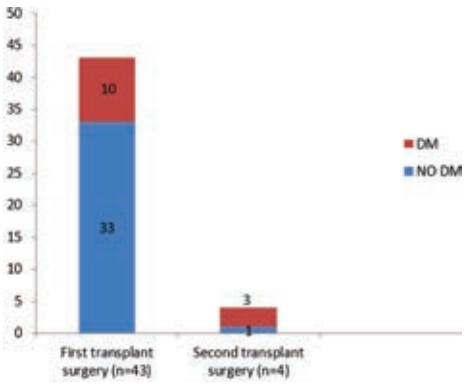


Fig. 4: Distribution of study population according to number of renal transplants underwent

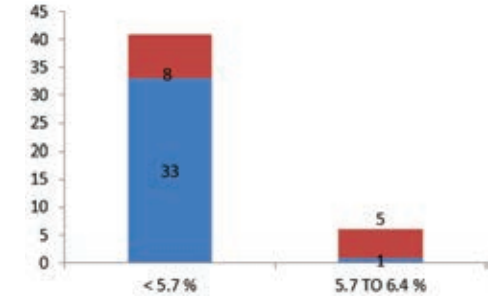


Fig. 5: Distribution of study population according to HbA1c levels

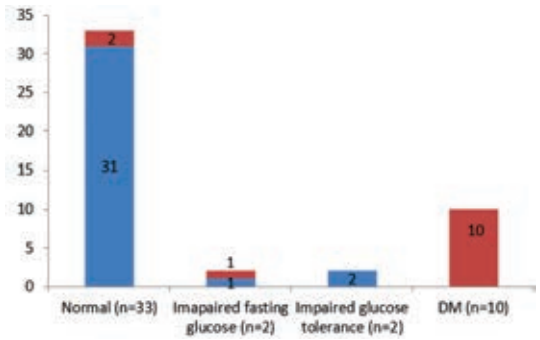


Fig. 6: Distribution of study population according to OGTT results after 1 month

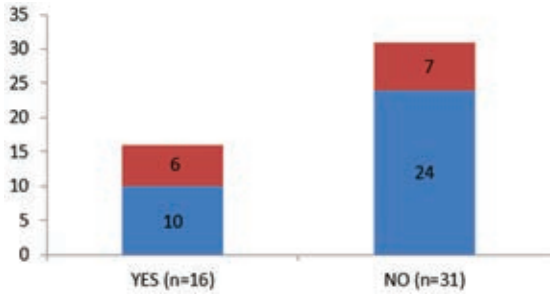


Fig. 7: Presence of acute rejection and development of NODAT

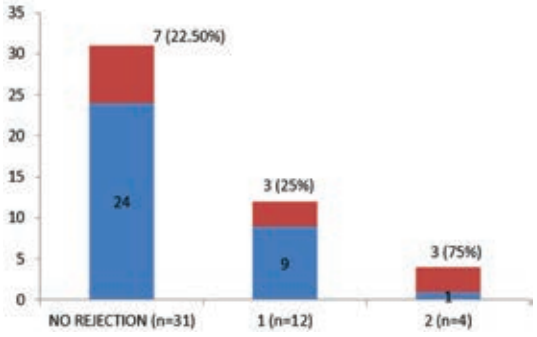


Fig. 8: Number of acute rejections and development of NODAT

other variables were higher in Non DM group as compared to DM group. All these variables were subjected to various tests to look for significant effect on NODAT. Mean age of study population was 37.25 years with standard deviation of 11.609. Mean age of study population who developed diabetes was 43.08 years with standard deviation of 9.096 and mean age of study population who did not develop diabetes at the end of 6 months was 35.03 years with standard deviation of 12.571. In ≤30 age group, we had 14 patients and none of them developed diabetes during follow-up period. Out of 12 patients in age group of 31 to 40 years, 5 (41.66%) developed diabetes. In 41 to 50 age group, 5 (35.71%) out of 14 patients developed diabetes and in 7 patients who were having age >50 years, 3 (42.85%) developed diabetes. In above study recipient's age had no significant effect on development of NODAT (p = 0.051).

In above study, 27 (54%) patients were having Chronic glomerulonephritis (CGN) as underlying kidney disease, 8 (16%) patients were having Chronic interstitial nephritis (CIN), 6 (12%) patients were having Chronic pyelonephritis (CPN) and , 2 (4%) were having Polycystic kidney disease, 6 (12%) were having hypertensive nephrosclerosis, and 1 (2%) patient was having hereditery nephropathy as underlying disease. 5 out of 26 patients with CGN (19.23%), 2 out of 8 (25%) patients with CIN, 3 out of 5 (60%) patients with CPN and hypertensive nephrosclerosis develops diabetes during follow-up period. Recipient's native kidney disease had no significant effect on development of NODAT (p = 0.198).

Out of 47 patients which were followed for 6 months, 4 patients were having second renal transplant surgery and for remaining 43 patients this was first transplant surgery. 3 out of 4 patients (75%) who were having second transplant surgery and 10 out of 43 patients (23.25%) having first transplant surgery developed diabetes during follow-up period of 6 months. study number of transplant surgery had significant effect on development of NODAT (p = 0.027). The patients having HbA1c >6.5% were not included in the study. Out of 47, 6 patients were having HbA1c in the range of 5.7-6.4%. Out of these 6 patients, 5 (83.33%) developed diabetes and out of remaining 41 patients with HbA1c <5.7, 8 (19.51%) developed diabetes. In our study pre-transplant HbA1c had significant effect on development of NODAT (p = 0.004). Out of 47 patients, 10 patients detected to have NODAT at the end of one month and they remained diabetic till the end of study. Out of 4 patients who had impaired OGTT after 1 month, 1 patient (25%) developed diabetes. In above study post-transplant 1 month OGTT had significant effect on development of NODAT (p = 0.0001). Total 16 patients had acute rejection during the study and 31 patients had no rejection. 9 out of 16 patients had presumed acute rejection and remaining 7 patients had biopsy proven rejection. Both biopsy proven and presumed rejections were considered for statistical analysis. Out of 16 patients who had acute rejection, presumed or biopsy proven, 6 patients (37.5%) developed diabetes and out of 31 patients with no rejection, 7 patients (22.5%) developed diabetes. In above study, acute graft rejection had no significant effect on development of NODAT (p = 0.279). Out of 16 patients who had acute rejection episode, 4 patients had 2 episodes of acute rejection during study period. Out of these 4 patients, 3 (75%) developed diabetes during study. Out of 12 patients who had single episode of rejection, 3 (25%) developed diabetes during study and 7 out of 31 (22.50%) patients developed diabetes in no rejection group. In above study, number of acute rejection had no significant effect on development of NODAT (p = 0.186).

In the above study, mean age of the population was 37.25 years with standard deviation of 11.609. Among 401 patients included in the study conducted by Sailaja Kesiraju[15], NODAT was observed in 59 patients (14.7%) after a mean follow-up time of 58.7 months. The mean age of the patients was 39.7±9.1 years and 69.1% were men and 30.1% were women. The incidence of NODAT was 2.74, 4.98 and 6.98% at 1, 3 and 5 years following transplantation. In a study conducted by Dharmik Patel *et al*[16]. it was reflected that patients with more than 45 years age having more chances to develop NODAT than patients with age less than 45 years (P<0.0001). Polycystic kidney disease may be associated with an increased risk of NODAT, although this has not been consistently observed [17-20]. In our study we had 2 polycystic kidney disease patients and none of them developed NODAT. In above study native kidney disease had no significant effect on development of NODAT (p = 0.198).

In a study by Yogesh N. V. Reddy, Georgi Abraham *et al*[21]. of all the patients, 59.8% did not show a worsening of their pre-transplant glucose tolerance status and either retained their pre-transplant IGT or normal glucose tolerance status, or even reverted back from IGT to normal glucose tolerance after transplantation. Of the 78 patients had normal glucose tolerance before transplantation, 34.6% remained as such after transplantation, 55.1% developed new-onset IGT and 10.3% developed NODAT. There were 24 patients with IGT before transplantation, of which 41.7% had only uremic-induced IGT, which reverted back to normal glucose tolerance after transplantation, 33.3% maintained their IGT status after trans-plantation without worsening and 25% developed NODAT. In a study conducted by Jayant T. Mathew *et al*[22]. on logistic regression analysis, patients with a 1-h glucose value) 50th percentile on

**Table 1: Descriptive analysis of study population**

| | Outcome | N | Mean | Std. Deviation | p-value |
|---|---|---|---|---|---|
| AGE (years) | Non DM | 34 | 35.03 | 12.571 | 0 . 5 1 |
| | DM | 13 | 43.08 | 9.096 | |
| Duration of dialysis (months) | Non DM | 34 | 12.65 | 14.327 | 0.002 |
| | DM | 13 | 29.62 | 20.201 | |
| Weight (kg) | Non DM | 34 | 58.272 | 13.4875 | 0.171 |
| | DM | 13 | 63.915 | 8.9500 | |
| BMI (kg/m2) | Non DM | 34 | 21.2644 | 4.42506 | 0.017 |
| | DM | 13 | 24.7631 | 3.98820 | |
| Waist circumference (cm) | Non DM | 34 | 82.2147 | 11.86224 | 0.032 |
| | DM | 13 | 90.1923 | 8.36794 | |
| HbA1c (%) | Non DM | 34 | 4.9206 | .45712 | 0.004 |
| | DM | 13 | 5.3385 | .52684 | |
| Fasting C-Peptide (ng/ml) | Non DM | 32 | 6.2853 | 3.71413 | 0.64 |
| | DM | 13 | 9.0538 | 5.66916 | |
| Total Cholesterol (mg/dl) | Non DM | 34 | 149.682 | 35.67167 | 0.212 |
| | DM | 13 | 163.692 | 28.66585 | |
| HDL-C (mg/dl) | Non DM | 32 | 44.2188 | 9.74095 | 0.367 |
| | DM | 13 | 41.3846 | 8.66543 | |
| LDL-C (mg/dl) | Non DM | 32 | 81.8438 | 28.25929 | 0.381 |
| | DM | 13 | 89.8462 | 25.31089 | |
| Triglycerides (mg/dl) | Non DM | 32 | 112.222 | 47.77821 | 0.020 |
| | DM | 13 | 170.622 | 63.00997 | |

the pre-transplant OGTT were found to have significantly greater risk (OR = 2.9, 95% CIs1.2-6.9, P = 0.01). When only the development of NODAT was considered as the outcome, risk factors in addition to higher 1-h OGTT value included greater age and a more rapid increase in BMI pre-transplant. The 2-h value >140 mg/dl that identified patients with impairment of glucose tolerance pre-transplant similarly showed an increased risk of developing either IGT or NODAT post-transplant (OR = 3.3, 95% CIs1.4-8.1, P = 0.01) when adjusted for the same covariates, however, it did not retain significance when only the development of NODAT was considered.

In above study, out of 5 patients with impaired GTT, 3 patients (60%) developed diabetes which was much higher compared to patients with normal GTT in which 2 (8.3%) out of 24 patients developed diabetes. In above study pre-transplant OGTT had significant effect on development of NODAT (p = 0.019).Also, pre-transplant HbA1c and OGTT after 1 month post-transplant also had significant effect on NODAT with p values being 0.004 and 0.0001 respectively. There is not much literature available on c-peptide in relation to NODAT. In previous studies insulin levels were correlated with development of NODAT. Recent studies demonstrate that impaired insulin secretion and insulin resistance characterize patients with IFG, IGT and NODAT[23,24]. In a study by Manisha Sahay *et al*[25]. while insulin resistance was universal, only patients with an additional insulin secretory defect developed overt NODAT[25].In above study mean fasting c-peptide levels were higher than normal in most of the study population but in patients developing NODAT had higher mean c-peptide levels than remaining population. In above study, acute pre-transplant fasting c-peptide level had no significant effect on development of NODAT (p = 0.64).

In a study by Manisha Sahay *et al*[25]. total cholesterol and LDL-cholesterol (224.5±28.49 and 159.85±26.30 respectively) were significantly (p<0.05) higher in group who developed NODAT compared to group who did not (205.18±17.93 and 140.64± 18.81respectively). There was not much difference seen in HDL-cholesterol and serum triglycerides. In a study by Yogesh N. V. Reddy, Georgi Abraham *et al*[21]. failure of triglyceride (P = 0.001) or low-density lipoprotein (LDL) (P = 0.03) to lower or high-density lipoprotein to rise (P = 0.001) and higher post- transplant LDL (P<0.001) and cholesterol levels (p = 0.002) were associated with development of NODAT.

## CONCLUSION

The results show that the incidence rate of NODAT is higher in Indian patients than other patients. In the above conducted study recipient's age did not have significant effect on outcome of the study may be due to small sample size. There is significant effect of pre and 1 month post-transplant GTT, pre-transplant HbA1c and pre-transplant serum triglyceride levels on the development of NODAT. Fasting c-peptide, total cholesterol, LDL-c and HDL-c have no significant effect on the development of NODAT in above study. Pre-transplant GTT and HbA1c can be recommended for screening the patients to detect pre-diabetic stage as this has significant effect on the development of NODAT.

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