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ORIGINAL ARTICLE

New-Onset Diabetes after Transplantation (NODAT) in Renal Transplant Recipients, A Retrospective Single Centre Study

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ABSTRACT

Objective: New onset diabetes after transplant (NODAT) is a known post-transplant complication contributing to morbidity and mortality. This study was aimed to find out the frequency of NODAT in kidney disease patients after one year.

Methods and subjects: The study was conducted retrospectively on 275 Asian patients who underwent kidney transplant. The demographic and clinical data was evaluated at the time, as well as 3, 6, and 12 months after kidney transplant. The etiology of end-stage renal disease (ESRD) or comorbidities was also documented. Every patient received a combination of Tacrolimus (Tac), Mycophenolate Mofetil (MMF), and Prednisone (Pred) as post-transplant immunosuppression. Patients who developed NODAT were compared with those who did not.

RESULTS: One year after the transplantation, the incidence of NODAT was 4.3 percent. Patients diagnosed with NODAT were older ($p = 0.001$) and had renal failure owing to Chronic glomerulonephritis with hypertension ($p = 0.001$), according to the results of the univariate analysis. The NODAT group had significantly greater rates of high blood pressure after transplantation ($p = 0.01$), heart failure ($p = 0.02$), and dyslipidemia ($p = 0.001$) than the other groups. Through the use of logistic regression, it was shown that high blood pressure after transplant, and dyslipidemia are all independently linked with NODAT.

Conclusion: Asian patients who had high blood pressure and dyslipidemia had a higher incidence of NODAT compared to those who did not have.

Keywords: kidney transplantation, prevalence, new-onset diabetes after trasplant

INTRODUCTION

Transplant-related problems, such as post-transplant diabetes mellitus (DM), may occur for a variety of reasons. (1) (2) A first occurrence of one of the two parameters three months after transplant i) two fasting plasma glucose values of ≥126 mg/dL (≥7.0 mmol/L) 30 days apart, (ii) three-month hemoglobin A1c of ≥ 6.5 percent following transplantation was used to label as NODAT. New-onset DM is five to six times as common in kidney transplant recipients during the first year than it is in those on the waiting list.(3) These problems have been associated to transplant failure as well as cardiovascular disease, the major cause of death in transplant patients.(4) (5) Insulin resistance & insulin hypo-secretion are hallmarks of NODAT, just as they are in type 2 DM. Insulin hypo secretion is a marker for glucose intolerance in the NODAT model. NODAT is associated with ethnicity, a history of diabetes in the family, a high BMI, and infection with CMV or HCV. This disease may be brought on by high dosages of glucocorticoids and calcineurin inhibitors which is a part of routine immunosuppressive therapy in these patients. (6, 7) NODAT is more common due to genetic reasons such as certain vitamin D receptor haplotypes. (8) Study participants who had a genetic variation in the Toll-like receptor-4 & TLR-6 genes were shown to have an increased risk of developing NODAT. (9) Interleukins, transcription factor 7-like 2, SLC30A8 zinc transporter member 8, matrix metalloproteinase and chemokine, ligand 5 genes have all been linked to the development of NODAT in various researches.(10-12) Thus, the incidence of NODAT in various communities may also be influenced by genetic factors as well. Renal transplant patient's enhanced longevity need proper monitoring, since complications might compromise their survival and quality of life. (13, 14) A cohort of kidney transplant patients was analyzed to determine the frequency of NODAT and its risk factors in our population.

METHODOLOGY

The local Committee of Ethics in Research gave its consent to proceed with this investigation using retrospective data. The medical records of kidney transplant patients who were registered at Pakistan Kidney and Liver Institute (PKLI) between July 2018 and December 2021 were looked at in order to compile an epidemiological, clinical, and therapeutic profile.

Patients who were under the age of 18, patients who had DM before to transplantation, patients who had first-degree relatives who suffered from DM, patients who had previously taken immunobiological medications, and patients who had had graft rejection were not eligible for the study. The total number of participants in the research were 275 (247/275 or 89.8 percent were males, 28/275 or 10.2 percent were females and the median age was 43 years; the age range was 18–75 years).

We studied body mass index before transplantation, cause of renal failure before transplantation, graft origin, and hepatitis C. A first occurrence of one of two parameters three months post-transplant was classified as NODAT. i) two 30-day fasting plasma glucose values of ≥ 126 mg/dL (≥ 7.0 mmol/L) (ii) hemoglobin A1c ≥ 6.5%.

Frequency and contingency tables were created using the data obtained. The Fisher exact test and the chi-square test were used to analyses the nominal data, while the unpaired t-test and the Mann–Whitney test were used to analyses the numeric data. These tests were used to compare the clinical and epidemiological characteristics of individuals who developed NODAT versus those who did not. Logistic regression was used to examine each variable independently. It was determined to use a 5% level of significance.

RESULTS

Table 1 of the research contains epidemiological, therapeutic & clinical, data from kidney transplant patients. Only three of the patients were infected with HCV. The incidence of NODAT was 4.3 percent. Table 2 compares the outcomes of patients who developed NODAT versus those who did not. The incidence of NODAT was greater in older patients, and in those with hypertension and dyslipidemia. NODAT patients also had greater blood pressure and chronic glomerulonephritis, two causes of renal failure that need transplantation.

One year after the transplantation, we discovered that the incidence of NODAT was 4.3 percent. Individuals who received NODAT were older and had renal failure than patients who did not get NODAT in the univariate analysis. The NODAT group had a significantly higher incidence of post-transplant hypertension, heart failure and dyslipidemia than the other groups. With logistic

regression, it was shown that high blood pressure after transplant, and dyslipidemia are all independently related with NODAT.

Table 1: contains the clinical, epidemiological, & therapeutic data of recipients of kidney transplants.

Variables		N	%
Ethnic background	Asian	275	100%
Cause of ESRD	Chronic Tubulointerstitial Nephritis	13	4.7
	Chronic Pyelonephritis	12	4.3
	IgA nephropathy	11	4.0
	Chronic Glomerulonephritis with Hypertension	125	45.4
	Reflux Nephropathy	6	2.18
	Obstructive Nephropathy	6	2.18
	Adult Polycystic kidney disease (ADPKD)	6	2.18
	Primary Hyper oxaluria	4	1.45
	Others	92	33.4
Co-morbidities	Heart failure	3	1.0
	Dyslipidemia	38	13.8
	Ischemic heart diseases	10	3.6
	Hypertension	229	83.2

Table 2: An evaluation of kidney transplant patients based on whether or not NODAT

	With NODAT	Without NODAT	P
Median age	48	41	0.001
Male gender	62	52	0.17
Cause of ESRD	Chronic Tubulointerstitial Nephritis 1 (8.3%)	Chronic Tubulointerstitial Nephritis 12 (4.5%)	0.001
	Chronic Pyelonephritis 3 (25%)	Chronic Pyelonephritis 9 (3.4%)	
	IgA nephropathy 0 (0%)	IgA nephropathy 11 (4.1%)	
	Chronic Glomerulonephritis 4 (33.3%)	Chronic Glomerulonephritis 121 (46%)	
	Reflux Nephropathy 1 (8.3%)	Reflux Nephropathy 5 (1.9%)	
	Obstructive Nephropathy 1 (8.3%)	Obstructive Nephropathy 5 (1.9%)	
	Adult Polycystic kidney disease (ADPKD) 2 (16.6%)	Adult Polycystic kidney disease (ADPKD) 4 (1.5%)	
	Primary Hyper oxaluria 0 (0%)	Primary Hyper oxaluria 4 (1.5%)	
Pre-transplant Median Body Mass Index (BMI) (kg/m^2)	24.9	24.5	0.49
Body Mass Index (BMI) 6-month post-transplant (kg/m^2)	25.5	25.4	0.78
Body Mass Index (BMI) 12- month post-transplant (kg/m^2)	26.4	26.3	0.89
Hypertension	97.4	85.6	0.01
Dyslipidemia	25.3	9.7	0.001
Heart failure	3.7	0	0.02
Coronary insufficiency	5	9.7	0.50

DISCUSSION

The incidence of NODAT was 4.3 percent following the transplant surgery in our study which comprised 275 post renal transplant patients on the same immunosuppresive regimen. Patients with diabetes in their first-degree relatives were excluded from the research, lowering the risk of developing type 2 DM.

Other study has shown that characteristics such as having a high body mass index (BMI), taking calcineurin inhibitors & corticosteroids, being elderly, and having an infection with CMV or hepatitis C are all associated with an increased risk of developing NODAT. (2) The presence of this problem in the group was not associated to BMI alone. The mean BMI of the sample, on the other hand, ranged from 24 to 26 kg/m2, which is within the accepted normal range.

Other writers have also mentioned NODAT's link to African–American heritage. (15) One of the most prevalent NODAT causes is tacrolimus, which was administered to all of the patients. A calcineurin inhibitor has been recognized for a significant amount of time as the single most essential part of immunosuppressive treatment in the medical specialty of kidney transplantation. (16) T-cell activation is inhibited, and hence interleukin-2 synthesis are inhibited, resulting in T-cell clonal growth failure. (17) According to a number of studies, patients who were treated with tacrolimus had a higher chance of developing NODAT than those who were treated with cyclosporine. Despite this, tacrolimus has been proven to be more successful than cyclosporine in reducing the risk of patient mortality, preserving graft viability, and preventing the development of hypertension. (18)

Because calcineurin is present in pancreatic cells, the mechanism behind tacrolimus-induced NODAT involves decreased insulin production. This medicine impairs mitochondrial permeability, inhibits the transcription factor NFAT, and targets the transcriptional coactivator cAMP-responsive element-binding protein. It also prevents muscle cells and adipocytes from absorbing glucose. Postreceptor insulin signalling, glucose transport, and pancreatic insulin production are all dependent on magnesium, making hypomagnesemia one of the possible causes of calcineurin-associated glucose intolerance. (19) NODAT is a risk factor for graft failure and lowers transplanted recipient survival. NODAT patients have conventional diabetes symptoms, including hyperosmolar coma, ketoacidosis, peripheral & diabetic nephropathy.(20). After 5 years of transplantation, serum creatinine levels in individuals with NODAT are considerably greater than in those without it. All of these issues result in an increase in mortality, mostly owing to cardiovascular events(20). Cosio and colleagues found a link between fasting glucose levels one year after transplantation and 5-year cardiovascular incidence. The NODAT group had considerably more hypertension and

dyslipidemia, both risk factors for atherosclerosis and cardiovascular events.(21)

CONCLUSION

The findings of this research indicate that individuals of Asian ethnic origin who have had kidney transplants have a greater prevalence of NODAT linked to increased levels of blood pressure and dyslipidemia in all transplant patients, notwithstanding the recipient's different ethnic backgrounds. Research that is both prospective and multicentric might be helpful in better understanding and preventing NODAT.

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