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ORIGINAL ARTICLE

Risk of New-Onset Diabetes after Transplantation among Kidney Transplant Recipients with Cytomegalovirus Infection: A Retrospective Analysis

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ABSTRACT

Background: New-onset diabetes after transplantation (NODAT) is one of the common complications reported in patients with kidney transplant and is associated with risk of infection, poor allograft and patient survival. There is conflicting research literature regarding the role of cytomegalovirus (CMV) infection in increasing the risk of NODAT development.

Objective: To assess the risk of development of NODAT in kidney transplant patients with CMV infection

Methods: A total of 59 kidney transplant patients were studied from March 2017 to February 2019. NODAT was defined as two readings of fasting plasma glucose of ≥126 mg/dL at three months post-transplant. CMV viral load was also documented. The 12 months post-transplant allograft and patient survival outcomes were also measured.

Results: Mean age was 43.4 ± 6.2 years. Nearly one-fourth, 14 (23.7%), of the patients had NODAT. CMV viral load and viremia were high in NODAT group; however, the result did not reach statistical significance. CMV DNA replication was statistically high during 1-6 months post-transplant for NODAT group (P<0.001). Only 7 (11.9%) recipients advanced to symptomatic CMV infection. Also, we found that high CMV viremia load was associated with poor kidney allograft function at 12 months.

Conclusions: In summary, this study showed that infection with CMV may not be a risk factor to develop NODAT in patients transplanted with kidney. An elevated CMV viral load may decrease the post-transplant allograft function at 12 months. The prompt diagnosis and timely management of CMV infection could substantially lessen the risk to develop NODAT subsequent worsening of allograft and patient survival.

Keywords: Kidney; Transplant; NODAT; New-onset Diabetes; Cytomegalovirus

INTRODUCTION

New-onset diabetes after transplantation (NODAT) is one of the common complications reported in patients with kidney transplant and is associated with risk of infection, poor allograft and patient survival (1). It has been shown to be associated with decreased overall survival of patients, mainly owing to development of cardiovascular ailments (2). The incidence of NODAT is reportedly between 2% and 50% in recipients of kidney transplant (3).

It is suggested that the window of first six months of post-transplantation is the most vulnerable period to develop NODAT. The post-transplantation glucose intolerance is associated with development of type II diabetes mellitus. Indeed, the transition from glucose intolerance to overt type II diabetes mellitus is very much rapid in kidney transplant recipients than the general population (1, 4). A number of risk factors such as modifiable (Obesity; Hepatitis C Virus infection; and Cytomegalovirus infection), non-modifiable (Recipient age above 45; Family history of diabetes mellitus; African-Americans or Hispanics origin of transplant recipient; and Recipients harboring specific human leukocyte antigens; HLA-B13, HLA-B15, HLA-B27 and HLA-B42) and transplant-associated (Pre-transplant glucose intolerance; Use of immunosuppressive therapy such as Corticosteroids, Tacrolimus or Sirolimus; Primary kidney disease, for example, autosomal dominant polycystic kidney disease; Kidney allograft received from male or deceased donors; HLA mismatch; Delayed allograft function; and Acute allograft rejection episodes) risk factors have been documented in the literature that predisposes kidney transplant recipients to NODAT (1, 2).

Cytomegalovirus (CMV) infection, caused by Herpesvirus organism, is a very prevalent post-transplant infection and is independently associated with increased risk of kidney allograft loss and poor patient survival (5). At the time of kidney transplantation, two-thirds of the recipients and/or donors are CMV-positive, reflected by existence of measurable anti-CMV IgG antibodies in the plasma. It is because of increased exposure to the Herpesvirus with increasing age in the general population (6). CMV infection can be asymptomatic in immunocompetent individuals or may present as fever with no known etiology, flu-like symptoms or mononucleosis-like syndrome. The dormant virus is often transmitted through blood transfusion or transplanted allograft and may reactivate in post-transplant period. Similarly, the possibility of CMV infection is very high in CMV sero-negative transplant recipients who receive kidney from CMV sero-positive donors. Apart from acute kidney rejection and decreased allograft and patient survival, CMV infection is linked with tubular atrophy, renal artery stenosis and interstitial fibrosis (7).

Lately, CMV infection has also been shown as a factor that increases the risk of NODAT in kidney transplant recipients (8). Notwithstanding above, several studies have suggested the role of CMV infection in NODAT otherwise (6). It is plausible to say that CMV infection is a grave post-transplant complication and identification of its role in NODAT development could have immense clinical implications. No such data regarding CMV infection and risk of NODAT in kidney transplant recipients is available in Pakistan. However, Mohammad et al. (2018), who studied for prevalence of NODAT in kidney transplant patients, did not find any association between CMV infection as a risk factor for NODAT (1). Therefore, the objective of our present study was to investigate whether CMV infection has any role in the development of NODAT in kidney transplant recipients in the light of existing research literature.

MATERIAL AND METHODS

We studied 59 kidney transplant patients, with gender distribution of 43 males 16 females, from March 2017 to February 2019. We evaluated the risk of NODAT owing to CMV viremia in patients who had kidney allograft transplant from a live kidney donor. The study's exclusion criteria were kidney transplantation in last 1 year; patients on Cyclosporin A or mTOR inhibitor as part of their immunosuppressive therapy; and patients with diabetes mellitus type I or II. A review of medical record was done to document demographic and clinical characteristics of the study subjects. We noted age, gender, nephropathy, comorbidities, immunosuppressive therapy and Human Leukocyte Antigen (HLA) mismatches.

NODAT was defined as two readings of fasting plasma glucose of ≥126 mg/dL at three months post-transplant. According to guidelines of American Transplantation, CMV infection was

defined as the presence of active CMV replication; CMV viremia regardless of any clinical symptoms (9). We also monitored patients' viremia levels; CMV DNA copies/mL, via quantitative Polymerase Chain Reaction (qPCR). Conventional to our kidney transplant center, for the first 3 months post-transplantation, we carried out qPCR at 1-week intervals and thereafter from 4th to 6th at 1-month interval and finally at 9th and 12th month.

During the period of monitoring, we retrospectively recognized the post-transplant patients who presented with symptomatic CMV disease, described as active CMV DNA replication accompanied by clinical signs and symptoms such as fever, fatigue, thrombocytopenia or leukocytopenia, and organ involvement which includes adrenalitis, hepatitis, nephritis, pneumonitis, pancreatitis, myocarditis, retinitis, or gastrointestinal disease. The subjects were divided into two categories according to the NODAT development during monitoring period; control and NODAT cohort. Both the cohorts were compared for CMV viremia and NODAT development throughout the duration of monitoring and 1 year post-transplantation. The 12 months post-transplant kidney allograft outcomes were also documented; eGFR (CKD-EPI method), allograft and patient survival. Kidney transplant recipients at risk of CMV infection/disease such as CMV sero-status positive donors and CMV sero-status negative recipients (D+/R−) were given the prophylaxis with oral Valganciclovir (an antiviral drug).

The data were entered, tabulated, and analyzed using statistical package for the social sciences (SPSS) software version 20.0 (SPSS Inc., Chicago, Illinois, USA). Results are presented as frequencies with percentages for categorical variables and mean ± standard deviation for continuous variables. To compare the continuous data between the two groups, t-test was used and summarized as mean and SD, whereas non-continuous data were differentiated using the Mann–Whitney U-test. Categorical data were compared using χ^2-test and presented as percentages and proportions. The P value <0.05 was considered statistically significant.

RESULTS

In this retrospective cohort study, a total of 71 patients undergoing live kidney donor transplantation were enrolled. Of these 71 kidney transplant participants, 5 patients were excluded from the study due to diabetes mellitus type II, 4 for diabetes mellitus type I, 2 for Cyclosporin A or mTOR therapy and 1 for <1 year of transplantation. The remaining 59 kidney transplant subjects were included for the final analysis (Figure 1). The mean age of the kidney transplant patients was 43.4 ± 6.2 years. Overall, 43 (72.9%) were male subjects, while 16 (27.1%) were females. We did not observe any statistical relationship between baseline characteristics of the control and NODAT group in terms of age, gender, nephropathy, comorbidities, immunosuppressive therapy and HLA mismatches. The predominant reason for kidney transplantation in both the cohorts' groups was glomerulonephritis (control; 80% and NODAT; 78.6%).

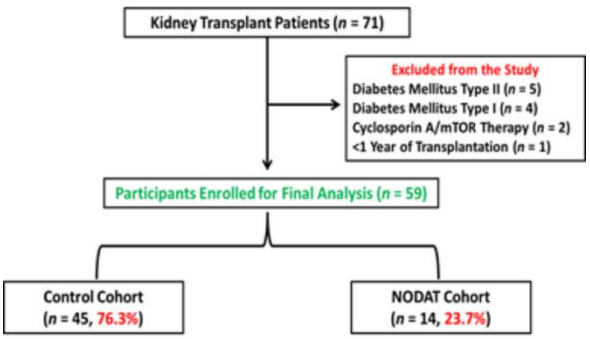

Figure 1: Flow Diagram of the Kidney Transplant Patients recruited for Final Analysis

In this study, nearly one-fourth, 14 (23.7%), of the patients had NODAT. The mean age for NODAT patients was higher. Both the cohorts were found to be homogenous as far as immunosuppressive therapy was concerned, as no significant differences were found for Tacrolimus (TAC) levels (4.7 ± 1.4 versus 4.3 ± 1.1, P = 0.10), Mycophenolate Mofetil (MMF) (986.2 ± 225.3 versus 903.7 ± 270.4, P = 0.52) and Prednisone (8.5 ± 2.2 versus 7.8 ± 1.7, P = 0.09) therapy. The CMV viral load and viremia were raised in NODAT cohort (4000 vs 3600 and 51.1 vs 47.6, respectively); however, the results did not reach statistical significance (P = 0.79 and P = 0.84, respectively). The demographic and clinical characteristics of the study cohorts have been presented in Table 1.

Table 1: Comparison of Clinical and Demographic Characteristics of Control versus NODAT Kidney Transplant Patients

Variables	Control (n = 45)	NODAT (n = 14)	P value
Age (Years, Mean ± SD)	50.6 ± 7.8	53.1 ± 9.4	0.15
Gender (n, %) Male Female	 32 (71.1) 13 (28.9)	 11 (78.6) 3 (21.4)	 0.21 0.11
Hypertension (HTN) (n, %)	17 (37.8)	4 (28.6)	0.35
Average HLA Mismatches (Mean ± SD)	3.2 ± 1.0	3.4 ± 1.2	0.87
Nephropathy (n, %) Glomerulonephritis Adult Polycystic Kidney Disease Diabetic Nephropathy Others	 36 (80) 6 (13.3) 3 (6.7) 0 (0)	 11 (78.6) 2 (14.3) 1 (7.1) 0 (0)	 0.23 0.45 0.19 -
CMV Load (copies/mL)	3600	4000	0.79
CMV Replication (%)	47.6	51.1	0.84
Immunosuppressive Therapy (Mean ± SD) Tacrolimus (TAC) Levels (ng/mL) Mycophenolate Mofetil (MMF) (mg) Prednisone (mg)	 4.3 ± 1.1 903.7 ± 270.4 7.8 ± 1.7	 4.7 ± 1.4 986.2 ± 225.3 8.5 ± 2.2	 0.10 0.52 0.09
Methylprednisolone Pulse Therapy except for Induction (%)	35.2	36.7	0.43

Abbreviations: NODAT, New-Onset Diabetes after Transplantation; SD, Standard Deviation; HLA, Human Leukocyte Antigen; and CMV, Cytomegalovirus

We also compared the CMV viremia load (copies/mL) in control and NODAT cohort between first (1-6 months) and second (7-12 months) half of post-transplantation period (Figure 2 and 3). We also found significantly high CMV DNA replication in 1 to 6 months post-transplant in NODAT patients (P<0.001). Upon comparing control group with NODAT cohort, control group had higher CMV viremia load than NODAT cohort during first (1-6 months) half of the post-transplantation (Figure 4). Conversely, in second (7-12 months) half of the post-transplantation, CMV replication was dominated by NODAT cohort (Figure 5). Nevertheless, no statistical relationship was found in both the above comparisons. Month-wise diagnosis of NODAT in kidney transplant recipients during post-transplantation has been shown in Figure 6.

The CMV viremia load during the 12 months post-transplant period of the kidney transplant recipients has been depicted in Table 2. We did not find any statistical significance between CMV DNA viremia and NODAT, suggesting that CMV might not be associated with NODAT development in kidney transplant recipients in the first 12 months. A total of 7 (11.9%) kidney transplant patients advanced to symptomatic CMV infection. In controls, 6 (13.3%) of the subjects developed symptomatic CMV infection, while in the NODAT cohort, only 1 (7.1%) of the patients was positive for symptomatic CMV infection (P = 0.82). The kidney allograft function was assessed through serum creatinine level and eGFR and no statistical significance was found for both of them (P

= 0.72 and P = 0.16, respectively) between control and NODAT cohort (Table 3). Finally, we also found that high CMV viremia load was associated with poor kidney allograft function at 12 months.

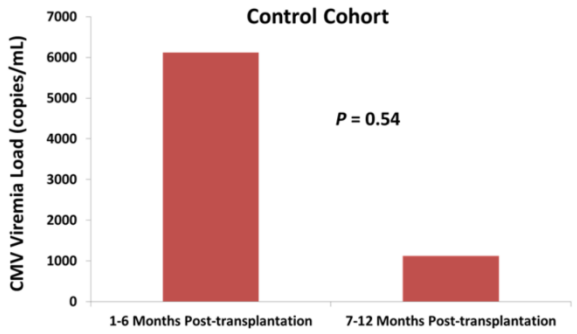

Figure 2: Comparison of CMV Viremia Load (copies/mL) between 1-6 Months Post-transplantation and 7-12 Months Post-transplantation in Control Cohort

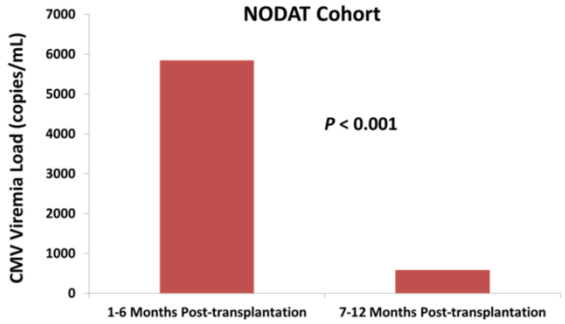

Figure 3: Comparison of CMV Viremia Load (copies/mL) between 1-6 Months Post-transplantation and 7-12 Months Post-transplantation in NODAT Cohort

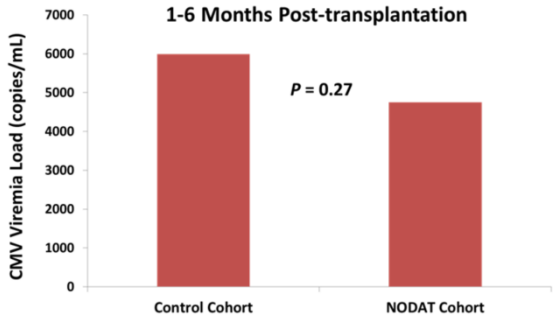

Figure 4: Comparison of CMV Viremia Load (copies/mL) between Control and NODAT Cohort at 1-6 Months Post-transplantation

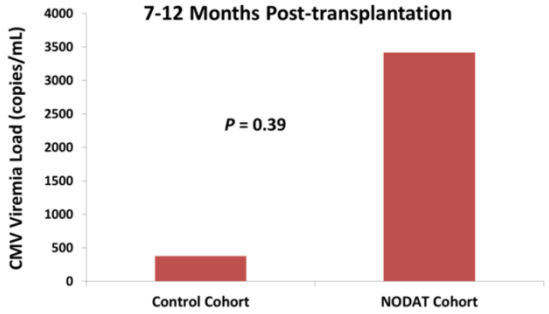

Figure 5: Comparison of CMV Viremia Load (copies/mL) between Control and NODAT Cohort at 7-12 Months Post-transplantation

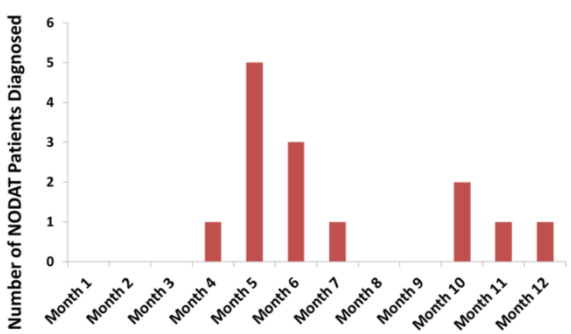

Figure 6: Month-wise Diagnosis of NODAT in Kidney Transplant Recipients during Post-transplantation

Table 2: The CMV Viremia Load (copies/mL) during the 12 months Post-transplant Period of the Kidney Transplant Recipients

Variables	Control (n = 45) CMV Viremia Load (copies/mL)	NODAT (n = 14) CMV Viremia Load (copies/mL)	P value
Month 1	2375.3	0	0.39
Month 2	5982.2	0	0.95
Month 3	15784.2	0	0.81
Month 4	3721.4	2197.2	0.31
Month 5	1064.5	19278.2	0.20
Month 6	2993.1	12435.4	0.35
Month 7	520.7	4731.8	0.47
Month 8	56.2	0	0.92
Month 9	349.4	0	0.32
Month 10	205.8	1285.1	0.52
Month 11	0	178.3	0.87
Month 12	27.2	149.4	0.41

Abbreviations: CMV, Cytomegalovirus; and NODAT, New-Onset Diabetes after Transplantation.

Table 3: Comparison of Kidney Allograft Function through Serum Creatinine and eGFR 12 months Post-transplantation between Control and NODAT Cohort

Variables	Control (n = 45)	NODAT (n = 14)	P value
Serum Creatinine 12 months Post-transplantation (mg/dL, Mean ± SD)	1.3 ± 0.5	1.5 ± 0.6	0.72
eGFR 12 months Post-transplantation (mL/min, Mean ± SD)	55.7 ± 12.1	52.3 ± 11.4	0.16

Abbreviations: NODAT, New-Onset Diabetes after Transplantation; SD, Standard Deviation; and eGFR, Estimated Glomerular Filtration Rate.

DISCUSSION

NODAT is the frequent complication of kidney transplantation and is significantly associated with infectious disease complications, allograft rejection, allograft loss and reduced patient survival (2). Studies have documented several modifiable, non-modifiable and transplant related risk factors that could induce NOADT development (1, 2).

The association between CMV infection and NODAT development is still debatable. A number of studies have suggested CMV infection as a risk factor for NODAT development (8). However, there are other studies who have presented the results otherwise (1, 6). Einollahi et al. (2014), in their meta-analysis, concluded high occurrence of NODAT in CMV infected patients and highlighted the significance of chemoprophylaxis of kidney transplant recipients at risk of CMV infection (10). Similar to the findings presented by Dedinská et al. (2016), we observed that NODAT diagnosis was more prominent during the first six months of post-transplantation (6). In our study, we did not find any relationship between CMV viremia and risk of NODAT

development. Our study findings were in agreement with earlier studies published lately (1, 6).

In terms of immunosuppressive treatment, both the research cohorts were homogenously distributed. We believe that this small number of symptomatic CMV infection cases could be ascribed to the rigorous surveillance of CMV viremia load through qPCR in post-transplantation period; we performed qPCR at 1-week intervals for the first 3 months and thereafter from 4th to 6th at 1-month interval and finally at 9th and 12th month. In addition, we also monitored for CMV viremia in 2nd year of post-transplantation in kidney transplant recipients at risk of CMV infection/disease such as CMV sero-status positive donors and CMV sero-status negative recipients (D+/R−) and were provided the prophylaxis with oral Valganciclovir (an antiviral drug). Previous studies have mentioned various methods to detect and monitor CMV infection such as identification of CMV viral DNA and proteins (10). For instance, active CMV infection can be spotted using CMV viral DNA in the plasma by qPCR or by identification of CMV pp65 antigen in leukocytes (11). A handful of studies did not document the benchmark for detection of CMV infection (12-15).

Studies have also witnessed the influence of CMV infection on allograft and patient survival. A study by Smedbråten et al. (2014) observed CMV infection as an independent predictor of kidney transplant patient mortality (HR 1.45, 95% CI = 1.03 – 2.04) (16). In their study, no CMV chemoprophylaxis or preemptive therapy was given to patients. However, this relationship between CMV infection and allograft and patient survival can be transformed by CMV chemoprophylaxis or preemptive treatment. Kliem et al. (2008) found that Oral Ganciclovir chemoprophylaxis for CMV was statistically linked with better 4 year allograft survival (uncensored) compared with intravenous (IV) preemptive treatment, especially in CMV sero-status positive donors and sero-status positive (D+/R+) patients. In fact, the chemoprophylaxis substantially improved allograft survival in D+/R+ sero-status cohort, when allograft survival was analyzed by death-censored approach (17). In D+/R- sero-status patients, Opelz et al. (2004) cited chemoprophylaxis therapy to be significantly improving allograft survival in both uncensored and censored for mortality (18). Post-transplant CMV viremia can lead to minimal allograft function and patient survival due to release of inflammatory cytokines and subsequent chronic inflammation (6). Indeed, unrestrained CMV DNA replication can directly or indirectly affect the kidney transplant recipient (19). Finally, we also found that a greater CMV viremia load was worsening the kidney allograft function at 12 months post-transplantation, identified by eGFR. Our findings are confirmed by previously published literature (20). The allograft and patient survival (censored for death) was poor in the NODAT cohort; however, without any statistical significance. Our study had few research limitations which includes retrospective nature of the study, single center research and small sample size.

CONCLUSION

In summary, this study showed that infection with CMV may not be a risk factor to develop NODAT in patients transplanted with kidney. An elevated CMV viral load may decrease the post-transplant allograft function at 12 months. The prompt diagnosis and timely management of CMV infection could substantially lessen the risk to develop NODAT subsequent worsening of allograft and patient survival.

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