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New Onset Diabetes after Renal Transplantation (NODAT): Prevalence, Risk Factors and Treatment

(Original article)

Authors

Lakshminarayana GR[1], Sheetal LG[2], Anil M[3], Rajesh R[4], George K[5], Unni VN[6]

[1]Consultant Nephrologist, Department of Nephrology, EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Malappuram, Kerala
[2]Associate Professor, Dept of Physiology, MES Medical College, Perinthalmanna, Malappuram, Kerala,
[3]Professor, Dept of Nephrology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala
[4]Professor, Dept of Nephrology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala
[5]Professor and Head, Dept of Nephrology, Amrita Institute of Medical Sciences and Research Centre, Kochi, Kerala
[6]Senior Consultant, Nephrology, CoE Nephrology and Urology, Aster Medicity, Kochi, Kerala

Corresponding Author

Dr Lakshminarayana GR

Consultant Nephrologist, Department of Nephrology, EMS Memorial Cooperative Hospital and Research Centre, Perinthalmanna, Malappuram, Kerala, India-679322

Email: *drlng23@gmail.com, Phone: (+91) 9495161833*

Abstract

Background: *This study was conducted to assess the prevalence rate, risk factors and response to treatment of NODAT after renal transplantation.*

Methods: *All consecutive non-diabetic renal transplant recipients (RTR) from 2005 to 2011; done at AIMS, Kochi, were included in the study. ADA criteria (2003) for NODAT was for its diagnosis.*

Results: *The study group included 125 (M:101, F:24) RTRs with a mean age of 31.53 years, with a mean follow-up of 32.01 months after surgery. The prevalence rate of NODAT was 23%. Majority (80 %) of recipients with NODAT, had it within first 6 months after surgery. The prevalence rate of NODAT was higher males and those aged >40 years. The prevalence rate of NODAT was higher in those with family history of diabetes mellitus and pre-transplant impaired glucose levels.The prevalence rate of NODAT was higher with Tacrolimus based regimen and also those receiving methyl prednisolone as part of antirejection therapy. Majority (55 %) of those with NODAT had normal BMI. The prevalence of graft dysfunction was higher in those with NODAT.*

Conclusions: *The prevalence rate of NODAT was 23%, with a peak incidence in initial 6 months after renal transplantation. The non-modifiable risk factors for NODAT were; age > 40 years, male gender, pre-transplant impaired glucose levels and family history of diabetes mellitus. The modifiable risk factors for NODAT were; immunosuppressive drugs (Tacrolimus > Cyclosporine A), antirejection therapy with Methyl prednisolone. The prevalence of graft dysfunction was higher in those with NODAT than those without NODAT.*

Key Words: *NODAT, Renal transplantation, Modifiable risk factors, non-modifiable risk factors,*

Introduction

New-onset diabetes after transplantation [NODAT] is a well-recognized complication of organ transplantation especially after solid organ transplantation with occurrence at different post-transplant intervals. The NODAT shown to affect both the patient and renal allograft survival. The reported prevalence rate of NODAT varies widely (2-53 %) in literature, based on the diagnostic criteria and immunosuppressive protocols. [1-9] The prevalence rate of NODAT in Indian studies varied from 4.8-21.4%. [10-13]The risk factors of NODAT are classified as non-modifiable (age, gender, ethnicity, family history of diabetes mellitus), modifiable or potentially modifiable (immunosuppressive medications, life style, impaired glucose tolerance test, dyslipidaemia, HCV or CMV infection); the former helps to facilitate the identification of high risk individuals, and the latter two helps to optimize the management of NODAT.[14-22]The recommended treatment for NODAT is similar to type 2 diabetes mellitus; OHA, Insulin, education regarding diabetes and life style modification. [22-25]The present study was conducted to assess the prevalence rate, risk factors and response to treatment of NODAT in live related renal recipients (RTR).

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Aims and Objectives

1. To study the prevalence rate of NODAT and
2. To identify the risk factors for NODAT and response to therapy

Materials and Methods

All consecutive renal allograft recipients (live related donor) who underwent renal transplantation at Amrita Institute of Medical Sciences and Research Centre, Kochi, from 2005 to 2011. Subjects with diabetes mellitus prior to renal transplantation were excluded.

Diagnosis of NODAT

The International Consensus Guidelines (2003) on New-Onset Diabetes after Transplantation recommended that the diagnosis of NODAT be based on the American Diabetes Association criteria for the diagnosis of diabetes.[26] Accordingly, NODAT is diagnosed by finding two fasting plasma glucose (FPG) values (measured on different days) higher than 126 mg/dl; a plasma glucose level higher than 200 mg/dl at 2 h during a 75-g oral glucose tolerance test (OGTT) a random plasma glucose level higher than 200 mg/dl in a patient with typical diabetes clinical manifestations or A1C more than 6.5%.

Statistical Analysis

Mean ± standard deviation (SD) and percentages were used for summarizing the data. The variables were analysed by univariate and multivariate analysis to assess their significance. The primary endpoint of the analysis was occurrence of NODAT. The confidence interval (CI) was 95% and a $P <$ 0.05 was used for statistical significance. All statistical analyses were performed with SPSS version 17.0 and Analyse-it ® for Windows.

Results

This retrospective study included 125 consecutive nondiabetic RTRs (Males:101, Females:24) of age 11-55 years (Mean:31.52, SD:9.43), with follow-up of 3-69 months (mean:32.01, SD:18.74) after transplantation.None of the subjects had HCV or HBV or HIV infection. The demographic parameters of the subjects are summarised in table 1.

Prevalence of NODAT and its risk factors

29 (23%) subjects were diagnosed to have NODAT as per ADA criteria over follow-up of 3 – 69 months (Mean:31.52, SD:9.43).Majority (80 %) of recipients with NODAT, had it within first 6 months, suggesting peaking of incidence of NODAT in first 6 months after renal

transplantation. Subjects with age more than 40 years, had higher prevalence (31.52 % Vs 21.70 %) of NODAT. The mean age of patients with NODAT higher (39.69 years) than those without (29.99 years) NODAT (table 2).Males formed majority (86.20 %) of subjects with NODAT (table 3).The prevalence rate of NODAT was higher in males than females (24.7 Vs 16.67%) (table 3). Majority (59 %) of those with NODAT had family history of diabetes mellitus suggesting a higher predisposition (table 3).Pre-transplant impaired glucose levels were found in 21.6% (27) of subjects; 48 % of them (13/27) were diagnosed to have NODAT after surgery (Table 3).

All RTRs received standard triple immunosuppression in addition to antihypertensives and supportive management. The immunesuppressives were in the form of Cyclosporine A 5mg/kg/day in two divided doses, Mycophenolate Mofetil (MMF) 750 to 1000 mg twice daily and injection methyl prednisolone 500 mg was administered before the release of vascular clamps followed by prednisolone 0.5 mg per kg per kg daily post op day 1.Induction therapy was given in patients with high immunological risk (spousal donors) with interleukin 2 receptor antagonists (Daclizumab or Basiliximab). The Tacrolimus instead of Cyclosporine A was started in spousal donor recipients and young girls. None of subjects received steroids or CNI sparing regimen. The dose of prednisolone was tapered to by 0.3 mg/kg body weight orally during 3 months, gradually tapered to 7.5 mg/day over period of 6 months. None of the subjects in the study received CMV prophylaxis; however, they were evaluated for it, if any appropriate indications. The MMF was changed to Azathioprine if stable graft function without any episodes of graft rejections at end of 6 months in selected cases if subjects have financial difficulties.

The prevalence rate of NODAT was higher in those on Tacrolimus (45 % or 5 out of 11) than those on Cyclosporine A (21.05 %, 24 out of 114). 22.4 % (28 out of 125) subjects had episodes of acute rejections during the study period and was treated with antirejection therapy as per the protocol. The prevalence rate of NODAT was higher (28.57%, 8 out of 28) in subjects receiving methyl prednisolone as part of antirejection therapy than those who did not have rejections (21.65%, 21 out of 97). Antirejection therapy was the main reason for administering extra steroids.

Majority (55 %) of those with NODAT had normal BMI and 28 % were overweight, 14 % were underweight and only 3 % were having obesity, suggesting that Indians are predisposed to NODAT even with normal BMI. There was no statistically significant difference in BMI in those with and without NODAT (table 2).

Treatment of NODAT

Majority (58.62 %, 17 out of 29) of subjects with NODAT were treated with oral hypoglycemic agents (OHA) along with diet & life style modification. The 20.69 % (6 out of 29) of subjects were treated with combination of Insulin and OHA and additional 20.69 % (6 out of 29) were managed with Insulin. The 10.34% (3 out of 29) of subjects responded to diet & life style modification.

Effect of NODAT on graft function

Those with serum creatinine level >1.4 mg/dl, or rise in serum creatinine of 30% from the baseline were considered to have graft dysfunction. The prevalence of graft dysfunction was higher in those with NODAT (48.28 %, 14 out of 29) than those without NODAT (39.17%, 38 out of 97).

Table 1: Descriptive characteristics of study population				
	Minimum	**Maximum**	**Mean**	**Std. Deviation**
Age (years)	11	55	31.53	9.43
Sr. Creatinine (mg/dl)	0.5	4.2	1.48	0.58
Time after Transplantation (months)	03	69	32.01	18.74
BMI (kg/m2)	11	33	20.98	3.13

Table 2: Characteristics of subjects with and without NODAT			
Parameter	**With NODAT (Mean ± SD)**	**Without NODAT (Mean ± SD)**	**(p-value)**
Age (years)	36.69 ± 7.98	29.99 ± 9.36	0.001
Sr. Creatinine (mg/dl)	1.45 ± 0.58	1.59 ± 0.58	0.253
BMI prior to TX (kg/m2)	20.71 ± 3.23	21.74 ± 2.63	0.12
BMI after to TX (kg/m2)	22.01 ± 3.12	23.33 ± 3.28	0.051

Table 3: Characteristics of subjects with or without NODAT			
Parameter	Subjects with NODAT N= 29 out of 125 (23%)	Subjects without NODAT, N=96 out of 125 (77%)	Univariate analysis (p-value)
Age < 40 years	23	83	0.011
Age > 40 years	6	13	
Males	25	76	002
Females	4	20	
Positive family history of DM	17	12	0.02
Pre-transplant IGT	13	14	0.01
ART prior to development of NODAT	8	20	0.03

Discussion

New-onset diabetes after transplantation [NODAT] is a well-recognized complication after renal transplantation affecting both the patient and renal allograft survival, with varying prevalence rates in India.[10-13] Our study included 125 RTRs, with mean age of 31.52 years, with mean follow-up of 32.01 months after transplantation. The males formed majority (80.8%) of the RTRs; male: female of 4.2:1. The demographic profile of subjects was similar to other Indian studies. [10, 11]

The prevalence rate of NODAT in study was 23% as per ADA criteria. [26] The peak incidence of NODAT was seen in initial 6 months after renal transplantation. The prevalence of NODAT was higher (31.52%) in subjects with age of > 40 years.The prevalence rate of NODAT was higher in males (24.7%) than females (16.67%). Majority (59 %) of those with NODAT had family history of diabetes mellitus. The prevalence rate of NODAT was higher (48%)in subjects with pre-transplant impaired glucose levels. Hence, age > 40 years, male gender, pre-transplant impaired

glucose levels and family history of diabetes mellitus were the non-modifiable risk factors for NODAT in our study; consistent with other reported literature.[1-5,8-11, 19, 20, 22]

The type of immunosuppressive regimen accounts for the variability in incidence and prevalence rates of NODAT between studies. Both corticosteroids and Calcinurin inhibitors are diabetogenic by multiple mechanisms. [2, 4, 16]In our study the prevalence rate of NODAT was higher (45%) in subjects on Tacrolimus based regimen than those with Cyclosporine A containing immunosuppressive therapies (21.05%). None of subjects received CNI or Steroid free regimen. 22.4% subjects had episodes of acute rejections during the study period and was treated with antirejection therapy as per the protocol. The prevalence rate of NODAT was higher (28.57%,) in subjects receiving methyl prednisolone as part of antirejection therapy than those who did not have rejections (21.65%).The higher prevalence of NODAT with Tacrolimus than Cyclosporine A based regime in our study is consistent with earlier studies. [6, 12, 20, 21]Higher incidence and prevalence rates of NODAT in relation to antirejection therapy with Methyl prednisolone is also consistent other earlier reports. [11]

Majority (55 %) of those with NODAT had normal BMI and 28 % were overweight, 14 % were underweight and only 3 % were having obesity, suggesting that Indians are predisposed to NODAT even with normal BMI, suggesting that subjects of Asian origin may have genetic predisposition to NODAT as reported in earlier studies. [20, 21]

Treatment of NODAT

The treatment advised for NODAT is similar to that for type 2 diabetes mellitus. [11, 22] In our study majority (58.62%) of subjects responded adequately to oral hypoglycemic agents (OHA-Metformin, Glibenclamide, Gliclazide, Glimepiride) along with diet& life style modification. The 20.69% of subjects needed combination of Insulin and OHA and additional 20.69% were managed with Insulin alone. The 10.34% of subjects responded to only diet &life style modification. Although; OHA are effective, their use could alter immunosuppressive drug levels due to competition for common cytochrome P-450 pathway or altered GI motility, their use should be carefully monitored.[11, 22]

Effect of NODAT on graft function

The prevalence of graft dysfunction was higher in those with NODAT (48.28 %) than those without NODAT (39.17%) in our study. The NODAT is a major risk factor for cardiovascular disease and mortality as well as associated with adverse impact on graft survival and graft loss rate of infections and increased health care costs.[1 ,2, 3]

Limitations:

1) Effect of HCV and CMV infection were not assessed as none of the patients had HCV infection and CMV titers were not monitored routinely, except in cases with suspicion of CMV infection. 2) The therapeutic drug monitoring of CNI or MMF was not done due to financial constraints. 3) HLA matching status of recipient with the donor and its effect on NODAT was not assessed. 4) Effect of NODAT on cardiovascular disease was not assessed.

Conclusions

The prevalence rate of NODAT in study was 23%, with a peak incidence in initial 6 months after renal transplantation. The age > 40 years, male gender, pre-transplant impaired glucose levels and family history of diabetes mellitus were the non-modifiable risk factors for NODAT in our study. The modifiable risk factors contributing to higher prevalence of NODAT included, immune-suppressive drugs (Tacrolimus > Cyclosporine A), antirejection therapy with Methyl prednisolone. Majority of those with NODAT had normal BMI and only minority were obese. Majority of the subjects responded to oral hypoglycemic agents (OHA-Metformin, Glibenclamide, Gliclazide,

Glimepiride) along with diet & life style modification. The prevalence of graft dysfunction was higher in those with NODAT than those without NODAT.

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