



Evaluation of Pre-Transplant Risk Factors as Independent Predictors on the New Onset of Diabetes after Renal Transplants (NODAT)



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Abstract

Background: One of the most potential complications in renal allograft recipients is post-operative impaired glucose tolerance leading to frank de novo Diabetes Mellitus known as New Onset Diabetes after Transplant (NODAT). It is multifactorial and is pathogenically similar to Type 2 Diabetes Mellitus. Having a variable incidence, it is usually associated with an increased risk of infection, cardiovascular morbidity, and graft dysfunction which can eventually cause mortality or loss of the allograft.

Methods: In this study we aimed at comparing pre-operative risk factors namely age, sex, gender, insulin resistance (estimated by HOMA-IR), β cell function (estimated by HOMA- β), pre-operative fasting plasma glucose, post-operative fasting plasma glucose, tacrolimus level, induction ATG and hepatitis C virus status as an implicating factor for those who developed NODAT in post-operative period versus those who maintained an euglycemic status throughout the study period (non-NODAT). The study was carried out at the renal transplant unit of NHRTIICS, Kolkata between Jan 2013 to Feb 2014.

Results: Among the 54 subjects included in the analysis, NODAT subjects (n=18) have significantly higher pre-operative insulin resistance levels (measured by HOMA-IR) than non-NODAT (n=36) subjects, $p=0.021$. Simultaneously, the beta cell function were significantly lower in the subjects in patients who developed NODAT compared to the non-NODAT subjects, $p=0.007$. Both the pre-operative and post-operative fasting plasma glucose were significantly higher in the patients who developed NODAT, $p=0.032$ and $p<0.001$ respectively. Tacrolimus levels were significantly higher in the NODAT patients, however, no significant difference was found with regards to induction ATG received ($p=0.96$) and hepatitis C virus status ($p=0.62$).

Conclusion: The incidence of NODAT is quite high in our renal transplant patients. Risk of development of post-transplant diabetes was more closely related to traditional risk factors namely age, pre-operative fasting plasma glucose, post-operative plasma glucose, pre-operative insulin resistance and immunosuppressive therapy.

Keywords: NODAT; Pre-operative risk factors; Independent predictors

Introduction

Renal transplantation (KT) is the treatment of choice for end-stage renal disease (ESRD); nevertheless, aftermath complications are a major source of concern, one of which is development of post-transplant Diabetes Mellitus, a frequent complication that represents one of the leading causes of morbidity and mortality. Diabetes occurs in a substantial number of subjects following renal transplantation. Post-transplant diabetes mellitus (PTDM) refers to newly diagnosed diabetes in post-transplant setting, irrespective of timing or whether it was present

but undetected prior to transplantation or not. However, the term PTDM should be utilized for clinically stable patients who have developed persistent post-transplantation hyperglycemia. On the other hand, new onset diabetes mellitus after transplant (NODAT) refers to the development of diabetes post-transplant in previously non-diabetic patients [1].

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. Many of the same risk factors that predispose non-transplant subjects to diabetes mellitus have been identified as risk factors for its development after transplantation. Such common risk factors include age, obesity, African-American race and Hispanic ethnicity, family history, and impaired glucose tolerance. Risk models for NODAT have been developed and validated using pre-transplant variables alone. In addition, some risk factors are unique to the transplant population. These include specific agents used for immunosuppression, human leukocyte antigen (HLA) mismatch, donor sex, and type of underlying renal disease [2]. Impaired glucose tolerance prior to transplant and hyperglycemia in the immediate perioperative period may identify subjects at higher risk for the development of NODAT [3,4].

Materials and Methods

This was a single centered retrospective real world observational study of 54 subjects who underwent renal transplantation over a period of one year in a tertiary care center in eastern India. NODAT was defined according to American Diabetes Association definition with fasting glucose level equal or greater than 126mg/dl on two separate blood tastings; and/or two hours OGTT values equal or greater than 200mg/dl; and/or glycosylated hemoglobin (HbA1C) equal or greater than 6.5. The Inclusion criteria were 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 American Diabetes Association guideline (not on oral hypoglycemic agents or insulin with fasting glucose <126mg/dL) and received immunosuppressive medications that include Tacrolimus. Subjects who were capable of understanding the study and given informed written consent for study participation were only included. Subjects with a diagnosis of diabetes mellitus prior to kidney transplantation based on ADA criteria for diagnosis of diabetes mellitus or those receiving anti-diabetic medications or those who were not capable of providing consent were excluded from the study.

Statistical methods

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD and results on categorical measurements are presented in Number (%). Significance is assessed at a level of 5%.

Results

Among the 54 subjects included in the analysis, mean age of the subjects were 46±10.33 years and 32.14±13.67 years in NODAT (n=18) and Non-NODAT (n=36) cohort respectively. There was a statistically significant difference between two groups with respect to age. The study has a slight male preponderance with only 13 (24.07%) were females and the rest 41 (75.93) were males. However, there was no significant between the two cohorts with respect to BMI (Table 1). In our study, NODAT

subjects have significantly higher pre-operative insulin resistance levels (measured by HOMA-IR) than non-NODAT subjects, p=0.021 (Table 1). Simultaneously, the beta cell function were significantly lower in the subjects in patients who developed NODAT compared to the non-NODAT subjects, p=0.007 (Table 1). Both the pre-operative and post-operative fasting plasma glucose were significantly higher in the patients who developed NODAT, p=0.032 and p<0.001 respectively (Table 1). Tacrolimus levels were significantly higher in the NODAT patients, however, no significant difference was found with regards to induction ATG received (0.96) and hepatitis C virus status (0.62) (Table 1).

Table 1: Comparison of variables between subjects with and without NODAT.

Characteristic	NODAT (Mean ± SD) (N=18)	NON-NODAT (Mean ± SD) (N=36)	p
Age (in years)	46 ± 10.33	32.14 ± 13.67	0.037
BMI (kg/m ²)	19.33 ± 3.08	19.99 ± 3.45	0.81
Female sex-no. (%)	3 (16.66%)	10 (27.77%)	
Male sex-no. (%)	15 (83.33%)	26 (72.22%)	0.51
HOMA-IRCP (pre-operative insulin resistance level)	0.66 ± 0.17	0.24 ± 0.18	0.021
HOMA-β	32.61 ± 19.85	116.95 ± 45.76	0.007
Pre-operative fasting plasma glucose (mg/dl)	94.17 ± 9.93	76.09 ± 11.51	0.032
Post-operative fasting plasma glucose (mg/dl)	161.20 ± 29.60	99.21 ± 10.80	<0.001
Tacrolimus level	13.55 ± 5.62	7.61 ± 4.63	0.006
Induction ATG	12(66.66%)	22(61.11%)	0.96
Hepatitis C virus status	0	1 (2.78)	0.62

Discussion

According to International Consensus Guidelines on NODAT, 2003 recommendations, American Diabetes Association (ADA) criteria for type 2 diabetes published in 2003 should be used for diagnosis. The guidelines recommends fasting plasma glucose (FPG) ≥126mg/dL, 2-hour post-glucose ≥200mg/dL and random plasma glucose =200mg/dL, on three or more occasions [5]. Risk of diabetes increase to nine folds in solid organ transplant recipients than their age matched controls. The incidence rates are even higher in the first six months after transplantation [6].

New onset diabetes mellitus after transplantation (NODAT) is a well-known complication reported to occur in 2% to 53% of renal transplant subjects [7]. Such a wide variation may be because of lack of a universal agreement on the definition of NODAT, the duration of follow-up, and the presence of modifiable and non-modifiable risks factors [8]. From Indian studies, the incidences of NODAT were 19.12% by Prakash J et al. [9] while Sharma A et al. [10] and Bora GS et al. [11] found incidence of

NODAT was 16.75% and 54.5%, respectively. So there is wide variation among incidence. In our study the incidence of NODAT is 33.33%. Out of 18, 15 (83.33%) were male and 3 (16.67%) were female, which is asserting with the existing results. In one of the recent Indian studies by Prakash J et al. [9], mean age of NODAT was 40.4 and in non-NODAT was 31.13 [9]. Similar finding was found in our study, mean age of the subjects was 46 ± 10.33 years and 32.14 ± 13.67 years in NODAT (n=18) and Non-NODAT (n=36) cohort respectively. There was a statistically significant difference between two groups with respect to age.

Obesity independently correlates with the development of NODAT [12,13]. 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 to 30 and nearly doubled if the BMI was >30 [14]. Our study results didn't find any significant difference in BMI between the NODAT (19.33 ± 3.08) and non-NODAT cohort (19.99 ± 3.45). The primary reason for not getting any significant difference is that all of the included patients had a low BMI, primarily attributable to the poor socio-economic status of our country.

According to International Consensus Guidelines on NODAT, 2003, the guidelines also recommends to preferred FPG test for diagnosing NODAT [7]. The subjects with diabetes and NODAT cohort showed increased fasting blood glucose levels, whereas normal cohort subjects were well within the normal limits [15,16]. Our study results were also providing evidence in the same line where the subjects who developed NODAT had significantly higher level of pre-operative fasting plasma glucose and post-operative fasting plasma glucose.

Consequently, high incidences of de novo hyperglycemia immediately after transplantation have been reported. This may be associated with the exposure of pancreatic β -cells to several stress factors, collectively the surgical procedure, weight gain due to physical inactivity immediately after surgery (insulin sensitivity), high doses of corticosteroids and initiation of calcineurin-inhibitor (CNIs) [17]. The underlying mechanism of development of NODAT can be classified into insulin resistance and defect in insulin secretion [7]. Preoperative impaired glucose tolerance generally identifies transplant candidates who are at higher risk for the development of NODAT. This was supported by one study in which impaired glucose tolerance was identified in 18 percent of non-diabetic patients prior to transplantation. Among 31 patients who developed NODAT after transplantation, 16 (52 percent) had impaired glucose tolerance pre-transplant [3]. In multivariate analysis, pre-transplant impaired glucose tolerance was associated with the development of NODAT (RR 2.4, 95% CI 1.1-5.3) [18,19]. Thus corroborating with the previous findings, the present study demonstrates that pre-operative insulin resistance (as measured by HOMA-IR) is significantly higher in the NODAT than non-NODAT cohort.

NODAT is consistent with type 2 diabetes and responds to the usual anti-diabetes agents. However, severe hyperglycemia during the early post-transplant period may necessitate the use of insulin. Also, high-dose glucocorticoid therapy for induction of immunosuppression (or treatment of acute rejection) may require the use of insulin therapy for glycemic control. After hospital discharge, close monitoring of blood glucose during the first month and every three months for the first year is recommended [17]. In the present study, tacrolimus levels were also significantly higher in the NODAT cohort as compared to the non-NODAT cohort. Thus from the above discussion, in the present study, tacrolimus levels, pre-operative insulin resistance levels and beta cell function were all significantly implicated in the development of NODAT.

Conclusion

The incidence of NODAT is quite high in our renal transplant patients. Risk of development of post-transplant diabetes was more closely related to traditional risk factors namely age, pre-operative fasting plasma glucose, post-operative plasma glucose, pre-operative insulin resistance and immunosuppressive therapy.

Limitations

The study has many limitations and the results should be interpreted in view of the limitations. As with any observational study, this study lacks the vigilance of a controlled environment and adverse events are under reported. Larger and more comprehensive trials are required to establish and further validate our findings.

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