

Effect of New Onset Diabetes after Transplantation (NODAT) On Graft Survival in Renal Transplant Recipients.

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ABSTRACT

Background: Newonset diabetes after transplantation (NODAT) refers to diabetes that occurs in previously nondiabetic persons after solid-organ transplantation, bone marrow and hematopoietic stem cells. New Onset Diabetes After Transplantation (NODAT) is one of the metabolic complications after kidney transplantation which affects adversely the allograft kidney and patient outcomes. **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, between July 2013 to June 2016.All the patients who underwent renal transplantation during this period in our institute were enrolled in this study.In the post renal transplant period , patients were classified as those who developed NODAT and as normal patients. Effect of NODAT on the graft survival was studied by comparing the serum urea, creatinine and urinary protein between the NODAT and the normal patients. **Results:** A total of 100 patients of End Stage Renal Disease (ESRD) who underwent renal transplantation in department of nephrology were enrolled in our study.Out of 100patients, 79 were males and 21 were females. A total of 17 patients developed NODAT in our study. It was observed that the patients developing NODAT in post renal transplantation period were having a higher values of serum creatinine and urea as compared to normal patients. Moreover proteinuria was more commonly present in NODAT patients than normal patients. **Conclusion:** The development of NODAT is associated with a poor graft function in the post transplant period.

Keywords: Glycosylated Hemoglobin (HbA1C), Impaired Glucose Tolerance (IGT), Fasting Blood Glucose, Postprandial Blood Glucose, New Onset Diabetes After Transplantation (NODAT).

INTRODUCTION

New-onset diabetes after transplantation (NODAT) refers to diabetes that occurs in previously nondiabetic persons after solid-organ transplantation, bone marrow and hematopoietic stem cells.^[1,2] New Onset Diabetes After Transplantation (NODAT) is one of the metabolic complications after kidney transplantation which affects adversely the allograft kidney and patient outcomes.^[3,4] Historically, post-transplant diabetes has been variably defined as having random glucose levels greater than 200

mg/dL or fasting glucose levels greater than 140 mg/dL, or the need for insulin or oral hypoglycaemic agents in the post-transplant period. In 2003, the International Expert Panel consisting of experts from both the transplant and diabetes fields set forth the International Consensus Guidelines for the diagnosis and management of NODAT.^[5] 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).^[6]

The reported incidence of NODAT ranges from 10-30% in adult kidney transplant recipients on CNIs and steroids.^[7,8] The wide variations in the reported incidence may be due to variations in treatment protocols employed across the transplant centres, duration of follow-up and lack of standard definition of the condition. NODAT after transplantation has been reported to occur 2.5% to 25% of liver transplant recipients, 4% to 40% of heart transplant

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recipients, and 30% to 35% of lung transplant recipients.^[9-11]

Risk factors for NODAT are classified as

1. **Modifiable risk factors:** such as lifestyle, dyslipidaemia, Obesity, hypertension, proteinuria, hypomagnesemia, Impaired glucose tolerance before transplantation, immunosuppressive medications.
2. **Non-modifiable risk factors:** like age, ethnicity, family history of diabetes mellitus, recipient male gender, presence of certain human leukocyte antigens (HLA) such as HLA A30, B27, and B423, donor-recipient (DR) mismatch, male donor. Polycystic kidney disease has been suggested to confer an increased risk of developing diabetes after renal transplantation in some studies but not in others.^[12-15]
3. **Potentially Modifiable Risk Factors:** HCV-associated NODAT, Cytomegalovirus-associated NODAT.

Clinical studies evaluating the impact of NODAT on patient and allograft outcomes after solid organ transplantation have yielded variable results. Nonetheless, there has been ample literature suggesting that kidney transplant recipients who develop NODAT are at a two to three-fold increased risk of fatal and nonfatal cardiovascular disease events as compared to nondiabetic patients.^[16] Data from the United Renal Data System consisting of over 11,000 Medicare beneficiaries who received primary kidney transplants between 1996 and 2000 demonstrated that compared to “no diabetes”, NODAT was associated with a 63% increased risk of graft failure (P, 0.0001), a 46% increased risk of death-censored graft failure (P, 0.0001) and an 87% increased risk of mortality (P, 0.0001).^[17]

NODAT is associated with a higher risk of complications, such as infections and cardiovascular disease thus, representing a higher life threatening risk and a higher cost for the Health System. So, we should try to identify the risk factors for NODAT and at an earlier stage. Early diagnosis combined with appropriate therapy will result in the success of the procedure as far as patient survival and transplantation durability is concerned.

Aims

To study the effect of NODAT on graft survival in renal transplant recipients.

MATERIALS AND METHODS

Study design

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, between July 2013 to June 2016.

Study Population

Inclusion Criteria

All the patients who underwent renal transplantation during this period in our institute were enrolled in this study.

Exclusion Criteria

Recipients who had pre-existing diabetes at the time of transplantation were not included in this study.

Consent

An informed consent was taken from all the patients.

Ethical Clearance

The study was cleared by Institutional Ethics Committee.

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. In our study, we 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 made according to the American Diabetes Association Criteria:

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

Follow Up Of the Patients

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

In the post renal transplant period, patients were classified as those who developed NODAT and NORMAL PATIENTS. Normal patients were defined as those patients who did not develop NODAT in the post transplantation period. Effect of NODAT on the graft survival was studied by comparing the serum urea, creatinine and urinary protein between the NODAT and the normal patients.

RESULTS

A total of 100 patients of End Stage Renal Disease (ESRD) who underwent renal transplantation in department of nephrology were enrolled in our study. Out of 100 patients, 79 were males and 21 were females. A total of 17 patients developed NODAT in our study. Out of these 17 patients, 11 were males and rest 6 patients were females. All the baseline investigations were repeated from time to time in the post renal transplantation period.

We were aimed at establishing the effect of NODAT on graft survival. Three established parameters were chosen to study the functioning of graft in the post renal transplantation period. These parameters were serum urea, serum creatinine, and the presence of proteinuria. Patients were divided in to two groups: Those who developed NODAT and NORMAL PATIENTS. Normal patients were those patients who did not develop NODAT in the post renal transplantation period. A comparison was done between the two groups to establish the effect of NODAT on graft survival.

1. Urea and Creatinine

It was observed that average serum urea and creatinine of NODAT patients measured at 1 month , 3 months and 1 year in the post transplantation period were more as compared to the average serum urea and creatinine of normal patients at the same time respectively which is as shown in figure (1) and figure (2)

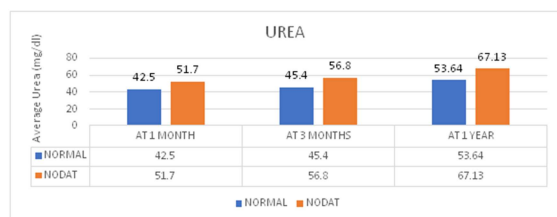


Figure 1: showing the average serum urea in post transplant period.

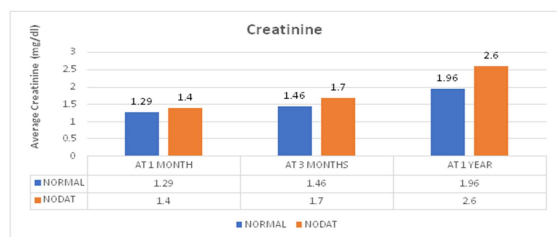


Figure 2: showing the average serum creatinine in post transplant period.

Therefore we observed that the patients of NODAT had an adverse effect on the graft survival as shown by values of serum urea and creatinine in the post transplant period. Decreased renal function in the NODAT patients was statistically significant ($p < 0.05$)

Proteinuria

In our study, a total of 22 patients showed proteinuria at 3 months after transplantation. Out of these 22 patients, 12 patients were of NODAT and rest 10 patients were normal patients. 12 out of 17 (70.5 %) NODAT patients were having proteinuria against 10 out of 83 (12%) normal patients. This result was statistically significant ($p < 0.05$).

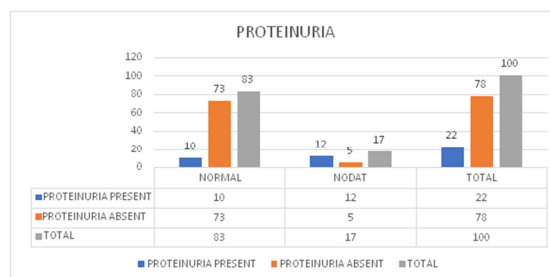


Figure 3: showing proteinuria in post renal transplantation period.

DISCUSSION

NODAT is a common entity occurring after renal transplantation. There is ample amount of existing literature which supports that the development of NODAT has an adverse outcome on the graft survival. In our study, we observed that the patients of NODAT had a higher average value of serum urea and creatinine as compared to normal patients. These results were statistically significant ($p < 0.05$). In a study conducted by Prasada Rao KV, Praveen Kumar K, it was observed that serum urea and creatinine were raised more in NODAT as compared to normal patients.^[18] In addition to the risk of developing the well-known long term complications of diabetes, NODAT also identifies patients at high risk for adverse clinical outcomes: loss of the renal allograft, infections, cardiovascular events, and increased mortality among renal transplant patients.^[19,20] In our study, proteinuria was more commonly associated with NODAT patients as compared to normal patients. This observation was statistically significant. Hence we concluded from our study that the development of NODAT in the post renal transplantation period is associated with a poor graft survival as evidenced by increased serum urea, creatinine and presence of proteinuria.

CONCLUSION

NODAT is associated with a higher risk of complications, such as poor graft survival ,

infections and cardiovascular disease thus, representing a higher life threatening risk and a higher cost for the Health System. So, we should try to identify the risk factors for NODAT and at an earlier stage. Early diagnosis combined with appropriate therapy will result in the success of the procedure as far as patient survival and transplantation durability is concerned.

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