New-onset Diabetes after Renal Transplant and Associated Factors

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ABSTRACT

Objective: To assess the frequency and time of onset of new-onset diabetes after transplant (NODAT) and its associated factors.

Study Design: Observational study.

Place and Duration of Study: Department of Nephrology, Bahria International Hospital, Lahore, Pakistan, from April 2016 to April 2018.

Methodology: NODAT was diagnosed according to American Diabetes Association Criteria with fasting plasma glucose >126 mg/dl or random plasma glucose >200 mg/dl. Those with pre-existing diabetes and follow-up duration less than 12months, were excluded. Patients were divided in two groups: with and without NODAT, for statistical comparison.

Results: The study included 115 patients, 101 were males and the median age was 35.0 (29.0-46.0) years. During the one-year period of follow-up, 28 (24.3%) patients developed NODAT. The mean time of onset of NODAT was 5.3 ± 3.6 months. Family history of diabetes was positive in 46% patients in NODAT group, which was significantly higher as compared to 5.7% in non-NODAT group with p-value of <0.001, which is significant. All patients with more than three HLA mismatches developed NODAT. The mean fasting glucose levels (FPG) before transplant in NODAT group was 96.6 ± 15.4 mg/dl, which was significantly higher than FPG of non-NODAT group, where it was 80.5 ± 12.2 mg/dl. It was interesting to note that 35.7% of hepatitis patients developed NODAT as compared to 6 % in non-NODAT group with p = 0.001.

Conclusion: NODAT was observed in 24.3% patients. The pre-transplant FPG, family history of diabetes, increased HLA mismatches, and hepatitis C infection were the major associated factors.

Key Words: *New onset diabetes after transplant, Fasting plasma glucose, Renal transplant.*

How to cite this article: Khan AA, Ahmed W, Ayyaz A. New-onset Diabetes after Renal Transplant and Associated Factors. *J Coll Physicians Surg Pak* 2021; **31(12)**:1482-1486.

INTRODUCTION

New onset diabetes after transplant (NODAT) is a serious and common metabolic complication after a kidney transplant.[1] It contributes to significant mortality and morbidity and carries a substantial risk for cardiovascular disease. It is a strong and independent predictor of global mortality, graft failure, and death-censored graft failure.[2]

It may be diagnosed at any time after renal transplant by the same diagnostic criteria for non-transplant patients with either fasting plasma glucose ≥126 mg/dl or random plasma glucose ≥200 mg/dl along with the symptoms of polyuria, polydipsia, and unexplained weight loss.[3]

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Received: August 05, 2020; Revised: March 10, 2021; Accepted: April 02, 2021
DOI: https://doi.org/10.29271/jcpsp.2021.12.1482

The incidence of NODAT varies from 3 to 20% patients and this wide range of variations is attributed to different reasons, including the method to define diabetes, post-transplant period, type of study population, and immune-suppressive protocols used.[4] The definition of NODAT is based on the guidelines determined by World Health Organization (WHO) and American Diagnostic Criteria (ADA).[1,5] The HbA1c test is not routinely recommended for the diagnosis in first three months of renal transplant as the test loses validity until new hemoglobin (Hb) has been synthesized and glycated for reasonable period of time.[4] NODAT may be diagnosed after three months of transplant when HbA1c ≥6.5 %.[6]

The risk factors for the development of NODAT are traditional as well as non-traditional. The age, male gender, ethnicity, family history, autosomal dominant polycystic kidney disease (ADPKD) and deceased donors are usually recognized as non modifiable risk factors; whereas, obesity, HCV infection, and immune-suppressive drugs are the factors unique to renal transplant recipients.[7-9] The agents commonly associated with development of NODAT include glucocorticoids, calcineurin inhibitors, and mTOR inhibitors. Moreover, the increased HLA mismatches, DR

mismatch, and HLA B27 phenotype also carry an increased risk for NODAT.[2,10]

The pathogenesis of NODAT is multifactorial and recognized mechanisms of insulin resistance and decreased insulin secretion are involved. This is in line with the effects of immuno-suppressant agents. The patients on tacrolimus are more prone to develop NODAT as compared to patients on cyclosporin as observed in previous study which confirmed that tacrolimus use was associated with decreased insulin secretion.[9,11] During the first month of renal transplant, the risk of NODAT further increases with the tacrolimus trough level greater than 15 ng/ml.

Previously, NODAT was considered a minor problem, but it has emerged as a major issue recently due to its proven effects on cardiovascular mortality.[12] This has led to the robust pre-transplant assessment, which includes screening for the risk factors of NODAT. On the other hand, post-transplant monitoring is also required with weekly monitoring of fasting plasma glucose during first four weeks of transplant, followed by measurements at an interval of three months, six months and annually.[13]

The management of NODAT is similar to that of type 2 diabetes in the general population, beginning with the lifestyle modification and the pharmacotherapy comprises of oral hypoglycemic agents and insulin depending upon the severity of NODAT. Apart from this stepwise approach, immune-suppressive drugs should also be tailored to control or reverse NODAT, such as early withdrawal of glucocorticoids or switching tacrolimus to cyclosporine which is less diabetogenic. The HbA1c level should be kept below 7.0-7.5% to minimise the complications of NODAT.[14]

The objective of this study was to assess the frequency and time of onset of new-onset diabetes after transplant (NODAT) and its associated factors.

METHODOLOGY

An observational study was conducted in the Department of Nephrology, Bahria International Hospital, Lahore, Pakistan. All patients undergoing live related renal transplantation from April 2016 to April 2018 were included in the study and were followed up for 12 months after the operation. Patients with the previous history of diabetes, follow-up period less than 12 months, and missing information were excluded from the study.

NODAT was diagnosed according to ADA criteria with the symptoms (weakness, polyuria, weight loss and diabetic ketoacidosis) with fasting plasma glucose (FPG) >126 mg/dl or random plasma glucose (RPG) >200 mg/dl. The diagnosis of NODAT was made after one month of operation when kidney graft and immuno-suppressive regimen were stable and in the absence of infections, just to rule out patients with temporary hyperglycemia in early time of transplant.

All the patients received this institution's based standard immune-suppressant protocol with intra-venous methylprednisolone one gm over two days, followed by oral steroids one mg/kg/day and progressively tapered down to 10 mg/day over two months. The maintenance treatment consisted of prednisolone, mycophenolate mofetil and tacrolimus/cyclosporine. The treatment of NODAT patients comprised of dietary control, oral hypoglycemic agents and insulin.

Induction therapy and anti-thymocyte globulin (ATG) was given only in those candidates, where there were more than 3 HLA mismatches. Tacrolimus trough target level was maintained at 8-12 ng/ml for first 6months and then 6-8 ng/ml for the next six months.

The record of patients was extracted from Hospital Information System (HIS) software. Data were entered and analysed by using SPSS statistics version 20.0 for Windows. Quantitative data were described by using mean ± SD and median (IQR) for NODAT and non-NODAT groups. The data for all these variables were tested for normality by using Shapiro-Wilk's test; and those having normal distributed data for both groups were compared between two groups by using Independent sample t-test and for other variables, Mann-whitney U-test was applied.

The qualitative variables like gender, family history of diabetes, onset of diabetes, HLA mismatches, pre-transplant hepatitis B and C status and pre-transplant CMV status were all described by using frequency and percentages, and were compared between NODATs and non-NODATs by using Fisher Exact and Likelihood ratio depending on expected frequencies. P-value ≤0.05 was considered significant.

RESULTS

The study included 115 patients, who were enrolled immediately after renal transplant, and followed for 12 months. Out of these 115 patients, 101 (87.8%) were males and 14 (12.2%) females; the median age of these patients was 35.0 (29.0 – 46.0) years. The mean fasting plasma glucose level in the pre-transplant period was 84.4 ± 14.7 mg/dl, and median BMI was 21.0 (19.8 – 22.5) Kg/m^2. The median HbA1c level was 5.2 (5.0 – 5.4) % before transplant. During the one-year follow-up period, 28 (24.3%) patients developed diabetes, labelled as new onset diabetes after transplant (NODAT) and the mean duration of time after transplant when the greatest number of patients were confirmed to have NODAT, was 5.3 ± 3.6 months.

In NODAT group, 27 (96.4%) patients were males as compared to 85.1% in non-NODAT group and this difference was not statistically significant (p = value 0.182). The positive family history of diabetes was significantly higher in NODAT group (46.4%) as compared to non-diabetic patients (5.7%). All the patients having 4 or 5 HLA mismatches developed NODAT; while, frequency was less common in 3 or less HLA mismatches. Out of 87 non-NODAT patients, 73 (83.9 %) and 14 (50%) out of 28 NODAT patients had 3 HLA mismatches. NODAT developed more often in hepatitis-C positive patients, who underwent renal transplant as compared to hepatitis negative patients with p-value of 0.001. Only one CMV positive case after transplant developed diabetes in follow-up period.

Table I: Comparison of various risk factors between NODAT and non-NODAT.

		Group				p-value
		NODAT (n = 28)		Non-NODAT (n = 87)		
		N	%	n	%	
Gender	Male	27	96.4	74	85.1	0.182
	Female	1	3.6	13	14.9	
Family Hx	Yes	13	46.4	5	5.7	<0.001
	No	15	53.6	82	94.3	
HLA mismatch	None	2	7.1	4	4.6	<0.001
	Two	0	0.0	10	11.5	
	Three	14	50.0	73	83.9	
	Four	8	28.6	0	0.0	
	Five	4	14.3	0	0.0	
Hepatitis status	Positive	10	35.7	6	6.9	0.001
	Negative	18	64.3	81	93.1	
CMV status	Positive	1	3.6	0	0.0	0.243
	Negative	27	96.4	87	100.0	
Immunosuppressant	Cyc	1	3.6	16	18.4	0.068
	Tac	27	96.4	71	81.6	

Table II: Comparison of different risk factors between NODAT and non-NODAT.

	Group		p-value
	NODAT	Non-NODAT	
	Mean ± SD / Median (IQR)	Mean ± SD / Median (IQR)	
Age (Years)	35.0 (29-44)	35.0 (29-47)	0.669
BMI (kg/m^2)	21.3 (19.3-25.6)	20.9 (19.8-22.2)	0.249
*Pre Tx BSF (mg/dl)	96.6 ± 15.4	80.5 ± 12.2	<0.001
Pre Tx HbA1c (%)	5.0 (4.7-5.3)	5.3 (5.1-5.4)	0.002
Uric Acid (mg/dl)	5.7 (4.7-6.2)	5.1 (4.8-5.4)	0.204
Post Tx BSF (mg/dl)	203.5 (182.5-243)	87.0 (80-95)	<0.001
*Hb 1 (g/dl)	13.6 (11.3-14.5)	13.0 (11.0-14.4)	0.575
*Hb 2 (g/dl)	13.2 ± 2.2	12.9 ± 2.1	0.574
Hb 3 (g/dl)	13.5 (12.3-15.5)	13.2 (12-14.7)	0.348
*Hb 4 (g/dl)	13.8 ± 2.1	13.5 ± 1.6	0.466
*Hb 5 (g/dl)	14.1 ± 1.9	13.7 ± 1.5	0.219
BUN 1 (mg/dl)	16.8 (12.6-22.4)	15.0 (13-19)	0.317
BUN 2 (mg/dl)	17.9 (15-24)	15.0 (13-18)	0.021
BUN 3 (mg/dl)	17.4 (14-19.1)	16.0 (14-19)	0.704
BUN 4 (mg/dl)	17.0 (14-21)	17.0 (14-19)	0.742
BUN 5 (mg/dl)	19.1 (14.5-25.7)	18.0 (15-20)	0.270
Creatinine 1 (mg/dl)	1.2 (0.9-1.5)	1.1 (1-1.3)	0.859
Creatinine 2 (mg/dl)	1.1 (0.8-1.4)	1.1 (1.1-1.3)	0.382
Creatinine 3 (mg/dl)	1.0 (0.8-1.5)	1.2 (1.1-1.3)	0.300
Creatinine 4 (mg/dl)	1.2 (0.9-1.4)	1.2 (1.1-1.3)	0.347
Creatinine 5 (mg/dl)	1.1 (1.0-1.5)	1.3 (1.1-1.3)	0.241

*The variable with * were tested by Independent sample t-test. Mann-Whitney U-test was applied for comparison except those with *. Values in parenthesis are the IQR given as (Q1 – Q3).*

There were no episodes of rejection in our patients duringthis follow-up period. Twenty-seven (96.4%) out of 28 NODAT patients were taking tacrolimus as compared to 71 (81.6 %) out of 87 patients who did not develop diabetes and this difference was significant (Table I).

The mean fasting plasma glucose levels before renal transplant in NODAT group was 96.6 ± 15.4 mg/dl, which was significantly higher than non-NODATs, where it was 80.5 ± 12.2 mg/dl. The HbA1c level for NODAT group was significantly lower than non-NODAT group with p-value 0.002. The mean fasting glucose level for NODATs after transplant was 203.5 mg/dl (182.5-243 mg/dl) and it was 87.0 mg/dl (80-95 mg/dl) in non-NODATs.

There was no significant difference in BMI, uric acid, hemoglobin and creatinine values at quarterly follow-ups. However, the mean level of BUN (17.9 mg/dl) at 2nd follow-up was significantly higher (p = value 0.021) in NODAT group as compared to non-NODAT group where it was15.0mg/dl (Table II).

Thirteen (46.4%) patients had only weakness; whereas, 9 (32.1%) had symptoms of weight loss with weakness and 3 (10.7%) had diabetic ketoacidosis at the time of diagnosis of NODAT.

DISCUSSION

The kidney transplant is the most cost-effective treatment option for patients with ESRD. It not

only improves patient-survival but also quality of life. Nevertheless, this treatment option for kidney failure has some complications. New onset diabetes mellitus after kidney transplantation (NODAT) is a common and serious metabolic complication of kidney transplantation. It is associated with increased risk of infections and cardiovascular complications leading to poor graft survival and patient outcome.[14,15]

The occurrence of NODAT varied differently in different studies and this discrepancy may be attributed due to the use of different diagnostic criteria, racial differences,

different immunosuppressive protocols, intensity of routine screening and follow up.[16] The calculated rate of NODAT could be influenced by different immunosuppressive protocols used in different transplant centres. For instant, among calcineurin inhibitors, use of tacrolimus is associated with increased risk of NODAT as compared to cyclosporine.[4] Although, the present study did not compare these two medicines as only one patient in NODAT group was taking cyclosporine.

The reported rate of NODAT in the first year of transplantation is reported as 7-30% in recent studies.[14,17] In this study, 24.3% of patients were diagnosed with NODAT in the first year of transplant which is consistent with previous studies. It is also noted in recent studies that NODAT occurrence peaked in the first 3-6 months of post-transplant period; and the same was seen in this study as well.[18,19] The mean time to diagnosis of NODAT was 5.3 ± 3.6 months, with majority of patients developing NODAT in first six months. This may be because of higher doses of immunosuppressive medications used in the first 3-6 months.

The annual risk of developing diabetes after six months of transplant is comparable to that observed in non-transplant patients (6%-8%).[18,19] A previous study, conducted in Pakistan, found NODAT in 15.8% transplant patients, this difference may be because of majority of their transplant patients were on cyclosporine-based immunosuppression regime.[9]

In this present study, higher pre-transplant glucose level was an independent risk factor for the development of NODAT. Previous studies have also found similar relationship between pre-transplant glucose level and high risk of developing NODAT.[20]

Studies in general population have shown increasing risk of diabetes with positive family history of diabetes.[21] In the current cohort study, the family history of DM was found to be positive in 46.4% patients in newly diagnosed diabetes after transplant which is significantly higher than non-NODAT patients (5.7%).

Hepatitis C virus infection was more prevalent in the NODAT patient group as compared to non-NODAT patients (10 *vs*. 6; p = 0.001), this is in accordance with the previous studies.[9] One explanation for increased frequency of NODAT in hepatitis C positive patients is that hepatitis C virus triggers direct or immune mediated effect on B cells of pancreatic islets causing B cell dysfunction, insulin resistance due to liver dysfunction and abnormal metabolism of glucose [22]. Similar mechanism is involved in CMV infection.[23] In this study, only one patient was CMV positive by PCR who developed NODAT. It was also found in our study that patients with more than 3 HLA mismatches are more likely to develop NODAT.

Previous studies have shown increasing number of NODAT with increased age of patients.[21] This trend was not observed in this study, as the median age was 35.0 years in both groups and the difference was statistically insignificant. Similarly, BMI, haemoglobin, serum uric acid and creatinine levels were recorded but did not prove to be statistically significant in different groups.

This study has some limitations as it was a single-centre experience with male predominance gender population. This study could not assess the cardiovascular complications and graft survival in NODAT patients as already been mentioned in the literature, because of short follow-up period of one year. This study has also not compared the effects of immunosuppression agents' levels on the treatment strategy of NODAT, as it was beyond the scope of the present study.

CONCLUSION

It is essential to identify modifiable risk factors for NODAT in transplant patients. The family history of diabetes, hepatitis C infection, and pre-transplant high plasma glucose levels are independent risk factors for the development of NODAT, indicating a need for routine blood glucose screening, especially in those patients indicating a prior risk complication to do vigorous blood glucose monitoring for early intervention in case they develop NODAT.

ETHICAL APPROVAL:

The Ethical Committee of Bahria International Hospital, Lahore, approved the study design prior to initiation of the study.

PATIENTS' CONSENT:

The informed consents were obtained from all participants of study to publish the data of this study

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

AAK: Collected the data and entered in SPSS file, also written introduction, methodology and discussion.
WA: Proofread whole manuscript and helped in compiling the results.
AA: Contributed in writing results and references.

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