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# New Onset Diabetes Mellitus after Transplantation (NODAT)-An Analysis of Incidence, Risk Factors and its Effects on Renal Allograft

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## Abstract

**Aim:** New Onset Diabetes after Transplantation (NODAT) is one of the medical complications after kidney transplantation which affects adversely the allograft kidney and patient outcomes. The aim of this study was to know the incidence of development of NODAT, investigate risk factors and its effects on allograft kidney in our centre.

**Material and methods:** This is a retrospective observational study of the patients who underwent the kidney transplant at the Narayana Medical College & Hospital from June 2009 to May 2016. Patients were divided into NODAT and non NODAT groups.

**Results:** 21 out of 84 patients (25%) developed NODAT during the follow up period of 1st year post transplantation. We found age >30 years (OR: 3.8; P=0.012), family history of diabetes (OR: 8.6; P=0.0004), impaired fasting glucose (OR: 7.27; P=0.0003), postoperative hyperglycaemia (OR: 2.83; P=0.04), fasting triglycerides >150 mg/dl. (OR: 8.0 P=0.0001) and VLDL levels (42.52 ± 30.81 mg/dl. *vs.* 24.24 ± 5.51 mg/dl; P= 0.01) were risk factors for NODAT. Mean serum creatinine values were 1.23 ± 0.25 mg/dl *vs.*1.16 ± 0.35mg/dl (P= 0.42) and 1.61 ± 0.53 mg/dl *vs.* 1.44 ± 0.54 mg/dl (P= 0.24) at the end of 1st month and 1st year post-transplantation in NODAT and non NODAT groups respectively.

**Conclusion:** The cumulative incidence of NODAT was 25% by the end of the1st post-transplantation year. Increasing age, family history of diabetes, dyslipidemia, pre-transplantation impaired fasting glucose and postoperative hyperglycaemia were considered as risk factors, some of which can be quite modifiable.

**Keywords:** Allograft kidney; Kidney transplantation; New-onset diabetes after transplantation; Risk factors

## Introduction

Kidney transplantation is the preferred mode of treatment than to be on maintenance dialysis for patients with End Stage Renal Disease (ESRD). Short term and long term graft and patient survival following kidney transplantation have improved very much with current immunosuppressive medication. However, these patients are prone to a number of infectious and metabolic complications which will lead to increased medical expenses, morbidity and mortality. New Onset Diabetes After Transplantation (NODAT) is one of the metabolic complications after kidney transplantation which affects adversely the allograft kidney and patient outcomes [1,2]. Post- transplant diabetes mellitus (PTDM) was the older term used for the same complication. The reported incidence of NODAT ranges from 10-30% in adult kidney transplant recipients on CNIs and steroids [3,4]. The wide variations in the reported incidence may be due to variation in treatment protocols employed across the transplant centres, duration of follow-up, lack of standard definition of the condition, presence of modifiable risk factors such as lifestyle, dyslipidaemia, immunosuppressive medications, infections like Hepatitis virus (HVC) and cytomegalovirus (CMV) as well as non-modifiable risk factors like age, ethnicity, and family history of diabetes mellitus. Since the majority of reports indicate that NODAT is associated with diminished patient survival, identification of critical risk factors which can be modifiable may help to create conditions in order to improve transplant outcomes.

The aim of this study was to know the incidence of New Onset Diabetes after transplantation (NODAT), investigate risk factors, and its effects on allograft kidney in our centre.

## Materials and Methods

After obtaining approval from the ethical committee of the institute, a retrospective observational study of patients who underwent kidney transplantation from June 2009 to May 2016 at the Department of Nephrology and Transplantation Unit of Narayana Medical College and Hospital was conducted. Kidney transplant recipients aged between 10-54 years were included in this study.

Exclusion criteria were patients 1) with a history of pre-transplant diabetes mellitus 2) who received second renal transplantation 3) with graft failure requiring maintenance dialysis and 4) who died within 1 year of transplantation. Data of rest of the patients (study cohort n= 84) was analysed.

The following characteristics such as age, gender, body mass index (BMI), native kidney disease, family history of type 2 diabetes mellitus (T2DM), pre-transplant hepatitis C positivity, CMV infection, number of biopsy- proven rejection episodes and their treatments, type of renal

transplantation (living or deceased), immunosuppressive therapy and follow up visits were noted from the patients medical records. Biochemical data like fasting and random plasma glucose levels, pre transplant lipid profile and serum creatinine at the time of discharge from hospital and during follow-up visits were also recorded.

NODAT is diabetes that develops for the first time in the patient, following kidney transplantation and is defined by WHO and ADA criteria [5] as follows:

1. Fasting plasma glucose (FPG) ≥ 126 mg/dL.

2. Symptoms of hyperglycaemia i.e., polydipsia, polyuria and unexplained weight loss and a casual plasma glucose ≥ 200 mg/dL.

In addition, we considered that NODAT developed when the patients used antidiabetic drugs for a period of >1month at any time during the 1st year of post- transplantation.

Postoperative hyperglycemia is defined as random plasma glucose >200 mg/dl, or need of insulin therapy during the hospital stay in postoperative period, whereas Impaired fasting glucose is fasting plasma glucose ≥ 110 mg/dl and <126 mg/dl. Fasting is defined as no caloric intake for at least 8 hours.

Neither oral glucose tolerance test (OGTT) nor Glycosylated haemoglobin (HbA1c) level was used for diagnosing NODAT in our centre. However HbA1c levels were used to monitor glycaemia status in patients who developed NODAT.

Patients were divided into two groups: those who developed diabetes after transplantation as NODAT group and those who had not developed diabetes as a non NODAT group. Two groups were compared with respect to demographic, clinical and laboratory data to find out incidence and risk factors of NODAT and its influence on renal allograft function.

### Immunosuppression

All the patients received I.V.Methylprednisolone 500 mg (intraoperative) on day 0, and 250 mg on day 1 and day 2, followed by oral prednisolone 40 mg /day from day 3 to day 6, then subsequent tapering over 12 weeks to reach 7.5 mg to 5 mg/day. Calcineurin inhibitor therapy was started prior to transplantation (Day-2) using tacrolimus at the dose of 0.1 mg/kg/day (PO) in two divided doses and drug whole blood trough levels were maintained at 8-12 ng/ml in first 2 months, 6-10 ng/ml between 3-6 months and 4-6 ng/ml thereafter. In few patients, tacrolimus was changed to sirolimus during the follow-up visits at various points of the time. Cyclosporine A was given to HCV positive recipients at the dose of 7-8 mg/kg/day (PO) in two divided doses initially later tapered to 3 mg/kg/day over 3-6 months. Initially, all patients received Mycophenolate sodium at the dose of 720-1080mg/day (tab 360mg strength) starting two days prior to transplantation but changed to Azathioprine in few, during follow-up visits.

Biopsy proved acute cellular rejection was treated with methylprednisolone 500mg/day (IV) for three consecutive days. Antibody-mediated rejection (ABMR) was treated with plasmapheresis (1 plasma volume removal per session, total 5 sessions) and intravenous immunoglobulin (100 mg/kg/day, total 5 doses). Induction therapy was given with Rabbit Anti Thymocyte Globulin (ATG) - single dose 1.5 mg/kg on day '0' and Basiliximab- two doses on day '0' and on day 4, to deceased donor kidney recipients and spousal kidney recipients respectively. All the patients with induction therapy received a primary Cytomegalovirus (CMV) prophylaxis.

### Statistical analysis

Collected data were subjected to statistical analysis using IBM SPSS Version 20.0 (IBM SPSS, Chicago, USA). Results were compared between NODAT and non NODAT groups. Comparisons of categorical variables were done using Chi-square test and continuous variables by student's t-test. OR (odds ratio) with 95% CI (confidence intervals) was calculated for estimating the risk. The P value <0.05 was taken to indicate statistically the significant difference.

## Results

A total of 84 patients were included in this study, of which 74 were males and 10 were females (M: F=7.4:1) with age range of 10-54 years (Mean 30.11 ± 9.97) and BMI between 11.38 and 31.60 kg/m$^2$ (Mean 22.56 ± 4). The family history of diabetes was present in 16 (19.04%) patients. Native kidney diseases were CGN in 56 patients, CIN in 24 patients and ADPKD in 4 patients. Hemodialysis was the mode of renal replacement therapy in 83 (98.80%) patients, while 1 patient received pre-emptive transplantation. 2 patients were positive for Hepatitis virus C (HCV), 3 patients were positive for Hepatitis virus B (HBV) before transplantation and 8 patients were positive for Cytomegalovirus (CMV) after transplantation. 73 (86.90%) patients received kidneys from live donors while 11(13.10%) patients received kidneys from deceased donors. All the patients received steroid based triple immunosuppression (Table 1).

| Demographic and clinical characters | Study cohort (n = 84) Mean ± SD or Ratio or % |
|---|---|
| Age | 30.11 ± 9.97 |
| BMI (kg/m$^2$) | 22.56 ± 4.1 |
| Gender (M/F) | 74/10 (7.4:1) |
| Family history of Diabetes mellitus% | 16 (19.04%) |
| Native Kidney Disease | |
| CGN | 56 (66.67%) |
| CIN | 24 (28.57%) |
| ADPKD | 04 (4.76%) |
| Hemodialysis pre transplant. | 83 (98.80%) |
| Pre- emptive transplantation | 01 (1.20%) |
| HCV – RNA Positivity% | 02 (2.38%) |
| HBV Positivity | 03 (3.57%) |
| CMV Positive(PCR) | 08. (9.52%) |
| Donor Type | |
| Live | 73 (86.90%) |
| Deceased | 11 (13.10%) |
| Donor Gender | |
| Male | 23 (27.38%) |

| | |
|---|---|
| Female | 61. (72.62%) |
| Immunosuppression | |
| Induction received | 27 (32.14%) |
| Prednisolone use | |
| At 1month/at 12 months | 84. (100%) |
| Cyclosporine A use | 02 (2.38%) |
| Tacrolimus use | |
| At 1month | 82 (97.6%) |
| At 12 months | 76 (90.4%) |
| Sirolimus use at 12 months | 06 (7.14%) |
| Mycophenolate sodium in most patients, Azathioprine in few. | |
| BMI: Body mass index, CGN: Chronic glomerulo nephritis, CIN: Chronic interstitial nephritis ADPKD: Autosomal dominant polycystic kidney disease HCV: Hepatitis C virus, HBV: Hepatitis B virus, CMV: Cytomegalovirus | |

**Table 1:** Base line characteristics of the study patients.

21(25%) patients developed diabetes (NODAT) as per criteria over a follow-up period of 1 year, of whom 19 were males and 2 females. Patients with >30 years had increased risk of developing NODAT (OR: 3.8; CI: 1.30-11.10; P=0.012). 62.5% (10/16) patients with a positive family history of diabetes developed NODAT but only 16.18% (11/68) patients without family history of diabetes developed NODAT which was showing a highly significant difference (OR: 8.63; CI: 2.60-28.68; P<0.001). 11 out of 67 (16.4%) patients with normal fasting plasma glucose levels before transplantation developed NODAT whereas 10 out of 17 patients (58.8%) with impaired fasting plasma glucose levels developed NODAT which was highly significant (OR:7.27; CI: 2.28-23.25; P<0.001). 36.1% (13/36) patients with postoperative hyperglycaemia developed NODAT and 16.7% (8/48) patients without postoperative hyperglycaemia developed NODAT (OR: 2.83; CI: 1.02-7.83; P=0.04). Out of 21 patients with triglyceride levels >150 mg/dl, 12 (57.1%) developed NODAT and in 63 patients with triglycerides levels <150 mg/dl, only 9 (14.3%) developed NODAT which was highly significant (OR: 8.00; CI: 2.62-24.42; P<0.001). The acute cellular rejection was developed in 8 patients and was treated with pulse steroids: 50% (4/8) of them developed NODAT, but only 22.4% (17/76) patients without history of acute cellular rejection had NODAT (OR: 3.47; CI: 0.78-15.36; P=0.086) (Table 2).

| RISK GROUPS | NODAT | Non NODAT | P-VALUE | ODDS RATIO (95% C.I.) |
|---|---|---|---|---|
| Age | N N% | N N% | | |
| ≤ 30 years | 06 (13.6%) | 38 (86.4%) | | |
| > 30 years | 15 (37.5%) | 25 (62.5%) | 0.012* | 3.8 (1.30-11.10) |
| Sex | | | | |
| Male | 19 (25.7%) | 55 (74.3%) | | |
| Female | 02 (20.0%) | 08 (80.0%) | 0.697 | 1.38 (0.27-7.09) |
| BMI (kg/m$^2$) | | | | |
| <18.5 | 03 (21.4%) | 11 (78.6%) | | |
| 18.5 -24.9 | 09 (20.9%) | 34 (79.1%) | | |
| 25-29.9 | 08 (33.3%) | 16 (66.7%) | | |
| ≥ 30 | 01 (33.3%) | 02 (66.7%) | 0.688 | - |
| Family History of Diabetes | | | | |
| Yes | 10 (62.5%) | 06 (37.5%) | | |
| No | 11 (16.18%) | 57 (83.82%) | <0.0004** | 8.63 (2.60-28.68) |
| Native Kidney Disease | | | | |
| CGN | 12 (21.4%) | 44 (78.6%) | | |
| CIN | 08 (33.3%) | 16 (66.7%) | | |
| ADPKD | 01 (25.0%) | 03 (75.0%) | 0.530 | - |
| Fasting Plasma Glucose mg/dl | | | | |
| ≥ 110 and <126 | 10 (58.8%) | 07 (41.2%) | | |
| <110 | 11 (16.4%) | 56 (83.6%) | 0.0003* | 7.27 (2.28-23.25) |

| | | | | |
|---|---|---|---|---|
| Post operative Hyperglycaemia mg/dl | | | | |
| ≥ 200 | 13 (36.1%) | 23 (63.9%) | | |
| <200 | 08 (16.7%) | 40 (83.3%) | 0.04* | 2.83 (1.02-7.83) |
| HDL - C (mg/dl) | | | | |
| < 40 in male and < 50 in female | 14 (28.0%) | 36 (72.0%) | | |
| ≥ 40 in male and ≥ 50 in female | 07 (20.6%) | 27 (79.4%) | 0.441 | 1.50 (0.53-4.23) |
| Triglycerides (mg/dl) | | | | |
| ≥ 150 | 12 (57.1%) | 09 (42.9%) | | |
| < 150 | 09 (14.3%) | 54 (85.7%) | <0.0001** | 8.00 (2.62-24.42) |
| Donor Type | | | | |
| Live | 16 (21.9%) | 57 (78.1%) | | |
| Deceased | 05 (45.5%) | 06 (54.5%) | 0.093 | 2.97 (0.80-11.00) |
| Donor Sex | | | | |
| Male | 07 (30.4%) | 16 (69.6%) | | |
| Female | 14 (23.0%) | 47 (77.0%) | 0.480 | 1.47 (0.50-4.28) |
| Graft Dysfunction § | | | | |
| Yes | 08 (27.6%) | 21 (72.4%) | | |
| No | 13 (23.6%) | 42 (76.4%) | 0.691 | 1.23 (0.44-3.43) |
| Acute cellular rejection | | | | |
| Yes | 04 (50.0%) | 04 (50.0%) | | |
| No | 17 (22.4%) | 59 (77.6%) | 0.086 | 3.47 (0.78-15.36) |
| CMV infection | | | | |
| Yes | 03 (37.5%) | 05 (62.5%) | | |
| No | 18 (23.7%) | 58 (76.3%) | 0.391 | 1.93 (0.42-8.89) |
| HCV infection | | | | |
| Yes | 01 (50.0%) | 01 (50.0%) | | |
| No | 20 (24.4%) | 62 (75.6%) | 0.41 | 3.10 (0.19-51.87) |
| HBV infection | | | | |
| Yes | 02 (66.7%) | 01 (33.3%) | | |
| No | 19 (23.5%) | 62 (76.5%) | 0.09 | 6.53 (0.56-75.99) |
| INDUCTION TYPE | | | | |
| Yes | 10 (37.04%) | 17 (62.96%) | | |
| No | 11 (19.30%) | 46 (80.70%) | 0.08 | 2.46 (0.89 - 6.83) |

* - P < 0.05-significant. **- P <0.0001-highly significant. BMI: Body mass index, HCV: Hepatitis C virus, HBV: Hepatitis B virus, CMV: Cytomegalovirus. §: 30% rise of serum creatinine from the base line. HDL: High density lipoproteins cholesterol

**Table 2:** Risk estimation between categorical groups and NODAT with 95% CI.

The mean age was 35 ± 8.78 years in NODAT group and 28.48 ± 9.87 years in non NODAT group at the time of kidney transplantation (P=0.01). The mean BMI values for NODAT and non NODAT groups were 23.19 ± 3.89 kg/m$^2$ and 22.34 ± 4.05 kg/m$^2$ respectively (P=0.40). Mean triglyceride levels in NODAT group was 178.52 ± 103.099 mg/dl whereas it was 119.79 ± 30.363 mg/dl in non NODAT group (P=0.02). Mean HDL levels were 38.43 ± 11.316 mg/dl and 38.22 ± 7.22 mg/dl in NODAT and non NODAT groups respectively which was not a significant difference (P=0.93). Mean VLDL levels were 42.52 ± 30.818 mg/dl and 24.24 ± 5.517 mg/dl in patients with NODAT group and non NODAT group respectively which was statistically significant (P=0.01) (Table 3).

| Variable | NODAT (Mean ± SD) | Non NODAT (Mean ± SD) | P value |
|---|---|---|---|
| Age (Years) | 35.00 ± 8.786 | 28.48 ± 9.872 | 0.01* |
| BMI (Kg/m$^2$ ) | 23.19 ± 3.89 | 22.34 ± 4.05 | 0.40 |
| IFG | 96.52 ± 22.45 | 88.98 ± 14.45 | 0.08 |
| Post-operative hyperglycaemia | 205.10 ± 87.72 | 168.44 ± 74.37 | 0.07 |
| VLDL-C | 42.52 ± 30.18 | 24.24 ± 5.51 | 0.01* |
| LDL-C | 90.33 ± 24.54 | 86.11 ± 13.09 | 0.46 |
| TGL | 178.52 ± 103.09 | 119.79 ± 30.36 | 0.02* |
| TC | 171.24 ± 57.20 | 151.92 ± 22.12 | 0.15 |
| HDL-C | 38.43 ± 11.31 | 38.22 ± 7.72 | 0.93 |
| Tacrolimus – level | 10.96 ± 5.92 | 9.64 ± 4.03 | 0.51 |

* - P <0.05, is significant. Units are in mg/dl, Tacrolimus trough levels in ng/ml, initial 2months, BMI: Body mass index, IFG: Impaired fasting glucose, VLDL Very low density lipoproteins cholesterol, LDL: Low density lipoprotein cholesterol, TGL: Triglycerides, TC: Total cholesterol, HDL: High density lipoproteins cholesterol

**Table 3:** Comparison of continuous variable risk factors between NODAT (n=21) and non NODAT (n=63) groups.

Mean serum creatinine values in NODAT and non NODAT groups were 1.23 ± 0.25 mg/dl *vs.* 1.16 ± 0.35 mg/dl with P=0.42 at the end of 1 month and 1.61 ± 0.53 mg/dl vs. 1.44 ± 0.54 mg/dl with P=0.24 at the end of 1 year. Graft dysfunction as defined by a rise in serum creatinine of >30% from baseline was seen in 38.09% (8/21) in NODAT group, whereas it was 33.33% (21/63) in patients with the non NODAT group (OR:1.23; CI: 0.44-3.43; P= 0.691) (Table 4).

| Variable | NODAT (Mean ± SD) | Non NODAT (Mean ± SD) | P value |
|---|---|---|---|
| S.Creatinine at 1month | 1.23 ± 0.25 | 1.16 ± 0.35 | 0.42 |
| S.Creatinine at 1 year | 1.61 ± 0.53 | 1.44 ± 0.54 | 0.24 |
| Graft dysfunction§ | 8/21 (38%) | 21/63 (33%) | 0.69 |

* - P <0.05, is significant, Serum creatinine levels in mg/dl. § 30% rise of serum creatinine from the base line

**Table 4:** Comparison of allograft kidney function between NODAT (n=21) and non NODAT (n=63) groups.

## Discussion

Our study had shown that NODAT was a common metabolic complication in the kidney transplant recipient population with an incidence of 25% at the end of the first year. Majority of NODAT cases (2/3) occurred in the first six months, which corresponds to the period of high doses of immunosuppressive drugs. Regarding scientific literature, the incidence of NODAT is ranging from 10-30% in adult kidney transplant recipients on CNIs and steroids. The wide variations in the reported incidence may be due to variation in immunosuppressive protocols employed across the transplant centres, duration of follow-up and lack of standard definition of the condition [3,4]. According to the National Urban Survey for Diabetes, conducted by Diabetes Epidemiology Study Group in India (DESI), the prevalence of diabetes in the urban population of our country ranges from 6.1% to 16.6% across the different metropolitan cities, with highest being at Hyderabad [6]. Padmanabhan Guruprasad et al. in their prospective observational study reported the incidence of NODAT as 28% within the first 3 months of post transplantation [7].

### Risk factors

There was a significant relationship between the development of NODAT and increase in age, family history of diabetes, impaired fasting glucose, postoperative hyperglycaemia, high VLDL and hypertriglyceridemia. So they were identified as risk factors for NODAT in the current study.

We found age as a risk factor for the development of NODAT, but it is not surprising when we consider advancing age as a risk factor for

type 2 diabetes in general population. Mean age of our study cohort was around 30 years and the mean age of patients in NODAT group (35 years) was higher than those of non NODAT group (28.5 years) in our study. We observed >30 years of age was associated with significant risk for NODAT (P=0.012). Prakash Jai et al. reported about the higher mean age of onset of NODAT which was around 40 years [8]. Casio et al. showed that transplant recipients of age > 45 years were 2.2 times more likely to develop NODAT than those of age <45 years (p<0.0001) [4]. Younger age of the subjects with NODAT in our study can be explained by selection bias, small sample size and a possible continued shift in the age of onset of type 2 diabetes in general population [6,9,10] towards young age and KDIGO Transplant work up group, noted that the risk of NODAT increases linearly with age but there was no clear threshold [11].

The family history of type 2 diabetes is a risk factor of NODAT in the several studies [12,13]. 62.5% of patients with family history of diabetes had developed NODAT, while 16.18% patients without family history developed NODAT (p<0.001) suggesting a strong association of family history of diabetes with the occurrence of NODAT in our study.

Obesity is a well-known risk factor for type 2 diabetes in general population so it can be anticipated that higher BMI in transplant recipients places them at higher risk of NODAT. A number of studies have shown positive association in this regard [14,15]. We could not find any significant association between BMI and NODAT in the present study. Even though majority of patients in NODAT group had BMI in normal and overweight range with only 1 obese patient, still high prevalence of NODAT in our study suggests the greater baseline risk of type 2 diabetes in Asian-Indian phenotype i.e., increased abdominal adiposity and increased insulin resistance which predisposes Indians to NODAT even with normal BMI [10,16,17].

Impaired fasting plasma glucose before transplantation and postoperative hyperglycaemia during the immediate post-transplant period were risk factors for NODAT in the current study with the odds ratio of 7.27 and 2.2.83 respectively. Similar findings were given in the literature; Ramesh Prasad GV et al. [18] concluded that pretransplantation glucose levels were independently associated with incremental risk of development of NODAT even in patients with normal OGTT. Another study showed that requirement of insulin therapy during hospitalization in the immediate post-transplant period was associated with a 4-fold increase in NODAT (RR: 4.01; CI: 1.49 to 10.7; P=0.006) [19].

In this study, dyslipidemia especially pre-transplant high fasting triglycerides (not low HDL-C) were associated with NODAT. Patients with fasting triglyceride levels >150 mg/dl prior to transplantation were at greater risk than those with triglyceride levels <150 mg/dl (P <0.001). The Mean VLDL levels were also higher in NODAT group compared to non NODAT group (42.52 ± 30.81 *vs.* 24.24 ± 5.51; P= 0.01). Porrini et al. [20] showed the pre-transplantation high triglyceride levels as a risk factor for NODAT in patients treated with tacrolimus. Cosio et al. [1] also found the comparable results in a retrospective analysis of 1,811 kidney transplant recipients. Since hypertriglyceridemia is strongly associated with insulin resistance and the ratio of triglyceride to HDL-C is also shown to be a metabolic marker for insulin resistance in general population [21], we could support the association of hypertriglyceridemia with NODAT.

There is a tendency to develop type 2 diabetes in patients with positive hepatitis C virus serology in general population [22]. Studies have reported that positive HCV serology was a risk for development of NODAT with relative risk ranges from 1.3 to 1.4. [14,15]. Achieving sustained virological response with drugs might be beneficial in reducing the risk of NODAT [23]. With regard to CMV even asymptomatic CMV infection is a risk factor for NODAT [24]. But this finding has not been confirmed by others, moreover, there is no clear relationship between CMV serological status and risk of type 2 diabetes in general population [25,26]. In our study cohort, only 2 patients had positivity for HCV RNA, out of which only one patient developed NODAT and 8 patients were positive for CMV after transplantation of which 3 patients were from NODAT group during the follow-up period, so we could not conclude on these issues.

We found that percentage of NODAT was more in patients who received kidneys from deceased donors than from live donors (45.5% *vs.* 21.9%) but not statistically significant (P=0.093) and donor gender also had shown no association with NODAT risk, which was in accordance with a study published by Kasiske et al. [14] who found no association between donor source and risk of NODAT. In contrary, Gourishankar et al. [27] observed an increased risk of development of NODAT if the patient received allograft kidney from the deceased donor. So association studies between the risk of development of NODAT and donor characteristics were unclear.

The incidence of NODAT in patients who received induction was higher than in those who did not receive induction albeit, this difference did not reach statistical significance (p=0.08) in the present study. All patients in our study received steroid based triple immunosuppression i.e., corticosteroids, tacrolimus/cyclosporine A, and mycophenolate sodium/azathioprine, few patients received sirolimus during the follow-up period in place of tacrolimus. There was no significant difference in the trough levels of tacrolimus between NODAT and non NODAT groups in initial two months (p=0.515) in our study.

Immunosuppressive drugs cause hyperglycaemia either by insulin resistance or inducing insulin secretion defects. Glucocorticoids are diabetogenic mainly by insulin resistance and also by gluconeogenesis which is dose related [28]. Dose reduction of oral prednisolone to 5mg/day improves the glucose metabolism in first six months of renal transplantation [29]. But any dose reduction of immunosuppressant drug to alleviate diabetogenic effect must be weighed against the risk of acute allograft rejection which would require pulsed high dose steroid, again a risk factor for NODAT [30]. Acute cellular rejection was noted in 8 patients during the study period and was treated with pulse steroids, 50% (4/8) of them developed NODAT, but only 22.4% (17/76) patients without history of acute cellular rejection had NODAT (P=0.086) suggesting tendency to develop NODAT though P value is not significant. Bansal et al. [31] reported early steroid withdrawal in living donor first kidney transplant recipients was associated with higher overall acute rejections at 6 months, but no difference in graft and patient survival. Calcineurin inhibitors (CNIs), cyclosporine A and tacrolimus are known to impair insulin secretion because calcineurin/NFAT (nuclear factor of activated T-cells) signalling regulates function and growth of the beta cells of pancreas [32]. CNIs thus cause hyperglycaemia and overt NODAT, with tacrolimus having greater diabetogenic potential than cyclosporine A [33]. Earlier studies failed to demonstrate the diabetogenic effect of Sirolimus, [34] but now it increasingly being recognized as having diabetogenic potential [35] by causing hepatic insulin resistance [36] and beta cell toxicity [37].

### Effect of NODAT on graft function

Renal function as assessed by serum creatinine levels at the end of the 1st year was low in NODAT group compared to non NODAT group (means: Creatinine values: NODAT *vs.* non NODAT 1.61 ± 0.53 *vs.*1.44 ± 0.54 and p=0.24). We considered the 30% rise in serum creatinine from the baseline as graft dysfunction and there was no significant difference in the graft dysfunction between NODAT and non NODAT groups (38.09% and 33.33%).

Our study had certain limitations. This was retrospective single centre study with small sample size and OGTT was not performed so true incidence of NODAT might have been underestimated. The lack of significant association between some of the risk factors in the present study could be due to small sample size. Prospective studies with large sample size are needed to clarify these aspects.

## Conclusion

With an incidence of 25% in this study, it can be concluded that NODAT is a commonly seen metabolic complication after kidney transplantation in the Indian population and increasing age, family history of diabetes, dyslipidaemia, pre-transplantation impaired fasting glucose levels and postoperative hyperglycaemia were the risk factors, some of which can be quite modifiable. Correction of these factors could decrease the incidence and severity of NODAT in the renal transplant recipients.

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