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

Rahul Sudan[1], Mehroz Ahmed[1], Imtiyaz Ahmed Wani[2], Muzaffar Maqsood Wani[2], Khurshid Ahmed Banday[3], Gunjan Gupta[4]

[1]Senior Resident , Department of General Medicine , Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIMHS), Shri Mahant Indiresh Hospital (SMIH), Patel Nagar, Dehradun , India.

[2]Associate Professor, Department of Nephrology, Sher I Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, Jammu and Kashmir, India

[3]Professor, Department of Nephrology, Sher I Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar, Jammu and Kashmir, India

[4]Senior Resident, Department of Dermatology, Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIMHS), Shri Mahant Indiresh Hospital (SMIH), Patel Nagar, Dehradun, India.

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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 NODATis 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

Name & Address of Corresponding Author
Dr. Rahul Sudan
Senior Resident,
Department of General Medicine,
Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIMHS), Shri Mahant Indiresh Hospital (SMIH), Patel Nagar,
Dehradun , India.

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, Impairedglucose 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 hasbeen 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 results 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 wasobserved 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)

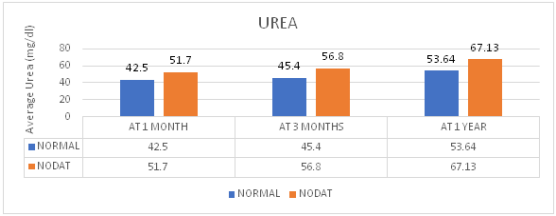

Figure 1: showing the average serum urea in post transplant period.

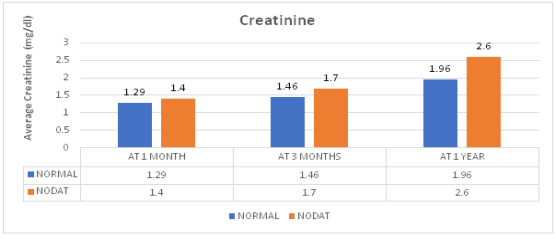

Figure 2: showing the average serum creatinine in post transplant period.

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. Decresed 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 ($p<0.05$).

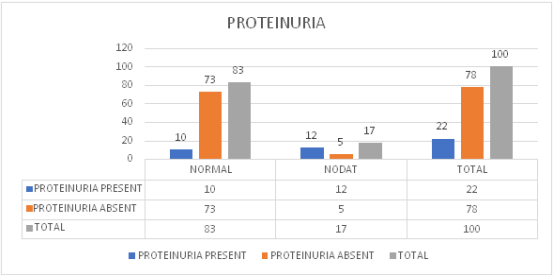

Figure 3: showing proteinuria in post renal transplantation period.

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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REFERENCES

1. Viberti G. Diabetes mellitus: a major challenge in transplantation. Transplant Proc 2001; 33(Suppl 5A):3S–7S.
2. Woo M, Przepiorka D, Ippoliti C, et al. Toxicities of tacrolimus and cyclosporine A after allogeneic blood stem cell transplantation. Bone Marrow Transplant 1997;20:1095–8.
3. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, et al. (2002) Patient survival after renal transplantation: IV. Impact of posttransplant diabetes. Kidney Int 62: 1440-1446.
4. Davidson J, Wilkinson AH (2004) New-onset diabetes after transplantation 2003 international consensus guidelines: an endocrinologist's view. Diabetes Care 27: 805-812.
5. Wilkinson AH, Davidson J, Dotta F, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation. Clin Transplant. 2005;19:291–298.
6. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Posttransplantation diabetes: a systematic review of the literature. Diabetes Care. 2002;25(3):583–592.
7. Guruprasad P, Kishore K, Mahajan S, Aggarwal S (2017) Active surveillance for adverse events among patients who underwent renal transplantation: A prospective observational study. Perspectives in Clinical Research 8: 118-123.
8. Prakash J, Rathore SS, Singh TB, Choudhury TA, Prabhakar, et al. (2012) New-onset diabetes after transplantation (NODAT): Analysis of pretransplant risk factors in renal allograft recipients. Ind J Transplant 6: 77-82.
9. Baid S, Cosimi AB, Farrell ML, et al. Posttransplant diabetes mellitus in liver transplant recipients: risk factors, temporal relationship with hepatitis C virus allograft hepatitis, and impact on mortality. Transplantation. 2001;72:1066–1072.
10. Knobler H, Stagnaro-Green A, Wallenstein S, et al. Higher incidence of diabetes in liver transplant recipients with hepatitis C. J Clin Gastroenterol. 1998;26:30–33.
11. Ye X, Kuo H-T, Sampaio MS, Jiang Y, Bunnapradest S. Risk factors for the development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. Clin Transplant. 2010;DOI 10. 1111:1–7.
12. Hamer RA, Chow CL, Ong AC, McKane WS. Polycystic kidney disease is a risk factor for new-onset diabetes after transplantation. Transplantation. 2007;83:36–40.
13. Ducloux D, Motte G, Vautrin P, Bresson-Vautrin C, Rebibou JM, Chalopin JM. Polycystic kidney disease as a risk factor for posttransplant diabetes mellitus. Nephrol Dial Transplant. 1999;14: 1244–6.
14. De Mattos AM, Olyaei AJ, Prather JC, Golconda MS, Barry JM, Norman DJ. Autosomal dominant polycystic kidney disease as a risk factor for diabetes mellitus following transplantation. Kidney Int. 2005;67: 714–20.
15. Hjelmesaeth J, Hartmann A. Insulin resistance in patients with adult polycystic kidney disease. Nephrol Dial Transplant. 1999;14(10): 2521–2.
16. Ojo AO. Cardiovascular complications after renal transplantation and their prevention. Transplantation. 2006;82(5):603–611.
17. Kasiske BL, Snyder JJ, Gilbertson D, Maras AJ. Diabetes mellitus after kidney transplantation in the United States. Am J Transplant. 2003;3(2): 178–185.
18. Prasada Rao KV, Praveen Kumar K (2018) New Onset Diabetes Mellitus after Transplantation (NODAT)-An Analysis of Incidence, Risk Factors and its Effects on Renal Allograft. J NephrolTher 8: 304. doi:10.4172/2161-0959.1000304
19. Hjelmesaeth J, Hartmann A, Leivestad T, Holdaas H, Sagedal S, Olstad M et al. The impact of early diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 2006;69:588–95.
20. Moon JI, Barbeito R, Faradji RN, Gaynor JJ, Tzakis AG. Negative impact of new onset diabetes mellitus on patient and graft survival after liver transplantation: long-term follow-up. Transplantation 2006;82: 1625-8.

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