Ten-year incidence of post-transplant Diabetes Mellitus in renal transplant patients

Fatemeh Habibnia1, Farshid Oliaei1, Hoda Shirafkan2, Mobarakhe Firoozjah1, Mobina Rezaei Roshan1 and Roghayeh Akbari2

Abstract

Background: Kidney transplantation is the treatment of choice for renal failure. Development of New-Onset Diabetes After Transplantation (NODAT) significantly increases kidney graft loss and mortality. This study aimed to evaluate the 10-years prevalence of NODAT in renal transplant patients.

Methods: In this cross-sectional study, medical records of non-diabetic patients undergoing kidney transplant in Shahid-Beheshti Hospital of Babol, between March 2009–2019 were retrospectively reviewed.

Results: Totally 284 patients with the mean age of 40.83 ± 12.94 years were included. New-Onset Diabetes After Transplantation was identified in 57 (20.1%) patients and 92.98% developed NODAT during the first month after transplantation. New-Onset Diabetes After Transplantation and non-NODAT patients were 43.8% and 34.38% female. Graft rejection occurred in 18 (31%) of NODAT and 78 (34%) of non-NODAT patients (p = .69). Patients with NODAT were about 10 years older (47.88 ± 11.06 vs 38.96 ± 13.12 years; p = .002). The pre-transplant Fasting Blood Sugar (FBS) was higher in the NODAT group (93.78 ± 13.78 vs 87.07 ± 11.56, p = .001) and post-transplantation cytomegalovirus (CMV) infection was higher in NODAT group (56% vs 40%, p = .021). New-Onset Diabetes After Transplantation patients had significantly higher BMI (27.16 ± 5.39 vs 23.94 ± 4.71, p < .001).

Conclusion: New-Onset Diabetes After Transplantation is more prevalent in subjects with older age, higher BMI, post-transplant CMV infection, and higher pre-transplant FBS but gender, pre-transplant dialysis and smoking were not associated with it. So, these patients should be followed-up more diligently.

Keywords

New-onset diabetes after transplantation, renal transplant, graft rejection, Diabetes

Dear Sirs!

Kidney transplantation is the treatment of choice for renal failure. Post-Transplant Diabetes Mellitus (PTDM) is an important complication following organ transplantation which significantly increases mortality, infection, transplant rejection, and kidney graft loss, and reduces the patients’ survival as well as healthcare costs.1

The PTDM criteria based on the world health organization (WHO) and the American diabetes association (ADA) is Fasting Plasma Glucose (FPG) ≥ 126 mg/dL (7.0 mmol/L) or two-Hour Plasma Glucose (2hPG) ≥ 200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) with 75 g oral glucose; or glycated

1Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Science, Babol, Mazandaran, Iran
2Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Science, Babol, Mazandaran, Iran

Corresponding author:
Roghayeh Akbari, Department of Internal Medicine, Ayatollah Rouhani Hospital, Keshavarz Boulevard, Babol, Mazandaran, Iran.
Email: roghayeh.akbari@yahoo.com
hemoglobin (HbA1c) ≥ 6.5% (at least 3 months post-transplant).2

Despite significant advances in managing and controlling immunological complications after transplantation, PTDM is still a problem3 and has serious consequences and long-term outcomes for patients.4 This study aimed to evaluate the 10-years incidence of New-Onset Diabetes After Transplantation (NODAT) in renal transplant patients in Shahid Beheshti Hospital of Babol, northern Iran between March 2009–2019. In this cross-sectional study, the medical records of 284 non-diabetic patients were reviewed. Finally, patients who developed NODAT were extracted and followed up until the end of the study. Risk factors, cytomegalovirus (CMV) IgM and IgG, HBsAg/Ab, HCV Ag/Ab, Glomerular filtration rate (GFR) and serum Creatinine within 3 days following transplantation were recorded. Fasting Blood Sugar (FBS) level was evaluated on days 1, 5, 30, 60, 180, and 360 and then annually.

**Results**

A total of 284 patients with a mean age of 40.83 ± 12.94 years (17–84 years) including 181 (63.7%) men were enrolled. New-Onset Diabetes After Transplantation was identified in 57 (20.1%) patients mostly (92.98%) during the first month after transplantation. Patients who developed NODAT were 43.8% female with a mean age of 49.00 ± 9.57 years and 56.14% male with a mean age of 46.97 ± 12.21 years 89% of the NODAT and 93% of the non-NODAT group had single transplantation. Thus, older age was a significant risk factor for NODAT development. Six patients who developed NODAT (10%) and 21 (9%) patients without NODAT were cigarette smokers (p = .769).

Graft rejection occurred in 18 (31%) of NODAT and 78 (34%) of non-NODAT patients (p = .69). Patients who developed NODAT were about 10 years older (47.88 ± 11.06 vs 38.96 ± 13.12 years; p = .002) and had higher frequency of positive HBsAg (3.5% vs 2.2%, p = .57) and HBCAb (5% vs 4%, p = .782). HBsAb was higher in patients without NODAT (0% vs 4%, p = .383). New-Onset Diabetes After Transplantation patients had significantly higher BMI (27.16 ± 5.39 vs 23.94 ± 4.71; p < .001) and 22.8% of them were overweight and 24.6% were obese. Also, 29.5% of the patients without NODAT were overweight. Rate of positive CMV infection before transplant was higher in non-NODAT group (82.45% vs 84.58%, p = .694), but post-transplantation CMV infection was significantly higher in NODAT group (56% vs 40%, p = .021). The mean Creatinine and GFR at different times in both groups are shown in Table 1.

Sixteen cases in non-NODAT and 5 cases in the NODAT group had graft loss. Fifty-three patients (92.98%) developed NODAT during the first month after transplant. The pre-transplant FBS was significantly higher in the NODAT group (93.78 ± 13.78 vs 87.07 ± 11.56, p = .001) and the occurrence of pre-transplant impaired fasting glucose (IFG) was significantly higher in NODAT patients (51.5% vs 27.7%, p = .01).

Age, BMI, Post-transplant CMV infection and pre-transplant FBS were the risk factors for the NODAT onset. CMV-positive patients were 2.3 times more likely to develop NODAT than other people. The chance of developing NODAT increases by 3% with each unit increase in blood sugar (OR = 1.03) and patients who had a rejection had a half chance of developing NODAT (OR = 0.51).

**Discussion**

In this study, the incidence of NODAT was 20.1% and the mean age of the NODAT patients was significantly higher. The higher prevalence of NODAT probably represents the

| Table 1. The mean Creatinine and GFR at different times in both groups. |
|---------------------------------|-----------------|-----------------|
| Creatinine                      | NODAT           | Non-NODAT       |
| Transplant day                  | 3.26 ± 2.34     | 5.25 ± 2.56     |
| The 1st day after the transplant| 1.55 ± 0.71     | 2.07 ± 1.32     |
| The 2nd day after the transplant| 1.19 ± 0.44     | 1.33 ± 1.13     |
| MDRD GFR                        | 29.87 ± 17.29   | 16.36 ± 11.37   |
| Transplant day                  | 55.14 ± 23.63   | 46.44 ± 22.74   |
| The 1st day after the transplant| 69.32 ± 25.86   | 74.87 ± 28.35   |
| Cockcroft GFR                   | 36.23 ± 17.80   | 20.34 ± 11.46   |
| Transplant day                  | 62.88 ± 22.25   | 50.32 ± 20.11   |
| The 1st day after the transplant| 76.58 ± 24.64   | 77.31 ± 25.79   |

MDRD = the modification of diet in renal disease.
predisposition of these patients to develop diabetes in general. We found that obesity is a risk factor for NODAT, with significantly higher BMI in NODAT compared to those with normal glucose after transplant.

In our study, the NODAT group had higher pre-transplant hyperglycemia compared to the non-NODAT group. Increasing glucose level before transplantation is associated with an increased risk of NODAT and patients with pre-transplant plasma glucose < 90 mg/dL have a lower risk of NODAT development.5

We found that post-transplant CMV infection was associated with an increased risk of NODAT. It is speculated that the CMV-induced release of pro-inflammatory cytokines may cause apoptosis and functional disturbances of pancreatic β-cells.6

We did not find Hepatitis B and C infection as the significant risk factors for NODAT due to the low incidence in our patients. Older age, BMI, post-transplant CMV infection, and pre-transplant FBS were the risk factors for the onset of NODAT in the present study but gender, pre-transplant CMV infection, type of dialysis (hemodialysis and peritoneal) and cigarette smoking were not associated with it. We found that with every 1-year increase in age, the risk of NODAT increased by 5%.

In this study, increased age was a significant risk factor for NODAT development. New-Onset Diabetes After Transplantation is a common complication in renal transplant recipients. Based on the results of this study, the prevalence of NODAT appears to be higher in subjects with older age, higher BMI, post-transplant CMV infection, and pre-transplant FBS but gender, pre-transplant CMV infection, type of dialysis and smoking were not associated with it. The significant risk of NODAT posed by these factors makes it prudent to follow up with these patients more diligently. In addition, larger multicenter prospective and long-term clinical trials are recommended to validate these findings.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD
Roghayeh Akbari © https://orcid.org/0000-0001-7385-1023

References
1. Khong MJ and Chong CP. Prevention and management of new-onset diabetes mellitus in kidney transplantation. Neth J Med 2014; 72(3): 127–134.
2. Organization WH. Report of a World Health Organization consultation: use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus. Diabetes Res Clin Pract 2011; 93: 299–309.
3. Abramowicz D, Oberbauer R, Heemann U, et al. Recent advances in kidney transplantation: a viewpoint from the Descartes advisory board. Nephrol Dial Transplant 2018; 33(10): 1699–1707.
4. Choudhury PS, Mukhopadhyay P, Roychowdhary A, et al. Prevalence and predictors of “new-onset diabetes after transplantation” (NODAT) in renal transplant recipients: an observational study. Indian Journal Endocrinology Metabolism 2019; 23(3): 273.
5. Cosio FG, Kudva Y, Van Der Velde M, et al. New onset hyperglycemia and diabetes are associated with increased cardiovascular risk after kidney transplantation. Kidney International 2005; 67(6): 2415–2421.
6. Hjelmesæth J, Müller F, Jenssen T, et al. Is there a link between cytomegalovirus infection and new-onset post-transplantation diabetes mellitus? Potential mechanisms of virus-induced β-cell damage. Nephrol Dial Transplant 2005; 20(11): 2311–2315.