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Original Research Article

New onset diabetes after transplantation (NODAT) in renal transplant recipients: a study from tertiary care center in Kashmir, India

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ABSTRACT

Background: New onset diabetes after transplantation (NODAT) is a common entity in the post-transplant period after several types of organ transplants like kidney, liver heart and lungs. NODAT is a common complication after solid organ transplantation and has been reported to have an adverse impact on patient and allograft outcomes. Risk stratification and intervention to minimize risk should be an integral part of management of transplant recipients.
Methods: A total of 100 patients who underwent renal transplantation were observed for the development of NODAT in the post transplantation period. Patients were evaluated in the pre- transplant and post-transplant period. Risk factors which were associated with the development of NODAT were analyzed.
Results: Out of 100 patients, 79 were males and 21 were females. The mean age of the patients undergoing renal transplantation was 40 years. The youngest patient was 18 years old and the eldest was 64 years old. Majority of the patients were in the age group of 31 to 50 years (60 patients, 60%). The incidence of NODAT in present study was 17%. The major risk factors for the development of NODAT were identified as male sex, positive family history of diabetes, history of alcohol intake before renal transplantation, hypertriglyceridemia, post renal transplantation hypomagnesemia, proteinuria, and use of drugs like tacrolimus and prednisolone.
Conclusions: NODAT has been identified as a risk factor for graft rejection, long-term graft failure, and decreased patient survival. Once NODAT has been diagnosed, specific anti-hyperglycemic therapy is essential to reach a tight glycemic control, which contributes to significantly reduced post-transplantation morbidity. Due to the importance of NODAT, diabetes education and its impact on the outcome of post-transplantation morbidity and mortality becomes crucial point of research among organ transplantation populations. Diabetes education in a group setting can be adopted for organ transplantation recipients with NODAT.

Keywords: Fasting blood glucose, Glycosylated hemoglobin, Impaired glucose tolerance, New onset diabetes after transplantation, Postprandial blood glucose

INTRODUCTION

Over the years, the precise incidence of new onset diabetes after transplantation (NODAT) has been difficult to determine due to the lack of a standard definition for

the condition. Historically, post-transplantation diabetes has been variably defined as having random glucose levels greater than 200mg/dL or fasting glucose levels greater than 126mg/dL, or the need for insulin or oral hypoglycemic agents in the post-transplantation period. In 2003, the International Expert Panel consisting of experts from both the transplantation and diabetes fields set forth the International Consensus Guidelines for the diagnosis and management of NODAT. It was recommended that the definition and diagnosis of NODAT should be based on the definition of diabetes mellitus and impaired glucose tolerance (IGT) described by the World Health Organization (WHO).[1-3]

Risk factors for the development of NODAT are categorized as non-modifiable, modifiable or potentially modifiable, the former category to facilitate the identification of high-risk individuals, and the latter two categories to optimize the management of NODAT.

Non-modifiable risk factors

Older age has long been observed to be an important risk factor for the development of NODAT.[4,5] There has been ample literature suggesting that African Americans and Hispanics are at increased risk for developing NODAT compared to whites. Similar to type 2 diabetes in the general population, both genetic and environmental factors have been suggested to play a role in the development of NODAT.[6] Other non-modifiable risk factors include recipient male gender; the presence of certain human leukocyte antigens (HLA) such as HLA A30, B27, and B42; increasing HLA mismatches; donor-recipient (DR) mismatch; deceased donor kidneys; male donor; and acute rejection history. Autosomal dominant polycystic kidney disease (ADPKD) has been suggested to confer an increased risk of developing diabetes after renal transplantation in some studies but not in others.[7-10]

Modifiable risk factors

Use of corticosteroids, calcineurin inhibitor associated NODAT, and use of sirolimus are important factors in this category.[11-14] Other modifiable risk factors are in the form of obesity, hypertension and hypertriglyceridemia.[15,16] Early reports from a single center study suggested an association between proteinuria on day 5 after transplantation and the development of NODAT.[17]

Potentially modifiable risk factors

Impaired glucose tolerance before transplantation, hepatitis C virus infection and cytomegalovirus infection are important factors in this category.[18,19]

Clinical studies evaluating the impact of NODAT on patient outcomes after solid organ transplantation have yielded variable results. Nonetheless, there has been ample literature suggesting that kidney transplant recipients who developed NODAT are at a two to three-fold increased risk of fatal and nonfatal cardiovascular disease events as compared with non-diabetic patients. The development of NODAT has also been shown to be associated with an adverse impact on patient survival as well as an increased incidence of infectious complications.

The aim of the present endeavor was to study the incidence of NODAT after renal transplantation in Kashmiri population and to establish the risk factors associated with NODAT.

METHODS

This study was conducted in Department of Nephrology at Sher I Kashmir Institute of Medical Sciences (SKIMS), a tertiary care center in Srinagar, Jammu and Kashmir, India, for a period of two years between July 2013 to June, 2015. An informed consent was taken from all the patients

Inclusion criteria

All the patients who underwent renal transplantation in authors' institute were enrolled in this study.

Exclusion criteria

Recipients who had pre-existing diabetes at the time of transplantation.

Evaluation

A total of 100 patients who underwent renal transplantation in our institution were enrolled in our study. All the patients were subjected to detailed history taking and clinical examination. Routine laboratory investigations in the form of complete blood count (CBC), kidney function tests (KFT), liver function tests (LFT), serum electrolytes, ultrasonography (USG) abdomen with pelvis, electrocardiogram (ECG), urine routine, were done in all the patients. Special investigations like two-dimensional echocardiography (2-D ECHO) and renal doppler were done in all the patients before renal transplantation.

Etiological diagnosis was made on the basis of history, clinical examination, and investigations. Records of renal biopsy wherever available were used to make help in diagnosis. Fundoscopic findings were considered as supportive evidence to label diabetic and hypertensive nephropathy. In present study, authors screened the patients for HCV, HBV, CMV and HIV before kidney transplant and all of them were negative.

After proper evaluation of all the patients, they were subjected to renal transplantation. All the patients received living donor renal transplantation (LDRT).

A diagnosis of NODAT was defined according to the American diabetes association criteria:

- Fasting plasma glucose level greater than or equal to 126mg/dl or
- Glycosylated hemoglobin (HbA1c) more than or equal to 6.5% or
- A 2hour value of plasma glucose in oral glucose tolerance test (OGTT) of equal to or more than 200mg/dl or
- A random plasma glucose concentration of more than or equal to 200mg/dl in the presence of symptoms.

Patients were classified as those who developed NODAT in the post renal transplantation period and as normal patients. Normal patients were defined as those patients who did not develop NODAT in the post transplantation period.

Follow up of the patients

- Fasting and post prandial blood glucose,
  -Weekly for first 4weeks after transplantation.
  -Then at 3months, 6months and annually thereafter but in the present study authors took up to 1year post renal transplant only.
- All renal transplant recipients were taken for the HbA1C levels after 3months.

RESULTS

Age/sex ratio

Out of 100 patients, 79 were males and 21 were females. Among 79 males, 11(13.92%) were NODAT patients and 68 (86.07%) were normal patients. Among 21 females, 6 (28.57%) were NODAT patients and 15 (71.42%) were normal patients. Thus, out of 100 cases of renal transplantation in total, 17 patients developed NODAT. Among NODAT cases, 6 patients (35.3%) were females and 11 (64.71%) were males. Thus, NODAT was more common in males with p value <0.05. The mean age of the patients undergoing renal transplantation was 40 years. The youngest patient was 18 years old and the eldest was 64 years old. Majority of the patients who underwent renal transplantation were in the age group of 31 to 50 years of age (60 patients, 60%) (Table 1).

Table 1: Sex distribution of NODAT patients.

	Normal	NODAT	Total	
Male	68	11	79	p value <0.05
Female	15	6	21	

Smoking status

Out of 100 patients, 51 were smokers (who had history of smoking before renal transplantation) and 49 were non-smokers. Among smokers, only 7 (13.72%) developed NODAT and rest 44 (86.27%) were normal patients. Among 49 non-smoker patients, 10 (20.40%) developed NODAT and rest 39 (79.60%) were normal patients. Results showed that the history of smoking was not a clear risk factor for developing NODAT.

Effect of history of alcohol intake

Out of 100 patients, 9 had history of alcohol intake before renal transplantation and 91 were non-alcoholic patients. Out of 9 alcoholic patients, 4 (44.4%) patients developed NODAT and 5 (55.6%) were normal patients. Among 91 non-alcoholic patients 13 (14.28%) developed NODAT and 78 (85.71%) were normal patients with p-value <0.05, which showed that history of alcohol intake was a significant risk factor for developing NODAT.

Body mass index (BMI)

Present study results showed that there was not significant difference between average BMI of NODAT patients as compared to BMI of other patients who did not develop NODAT.

Family history of diabetes

Out of 100 patients, 35 patients were having positive family history of diabetes mellitus and 65 patients were without any family history of diabetes (Table 2).

Table 2: patients with family history of diabetes who developed NODAT in post renal transplantation period.

	FHD	Without FHD	
NODAT	10	7	p value <0.05
Normal	25	58	
Total	35	65	

FHD = Family history of diabetes

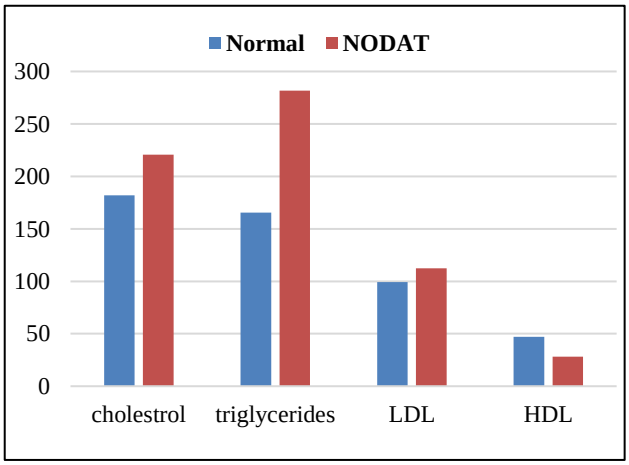

Figure 1: Lipid profile in NODAT and normal patient.

Out of 35 patients having positive family history of diabetes, 10 (28.57%) developed NODAT and 25 (71.42%) were normal.

Among 65 patients without having positive family history of diabetes, 7 (10.76%) developed NODAT and rest of the 58 (89.23%) were normal, with p-value <0.05. The results showed that the positive family history of diabetes was a significant risk factor for developing NODAT.

Lipid profile

It was observed that hypertriglyceridemia was a significant risk factor for NODAT (Figure 1).

Post-transplant parameters

Minerals

It was observed that NODAT patients had higher average value of serum calcium, less average value of serum phosphorus and less average value of serum magnesium as compared to normal patients (Table 3).

Urine examination post-transplant

Out of 100 patients, 24 patients were having proteinuria. Out of these 24 patients with proteinuria; 14 patients (58.33%) developed NODAT and 10 (41.66%) were normal patients with p-value <0.05 (Table 4).

Table 3: Values of different minerals in NODAT and normal patients.

	Normal			NODAT			
	Calcium	**Phosphorus**	**Magnesium**	**Calcium**	**Phosphorus**	**Magnesium**	
Average	8.08	3.11	2.02	8.4	2.74	1.86	
Median	8.2	3.2	2	8.4	3.05	1.8	
Mode	8.2	3.2	2	8.4	3.1	1.8	p-value
Standard deviation	0.75	0.56	0.13	0.47	0.66	0.15	<0.05
Maximum	9.3	5.4	2.3	9.3	3.77	1.8	
Minimum	3.5	1.67	1.8	7.2	1.6	1.2	

Table 4: Urine examination in the post renal transplantation period.

	Leucocytes	Erythrocytes	Sugar	Protein	
Normal	26	2	5	10	
NODAT	14	5	12	14	p-value <0.05
Total	40	7	17	24	

Fasting blood glucose

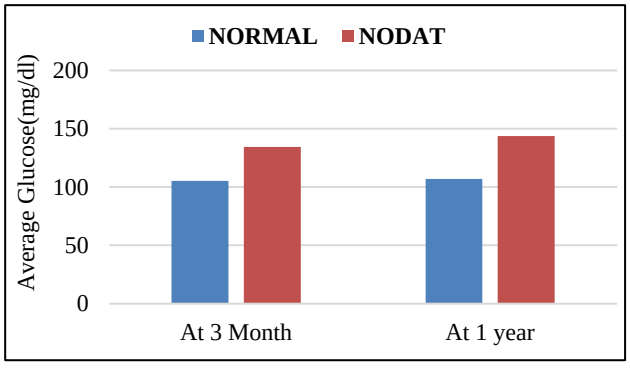

Figure 2: Fasting blood glucose levels in the post transplantation period.

Among NODAT patients average fasting blood glucose levels at 3 month and 1 year were 134.38mg/dl and 143.80mg/dl respectively which were higher as compared to average fasting blood glucose levels at 3 months and 1 year of 105.23mg/dl and 106.84mg/dl respectively in normal patients (Figure 2).

Post-prandial glucose

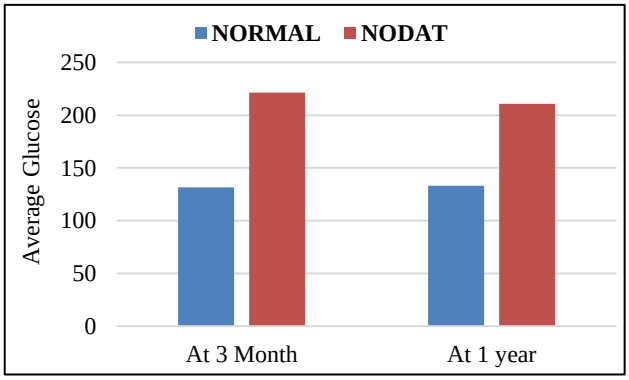

Figure 3: Post prandial blood glucose in the post renal transplantation period.

Among NODAT patients average fasting blood glucose levels at 3months and 1year were 221.50mg/dl and 210.80mg/dl respectively which were higher as compared to average fasting blood glucose levels at 3 months and 1 year of 131.72mg/dl and 133.07mg/dl in normal patients (Figure 3).

HbA1c

HbA1c is a useful indicator of detecting NODAT both at 3 months and 1 year with p-value <0.05.

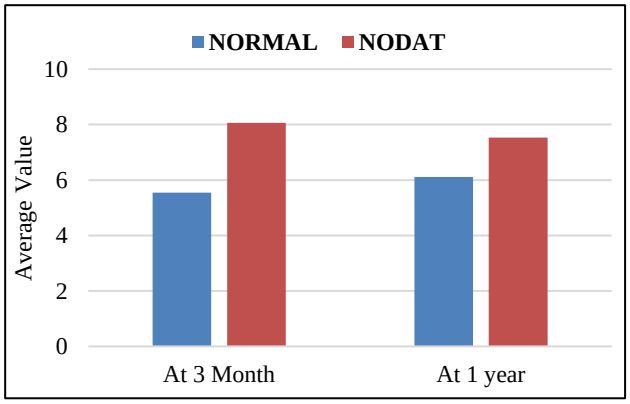

Figure 4: Fasting blood glucose levels in the post transplantation period.

Effect of drugs on NODAT

In present study, most commonly used immunosuppressants were prednisolone, tacrolimus and mycophenolate mofetil. It was observed that majority of the patients who developed NODAT were on tacrolimus and prednisolone. Authors used sirolimus, azathioprine, and cyclosporine in very small number of patients. Authors did not shift the patients from one drug to another, so authors were not able to compare diabetogenic effect of individual drug with respect to each other

DISCUSSION

Authors conducted this study in authors' institute to see the incidence of NODAT in the post renal transplantation patients of Kashmir valley. Present study results were obtained by analyzing 100 renal transplant patients. A total of 17 patients developed NODAT in the post renal transplantation period. NODAT is a common complication after solid organ transplantation and has variably been reported to have an adverse impact on the patient and allograft outcomes. Risk stratification and intervention to minimize risk should be an integral part of the management of transplant recipients. Clinicians must be familiar with the immune history of patient prior to manipulating their immunosuppressive therapies in an attempt to ameliorate NODAT risk. When lifestyle modification fails to achieve adequate glycemic control, medical intervention is often necessary.

In present study, authors took 100 patients. Out of which 17 developed NODAT and therefore incidence of NODAT in our study is 17 % which was comparable to international incidence of NODAT.20 Out of 100 patients, 79 were males and 21 were females with a male: female ratio of 3.76:1.

Out of 100 patients, 51 were smokers (who had history of smoking before renal transplant) and 49 were non-smokers. Among smokers, only 7 (13.72%) developed NODAT and rest 44 (86.27%) were normal patients. Among 49 nonsmokers, 10 (20.40%) developed NODAT and rest 39 (79.60%) were normal patients. Results showed that history of smoking was not a clear risk factor for developing NODAT. In contrast to that, a positive history of alcohol intake before renal transplantation was definitely associated with increased risk of NODAT in the posttransplant period. Our results showed that there is not significant difference between average BMI of NODAT patients as compared to BMI of normal patients.

It was seen in present study that a positive family history of diabetes was significantly associated with increased risk of postrenal transplantation NODAT. This observation was consistent with various studies done from time to time.[21-24]

It was observed that NODAT patients had higher average value of serum calcium, less average value of serum phosphorus and less average value of serum magnesium as compared to normal patients. It has been clearly mentioned in the literature that hypomagnesemia induced by calcineurin inhibitors (more common with tacrolimus) is due to renal magnesium wasting occurring through transcriptional inhibition of the renal magnesium transporter in the distal collecting tubule. Recently post transplantation hypomagnesemia was found to be an independent predictor of NODAT in both renal and liver transplant.[25-28]

It was observed that hypertriglyceridemia in prerenal transplantation period is a significant risk factor among NODAT patients. Out of 100 patients, 24 patients were having proteinuria and out of these 24 patients; 14 patients (58.33%) developed NODAT and 10 (41.66%) were normal patients with p-value <0.05.

Thus, authors concluded that the major risk factors for the development of NODAT were male sex, positive family history of diabetes, history of alcohol intake before renal transplantation, hypertriglyceridemia, post renal transplantation hypomagnesemia, proteinuria and use of drugs like tacrolimus and prednisolone.

The routine care of patients with NODAT should include an evaluation of HbA1C level every three months and regular screening for diabetic complications. It should be noted that HbA1C cannot be accurately interpreted within the first three months of post transplantation period due to various factors including possible blood transfusions in

the early post-transplant period and the presence of anemia or impaired allograft function. Blood transfusions may render the test invalid until new hemoglobin is formed and the presence of anemia and kidney impairment can directly interfere with the HbA1C assay.

NODAT has been identified as a risk factor for graft rejection, long-term graft failure, and decreased patient survival. Once NODAT has been diagnosed, specific antihyperglycemic therapy is essential to reach a tight glycemic control, which contributes to significant reduction in post-transplantation morbidity.

Due to the importance of NODAT, diabetes education and its impact on the outcome of post-transplantation morbidity and mortality becomes crucial point of research among organ transplant populations. Diabetes education in a group setting can be adopted for organ transplant recipients with NODAT.[29]

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