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PREVALENCE AND RISK FACTORS OF NEW ONSET DIABETES AFTER TRANSPLANTATION IN RENAL ALLOGRAFT RECIPIENTS: A SINGLE CENTRE OBSERVATIONAL STUDY

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ABSTRACT **Background:** New onset diabetes after transplantation (NODAT) is common after renal transplantation. It is associated with adverse outcome in post transplant patients leading to graft loss with considerable morbidity and mortality.The aim of this study is to evaluate the prevalence and risk factors of New Onset Diabetes after Transplantation in renal allograft recipients. **Methods:** In this cross sectional observational single centre study we evaluated the prevalence and various factors associated with new onset diabetes after transplantation in renal allograft recipients who had consented for the study. Detailed history and clinical examination of the participants were done. Details were also collected from the renal transplant record of the patient. The study variables compared between those patients who developed NODAT and who did not develop NODAT. **Results:** The prevalence of NODAT in our study was 23.3%. 61.9% of patient with NODAT developed the disease within 1 year of transplantation. Family history of diabetes mellitus, history of acute rejection, HCV infection were significantly associated with NODAT. Tacrolimus trough levels, serum uric acid levels were significantly higher in NODAT group. HCV infection and higher body mass index were independently associated with NODAT. **Conclusion:** The incidence of NODAT appears to be very higher in subjects with significant family history of Diabetes mellitus, acute rejection episodes, CMV infection, higher tacrolimus trough levels, higher uric acid levels and dyslipidemia. Increased BMI and HCV infection were found to be independent risk factors in the development of NODAT.

KEYWORDS : NODAT, Tacrolimus, cyclosporine, mycophenolate, immunosuppression

INTRODUCTION

The occurrence of diabetes for the first time post-organ transplantation in a previously non-diabetic transplant recipient is defined as "NODAT." It is only applicable to patients who did not have diabetes mellitus prior to the transplant and who are on a steady maintenance immunosuppressive regimen with no signs of ongoing acute infections. The diagnosis and categorization of NODAT(2003 consensus guidelines) was made in accordance with World Health Organisation (WHO) definition of diabetes and IGT(Impaired glucose tolerance).Identification of NODAT results in decreased longevity of renal allograft[1-3]as documented in prior studies.

Multiple studies revealed ,variable incidence of NODAT after kidney transplantation. In a study by Porrini et al NODAT prevalence was 27 %,31% and 30 % at post transplant months 3,12 and 36 respectively[4]. NODAT can hasten cardiovascular disease (CVD), which is one of the leading causes of death in the post-transplant period.It can also end in graft rejection in some subsets of patients. Recognizing high-risk cases and enforcing measures to limit the development of NODAT may ameliorate the transplant candidates' long-term risk of mounting a rejection response and graft survival.

The long-term survival of recipients may be enhanced by the identification of at-risk patients. A number of modifiable and non-modifiable risk factors contribute to the occurrence of NODAT in the recipient. They potentially include age, the male gender of the recipient, a family history of diabetes, the presence of HLA mismatches, and the donor being male. Apart from these, the modifiable factors include the presence of HCV infection, CMV viremia [5], obesity and the effect of immunosuppressive medications that can equally contribute to the occurrence of NODAT.

In this cross sectional observational study, we evaluated a cohort of renal allograft recipient patients attending our post transplant clinic to assess the prevalence, and various factors associated with the development and progression of NODAT.

MATERIALS AND METHODS

The study design is an observational cross-sectional study including all adult kidney allograft recipients attending the post-renal transplant clinic at Maduarai Medical College Hospital,Madurai.The individuals who took part in our study gave their prior, written consent.

The diagnosis was made on the basis of the International Consensus Guidelines of NODAT (2003), which recommended following ADA guidelines for the diagnosis of DM. A diagnosis of NODAT was defined according to the American Diabetes Association criteria (a fasting sugar value 126 mg/dL, glycosylated haemoglobin [Hb A1c] 6.5 percent, a 2-hour value in an OGTT 200 mg/dL, or a random plasma glucose value 200 mg/dL along with the occurrence of glycemic symptoms or any need for antiglycemic drugs). Patients with diabetes mellitus prior to transplant or with transient post-transplant diabetes (hyperglycemia within 1 month of transplant and spontaneously resolved within 3 months) were excluded from the study.

Patient characteristics like age, weight, BMI,gender,native kidney disease, dialysis vintage, nature of kidney transplant (live vs. cadaveric), nature of drugs used in induction as well as maintenance and rejection episodes, and history of DM in other family members were collected from direct patient interaction and medical records. Laboratory values like a complete haemogram, serum urea and creatinine, liver function tests, fasting and postprandial glucose, Hba1c, HIV, HCV, CMV, urinalysis, a fasting lipid profile, uric acid, and tacrolimus trough levels were obtained.

Statistical Analysis

Demographic, biochemical, and immunosuppressive parameters were compared among the subjects classified into the NODAT and Non-NODAT groups. The statistical analysis was performed using R programming and SPSS 22.0 software version.Utilizing the chi-square test and Fischer exact test, the demography and risk factors of the patients were analysed between those in NODAT as well as non-NODAT groups. Biochemical data among the two groups were analysed using an independent sample t test. To identify the important causal variables for the development of the NODAT logistic regression model was used.

RESULTS

A total of 90 subjects who fulfilled the essential inclusion criteria were enrolled in the study, of which 24 were female. Among the 90 patients, 21 (23.3%) were diagnosed with NODAT. Out of the 21 patients who were diagnosed with NODAT, 13 (61.9%) were diagnosed with the disease within 1 year of transplantation. In our investigation, the presence of NODAT was not connected to any sex preference. Although the mean recipient age in our study was higher at the time of kidney transplantation, it was statistically insignificant in our study. Positive family histories such as diabetes mellitus among the first-

degree relatives were significantly more common in the patients belonging to the NODAT group. Among the 90 patients, 71 underwent a live-related renal transplant. The presence of HCV co-infection (38.1%) posed a statistically significant risk for the development of NODAT among the recipients enrolled in our study.

In our study, the type of renal donor (whether living or deceased) was not associated with being a significant risk factor for the establishment of NODAT. Basiliximab was used as the induction agent in 42 patients, rabbit anti-thymocyte globulin in 33 patients, and no induction agents were used in 5 patients. The use of any particular agent was not found to be a significant factor in the development of NODAT. Four patients had a history of delayed graft function, but its presence was not significantly associated with NODAT. All the patients were treated with steroids. The majority of patients in our cohort (73.7%) received an immunosuppressive combination of Tacrolimus, Mycophenolate Mofetil, and Steroids. Six patients received a combination of Cyclosporine, MMF, and steroids; four patients received Tacrolimus, Azathioprine, and steroids; four patients received Cyclosporine, Azathioprine, and steroids; and two patients received Everolimus, MMF, and steroids. After comparing the different immunosuppressive regimens, none of them were significantly associated with NODAT. The occurrence of acute rejection episodes, HCV infection, and CMV infection were all significantly associated with NODAT patients in our study. Also, patients with NODAT had a high BMI (statistically significant, $p = 0.001$).

Systemic hypertension was significantly higher in the NODAT group (81% vs. 62.7%), but it was statistically insignificant. HbA1c levels, serum total cholesterol, triglyceride levels, and LDL levels were significantly higher in patients with NODAT. Although the mean blood urea and serum creatinine levels were higher in the NODAT group, they were found to be statistically insignificant. Serum uric acid levels were found to be significantly higher in patients with NODAT ($p = 0.002$). The mean Tacrolimus trough levels were found to be higher in the NODAT group in our cohort (6.3 ng/mL vs. 7.7 ng/ml).On logistic regression analysis, higher BMI and a history of HCV infection were found to be independent risk factors for NODAT.

Table 1 : Demographic And Clinical Variables

Variable	Non –NODAT N=69(%)	NODAT N=21 (%)	P value
Hemoglobin (gm/dl)	12.7±2.6	12.5±3.1	0.734
Blood Urea (mg/dl)	33.7±10.8	33.8±18.1	0.968
Serum Creatinine (mg/dl)	1.8±0.9	1.7±1.2	0.658
Serum Uric acid (mg/dl)	7.0±1.7	5.3±1.6	0.001
HBA1C	5.1±0.5	6.5±1.3	0.001
Serum total Cholesterol (mg/dl)	214.5±25.0	265.5±22.7	0.001
Serum triglyceride (mg/dl)	162.3±20.4	207.4±16.6	0.001
Serum LDL(mg/dl)	144.6±7.2	170.0±8.3	0.001
Tacrolimus trough level (ng/ml)	6.3±1.5	7.7±1.2	0.001

Table 2: Biochemical Parameters Of Patients

Variable	Non NODAT N=69 (%)	NODAT N=21 (%)	P Value
Mean age (in years)	37.1	35.9	0.614
Male	38 (64.4%)	18 (85.7%)	0.067
Female	21(35.6%)	3(14.3%)	
Mean Recipient Age (in years)	50.1	53.8	0.412
Family history of diabetes mellitus in first degree relative	20 (29.4%)	10 (45.5)	0.004
Live donor	53 (89.8%)	18 (85.7%)	0.691
Deceased donor	6 (10.2 %)	3 (14.3%)	
Delayed graft function	3 (5.1%)	1 (4.8%)	0.954
Acute rejection	11(16.1%)	5 (22.7%)	0.003
HCV infection	1(1.7%)	8(38.1%)	0.001
CMV infection	4(5.8%)	3(13.6%)	0.004
Basiliximab	30 (43.4%)	12(57.1%)	0.948
ATG	25(36.2%)	8(38.1%)	
No induction	14(20.2%)	1 (4.7%)	
Body mass index (kg/m^2)	23.8±3.2	26.8±4.5	0.001
Hypertension	37(62.7%)	17 (81.0%)	0.04

Table 3: Factors That Affecting DM Using Binary Logistic Regression Model

Predictors	p-value	OR	95% C.I.for OR
HCV infection	0.043	64.700	[1.146 -3654.386]
BMI	0.008	1.052	[1.013- 1.092]

DISCUSSION

The prevalence of NODAT was 23.3% in our study population. According to previous studies, the incidence of NODAT is between 4% and 25% [6]. The majority of patients (61.9%) developed NODAT within 1 year of transplantation. This is similar to a multicenter study by Malik et al., in which the incidence of NODAT after renal transplantation was around 29% and approximately two-thirds of the patients developed NODAT within 1 year of transplantation[7]. In an analysis of the US Renal Data System (USRDS) consisting of primary kidney transplant patients, Kasiske et al. showed a strong association between older age and NODAT[8]. In our study, although the mean age in the NODAT group was higher, it was statistically insignificant.

With one study indicating a sevenfold increase in the illness, there is significant evidence that people with first-degree relatives who have had diabetes are at an elevated risk of having NODAT. Across all forms of solid organ transplantation, the higher prevalence of NODAT connected to a familial history of diabetes has been established. A definitive family history of diabetes mellitus was linked to a 50 percent increase in the chance of acquiring NODAT in a multicenter study carried out in Spain on subjects involving kidney, heart, and lung transplants [9]. Additionally, a substantial link between the emergence of NODAT and a first-degree relative's history of diabetes mellitus was found by our research.

The implication of steroid regimens in the progress of NODAT was initially recognised by Starlz among the kidney transplant subjects in 1964 [10,11].Steroids tend to produce dose-related hyperglycemia, as evidenced by multiple studies. In many studies, the proportion of kidney recipients who were diagnosed with glucose intolerance came down significantly when oral prednisolone tapering to a dose of 5 mg daily was achieved [12,13].Similarly, even a mild increase of 0.01 mg/kg/day resulted in weight gain and a 5% threat of the emergence of NODAT. Luan et al. found that post-transplant regimens that were steroid-free resulted in a significantly lower risk of NODAT incidence in comparison to regimens containing steroids [14]. Because all of the patients in our cohort were given steroids, we were unable to assess the effect of steroids on the incidence of NODAT.

There were multiple trials implicating the role of calcineurin inhibitors in NODAT. Tacrolimus was found to be more likely than Cyclosporine to cause NODAT[15,16].Tacrolimus regimens had a statistically higher incidence of NODAT development at six months compared to cyclosporine-based regimens, according to the DIRECT STUDY, a multicenter, open-label, and randomised study that compared glycemic disturbances among renal transplant recipients[17].Elevated Tacrolimus trough levels were a significant risk factor for NODAT, according to a single-center investigation by Maes et al. Despite comparing many immunosuppressive regimens in our study, no particular regimen was identified as a risk factor for NODAT. This might be because tacrolimus and an MMF-based regimen were used to treat the majority of our patients. Tacrolimus trough levels, on the other hand, were found to be significantly higher in the NODAT group.

It has been previously established that acute rejection events increase the risk of development of NODAT.Higher need for steroids as well as other immuosupressive drugs may be the etiology behind this.The combined analysis of 12 case control studies revealed that the risk of developing NODAT following renal transplantation is 1.95 times higher in cases of acute rejection [19]. Acute rejection events were also identified as a potential risk factor for NODAT development in our study population.

NODAT occurrence has been linked to the existence of HCV infection as a potential risk factor in many trials.Resistance to insulin, diminished liver glucose reuptake are possible explanations for the NODAT incidence[20,21] HCV infection was found to be an independent risk factor in the emergence of NODAT in our sample population.

An established risk factor for NODAT is obesity. In a study by Bonato V. Barni [22], the BMI (body mass index) at baseline was found to be a decisive factor in the development of post-transplant diabetes. Patients with NODAT were frequently overweight and had higher incidences of acute rejection episodes than their counterparts. In our investigation,

higher BMI was found to be an independent risk factor for the emergence of NODAT. Patients with NODAT had considerably higher rates of dyslipidemia and hypertension in our study. According to a study by Bayer et al.[24], the prevalence of NODAT at one year significantly increased in accordance with the increasing number of metabolic syndrome elements.

Previous research by Hjelmesaeth et al.[25]revealed that asymptomatic CMV infection may influence the occurrence of NODAT.A fourfold increased incidence of NODAT was linked to the presence of asymptomatic CMV viremia, particularly during the first three months after kidney transplantation.In an observatory study involving 160 non-diabetic kidney transplant subjects, CMV viremia-induced pro-inflammatory milieu with resultant pancreatic beta cell dysfunction is the proposed mechanism for the risk of developing NODAT. In a similar vein, our study revealed a strong correlation between NODAT and CMV infection.

In a ten-year cohort study of renal transplant recipients by Tanaka et al. [27], a significant association between uric acid levels and NODAT was found after adjusting for other identifiable risk factors, including factors affecting serum uric acid. In our study, higher uric acid levels were also identified as a potential risk factor for NODAT occurrence.

Our study has a few limitations. Firstly, the number of participants was limited. Secondly, as all the patients were treated with steroids, we were not able to assess the effect of a steroid-free regimen on the development of NODAT. Moreover, most of the patients were on a Tacrolimus and MMF regimen and therefore could not assess the significant effect of each immunosuppressive regimen.

CONCLUSION

NODAT in renal transplant recipients is a common yet important complication. In our study, the prevalence of NODAT appeared to be higher in subjects with a family history of diabetes mellitus, acute rejection episodes, CMV infection, higher Tacrolimus trough levels, higher uric acid levels, and dyslipidemia. Increased BMI and HCV infection were found to be independent risk factors for the development of NODAT. Identification of potential causative and contributing factors for NODAT, as well as measures to reduce such factors, should be part of the treatment of kidney recipients.

REFERENCES

1. Davidson JA, Wilkinson A. New-onset diabetes after transplantation 2003 international consensus guidelines: an endocrinologist's view. Diab Care. 2004 Mar 1; 27(3):805-12.
2. Wilkinson A, Davidson J, Dotta F, Home PD, Keown P, Kiberd B, et al. Guidelines for the treatment and management of new-onset diabetes after transplantation 1. Clinical Tansplantat. 2005 Jun; 19(3): 291-8.
3. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC. Post transplantation diabetes: a systematic review of the literature. Diab Care. 2002 Mar 1;25(3):583-92
4. Porrini EL, Díaz JM, Moreso F, Delgado Mallén PI, Silva Torres I, Ibernon M, et al. Clinical evolution of post-transplant diabetes mellitus. Nephrol Dial Transplant. 2016;31:495–505
5. Pham PT, Pham PM, Pham SV, Pham PA, Pham PC. New onset diabetes after transplantation (NODAT): an overview. Diabetes MetabSyndrObes. 2011;4:175-86. doi: 10.2147/DMSO.S19027. Epub 2011 May 9. PMID: 21760734; PMCID: PMC3131798.
6. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, White HD, Nordlander R, Maggioni A, Dickstein K, Zelenkofske S, Leimberger JD, Califf RM, Pfeffer MA: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 351: 1285–1295, 2004 https://doi.org/10.1056/NEJMoa041365
7. Malik, R., Jia, Y., Mansour, S., Reese, P., Hall, I., Alasfar, S., Doshi, M., Akalin, E., Bromberg, J., Harhay, M., Mohan, S., Muthukumar, T., Schroppel, B., Singh, P., Weng, F., Thiessen-Philbrook, H. and Parikh, C., 2021. Post-Transplant Diabetes Mellitus in Kidney Transplant Recipients: A Multi-Center Study. *Kidney360*, pp.10.34067/KID.0000862021.
8. 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.
9. Martinez-Castelao A, Hernandez MD, Pascual J, et al. Detection and treatment of post kidney transplant hyperglycemia: a Spanish multicenter cross-sectional study. Transplant Proc. 2005;37(9):3813–3816.
10. Cosio FG, Pesavento TE, Osei K, Henry ML, Ferguson RM. Posttransplant diabetes mellitus: increasing incidence in renal allograft recipients transplanted in recent years. Kidney Int. 2001;59(2): 732–737
11. Jindal RM, Revanur VK, Jardine AG. In: Hakim N, Stratta R, Gray D, editors. Immunosuppression and Diabetogenicity, 1st ed. (Pancreas and islet transplantation). New York: Oxford University Press; 2002: 247–27.
12. Hjelmesaeth J, Hartmann A, Kofstad J, Egeland T, Stenstrom J, Fauchald P. Tapering off prenisolone and cyclosporine the first year after renal transplantation: the effect on glucose tolerance. Nephrol Dial Transplant. 2001;16:829–835.
13. Hjelmesaeth J, Hartmann A, Kofstad J, et al. Glucose intolerance after renal transplantation depends upon prednisolone dose and recipient age. Transplantation. 1997;64(7):979–983
14. Luan FL, Steffick DE, Ojo AO. New-onset diabetes mellitus in kidney transplant recipients discharged on steroid-free immunosuppression. Transplantation. 2011; 91(3): 334–341.
15. Woodward RS, Schnitzler MA, Baty J, et al. Incidence and cost of new onset diabetes mellitus among US wait-listed and transplanted renal allograft recipients. Am J Transplant. 2003;3(5):590–598.
16. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation. N Engl J Med. 2007;357(25): 2562–2575.
17. Vincenti F, Friman S, Sceuermann E, et al. Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. Am J Transplant. 2007;7(6): 1506–1514.
18. Maes BD, Kuypers D, Messiaen T, et al. Posttransplant diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation. 2001;72(10):1655–1661.
19. Xia, M., Yang, H., Tong, X., Xie, H., Cui, F. and Shuang, W., 2020. Risk factors for new-onset diabetes mellitus after kidney transplantation: A systematic review and meta-analysis. *Journal of Diabetes Investigation*, 12(1), pp.109-122.
20. Bloom RD, Lake JR. Emerging issues in hepatitis C virus-positive liver and kidney transplant recipients. Am J Transplant. 2006;6(10): 2232–2237.
21. 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.
22. Bonato V, Barni R, Cataldo D, et al. Analysis of posttransplant diabetes mellitus prevalence in a population of kidney transplant recipients. Transplant Proc. 2008; 40(6):1888–1890.
23. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. J ClinEndocrinolMetab. 1982;54(2): 254–260
24. Bayer ND, Cochetti PT, Kumar MSA, et al. Association of metabolic syndrome with development of new-onset diabetes after transplantation. Transplantation. 2010;90(8):861–866.
25. Hjelmesaeth J, Sagedal S, Hartmannn A, et al. Asymptomatic cytomegalovirus infection is associated with increased risk for new-onset diabetes and impaired insulin release after renal transplantation. Diabetologia. 2004;47(9);1550–1556.
26. Hjelmesaeth J, Muller F, Jenssen T, Rollag H, Sagedar S, Hartmann A. Is there a link between cytomegalovirus infection and new-onset posttransplant diabetes mellitus Potential mechanisms of virus induced β-cell damage.Nephrol Dial Transplant. 2005;20(11): 2311–2315.
27. Tanaka, K., Sakai, K., Kushiyama, A. *et al.* Serum uric acid is an independent predictor of new-onset diabetes after living-donor kidney transplantation. *Ren Replace Ther* 4, 28 (2018). https://doi.org/ 10.1186/s41100-018-0169-4