ORIGINAL ARTICLE

Antibody Response of COVID-19 Vaccine in Subjects after Renal Transplantation - A Case Control Study

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ABSTRACT

Objective: To evaluate the immune response to COVID-19 vaccination in patients after renal transplantation.

Study Design: A case-control study.

Place and Duration of Study: The study was conducted at the Kidney Transplant Department, Shaikh Zayed Hospital Lahore, Pakistan from September 2020 to September 2021.

Methods: A total of 180 renal transplant recipients who had received a third dose of the Pfizer vaccine were selected for the study. The patients were evaluated before and after vaccine administration for seropositivity and anti-spike antibody levels. The results were compared with a control group of 50 healthy controls. T-cell response was assessed in only 50 transplant recipients.

Results: 50 (27.7%) KTRs and 48 (96%) controls achieved optimum antibody level (4160 AU/ml) (*P*<.001). All (100%) of the controls were seropositive after 3rd dose. Among kidney transplant recipients (KTRs), there was a significant increase in the median anti-spike antibody level from 13.7 AU/ml before to 515.46 AU/ml after the 3rd dose (*P*< .001). There also was a significant increase in log-transformed antibody level after 3rd dose in both the study and control group (*P*<.001). Of 50 randomly selected subjects, 6 (12%) showed positive T cell response.

Conclusion: Pfizer vaccine improved antibody response in renal transplantation recipients.

Keywords: *COVID-19, Immunity, Renal Transplantation, Vaccination.*

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Introduction

Patients with chronic kidney disease (CKD) have been significantly affected during the COVID-19 pandemic, which resulted in increased hospitalization, mortality, and a decrease in renal transplants. CKD patients have comorbidities, such as cardiovascular disease, diabetes, and hypertension, which increase the risk and severity of infection. The mortality rate in kidney transplant recipients is 20 to 28% compared to 1 to 5% in the general population.[1] Vaccination is a significant tool for preventing infection. Nephrology societies have recommended that CKD patients be vaccinated urgently.[2] Various international agencies have authorized the emergency use of different vaccines. The efficacy of the inactivated vaccine was reported to be 50.3%, and for BN162b2, mRNA-1273, and Gam-COVID-Vac to be 96%, 94.2%, 91.5% respectively. Earlier studies show that CKD patients have reduced response to vaccination.[3] Studies on kidney transplant recipients (KTRs) with immunosuppression also show attenuated response to vaccines.[4]

Patients with kidney transplants are at increased COVID-19 infection and death, thus these patients

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must receive the vaccination.[5] Different studies showed that kidney transplant recipients (KTRs) who receive two doses of mRNA vaccine demonstrated diminished cellular and humoral response, seroconversion rates in these range from 36 to 54% vs. 100% in healthy individuals.[6-8] T-cell response ranges from 30 to 54% vs. 95% in healthy individuals.[9] Moreover, the studies reported that fully vaccinated KTRs contracted COVID-19 which led to death in these patients.[9]

European Medicines Agency (EMA) has recommended a third vaccine dose in severely immunocompromised patients.[10] Studies on the safety and effectiveness of a third dose of mRNA vaccine among solid organ transplant (SOT) patients reported that 32 to 55% demonstrated humoral response.[11, 12] Previous studies reported that various SOT types have varied response to two-dose mRNA vaccines, KRTs are less responsive than liver and heart transplant recipients but more than lung transplant recipients.[13,14] As KTRs are among the most vulnerable groups, thus prompt vaccination is important. Many studies have been conducted to assess the result of vaccines in these patients, but there is scarcity of local data on this topic. The aim of this study is to assess humoral and cellular response to third dose of the Pfizer vaccine among kidney transplant recipients.

Methods

A case-control study was conducted at the Kidney Transplant Department, Shaikh Zayed Hospital, Lahore from September 2020 to September 2021 after obtaining approval from the Ethical Review Committee of the hospital vide letter no: 39-48, held on 18th July 2021. A total of 180 kidney transplant recipients who received a third dose of the Pfizer vaccine were selected for study by consecutive sampling technique. Informed consent of the participants was taken. Antibody levels of the participants before and after the dose were recorded. 50 healthy controls who were also immunized with 3rd dose were included in the study. Blood samples of the participants were collected 3 weeks post-third dose for assessing cellular response and anti-spike antibody levels.

Demographic data and information related to immunosuppressive medication regimens was collected. SARS-CoV-2 IgG II Quant assay was used to test anti-spike SARS-CoV-2 antibodies in the blood samples. Creatinine and calcineurin inhibitor (CNI) levels were recorded on follow up visit. The CKD-EPI equation was used to calculate renal function. T-cell response was calculated in 50 randomly selected subjects SARS-CoV-2 interferon-gamma (IFNg) release assay. Whole blood was stimulated with spike antigen, and IFNg secreted in response was measured through ELISA.

All data was analyzed by SPSS 24. Frequency was used to present categorical data and was compared by Fisher's or *Chi-square* test. Continuous data was represented as mean and compared using *t*-test. The association between response and study variables was assessed by univariate and multivariate logistic regression analysis. The association between study variables and higher log-transformed antibody titer was analyzed by linear regression analysis. *P* value < 0.05 was considered statistically significant.

Results

The mean age of the participants was 58± 12 years. The median duration between 3rd dose and the antibody test was 28 days. Fifty (27.7%) KTRs and 48 (96%) controls achieved optimum antibody level (4160 AU/ml) (*P*< .001).

Table-1 shows characteristics of KTRs based on cut-off antibody response of > 4160 AU/ml. According to univariate analysis older age, low antibody level after 2nd dose, diabetes mellitus, and lower eGFR indicated the absence of response. (Table-1).

According to multivariate analysis immunosuppression reduction (*P*=0.008) and antibody levels after 2nd dose (*P*<0.001) were significantly associated with response. (Table-2).

A comparison of KTRs and healthy controls is shown in table-3. 100% of controls were seropositive after 3rd dose, before 3rd dose no subject in the control group had an antibody level >4160 AU/ml. Among KTRs, there was a significant increase in the median anti-spike antibody level from 13.7 AU/ml before to 515.46 AU/ml after the 3rd dose (*P*< 0.001). There also was a significant increase in log-transformed antibody level after 3rd dose in both the study and control group (*P*<.001).

There was a significant association between higher log antibody levels and factors including

immunosuppression reduction, treatment, baseline antibody levels, and non-diabetic status. Of 50 randomly selected subjects, 6 (12%) showed positive T cell response.

Table-1: Comparison of KTRs based on cut off value >4160 AU/ml

Variable	Response (n=150)	No response (n=130)	*t*-value	*P*-value
Age*	58 ±11.2	53.4 ± 10.9	3.11	0.001
Female gender**	60 (40%)	38 (29.2%)	1.12	0.13
Duration between transplant and vaccine dose*	5.4 ± 5.6	6.9 ± 7.6	0.35	0.36
Living donor**	135 (90%)	95 (73%)	2.52	0.006
eGFR*	69.10 ± 19.80	56.8 ± 19.5	3.11	0.001
Diabetes mellitus **	14 (9.3%)	30 (23%)	1.84	0.03
Baseline log antibody level*	2.45 ± 0.51	0.91± 0.68	3.22	<0.001
Duration between second and third dose*	159.80 ± 2245.20	163.21 ± 150.01	0.60	0.27
Immunosuppression reduction**	25 (16.7%)	18 (13.8%)	0.19	0.42
BMI*	26.2 ± 4.09	26.10 ± 4.42	1.17	0.88
High antimetabolite dose **	90 (60%)	83 (63.8%)	0.77	0.78
High tacrolimus level**	70 (46.7%)	80 (61.5%)	1.34	0.09
Cyclosporine use **	30 (20%)	20 (15.3%)	0.19	0.42

**T-test, **Fisher's exact test*

Table-2: Univariate and multivariate analysis

Variable	Univariate analysis				Multivariate analysis			
	OR**	95% CI***	*t-value*	*P-Value*	OR	95% CI	*t-value*	*P-Value*
Age	0.95	0.94-0.99	2.90	0.002	-	-		-
Female gender	1.65	0.85-3.23	1.11	0.13	-	-		-
Duration between transplant and vaccine dose	0.97	0.94-1.02	0.35	0.36	-	-		-
Living donor	3.57	1.32-9.66	2.33	0.01	-	-		-
Estimated glomerular filtration rate	1.03	1.01-1.04	3.11	0.001	-	-		-
Diabetes mellitus	0.35	0.13-0.95	1.75	0.04	-	-		-
Duration between 2nd and 3rd dose	0.98	0.97-1.01	0.59	0.27	-	-		-
Immunosuppression reduction	1.40	0.61-3.24	0.18	0.42	9.08	1.78-46.50	2.33	0.01
Baseline log antibody level	21.97	9.02-57.53	2.43	<0.001	30.80	10.99-87.38	2.43	<0.001
BMI	1.08	0.93-1.07	1.16	0.87	-	-		-
High antimetabolite dose	0.91	0.46-1.75	0.76	0.77	-	-		-
High tacrolimus level	0.58	0.30-1.1	1.30	0.09	-	-		-
Cyclosporine use	0.34	0.15-1.98	0.38	0.35	-	-		-

**Logistic regression analyses were performed; **Odds Ratio; ***Confidence Interval*

Table-3: Comparison between healthy controls and Kidney Transplant Recipients (KTRs)

Variable	KTRs (n=180)	Controls (n=50)	*Chi-square* value	*P*-value
Age*	58± 12	70 ± 6	165.8	<0.001
Female gender**	58 (32.2%)	24 (48%)	188.0	0.025
Diabetes mellitus**	33 (18.3%)	6 (12%)	211.8	0.229
BMI*	26.1 ± 4.5	25.5 ± 3.2	220.3	0.37
Serum creatinine*	1.2 ± 0.8	0.84 ± 0.210	165.6	<0.001
Duration between second and third dose*	160.2 ± 17.3	200.6 ± 8.5	146.3	<0.001
Baseline antibody level*	12.7 (2.8- 110.3)	510.2 (260.3 860.6)	166.5	<0.001
Antibody level after booster dose*	620.3 (20.2- 480.1)	22700.10 (12433-40433.4)	152.1	<0.001
Baseline log antibody level*	1.2 ± 0.8	2.4 ± 0.3	145.6	<0.001
Log antibody level after third dose*	2.4 ± 1.2	4.2 ± 0.3	155.5	<0.001
Adjusted log antibody after third dose*	2.2 (3.5-4.68)	3.8 (2.10-2.60)	152.1	<0.001
Antibody level>4160 AU/ml**	50 (27.7%)	48 (96%)	153.5	<0.001

**Mann-Whitney U test, ** Chi-Square test*

Discussion

In the current study, we observed 27.7% KTRs achieved the optimum antibody level. Only 12% KTRs showed positive T cell response. The response reported in current study is in line with the findings of previous studies on SOT recipients which found improved antibody response after 3rd dose of the mRNA vaccine.[13] A study on KTRs reported seropositivity rate improved in 32% of subjects following the third dose.[15] Another study found that 37% previously negative kidney transplant recipients responded to the third dose of the BNT162b2 vaccine.[16] A study on SOT reported the highest seropositivity rates among KTRs in response to BNT162b2.[12]

In the current study cutoff > 4160 AU/ml was used, and results suggested that controls were seronegative before third dose. The mean age of the controls was 68 years, and there was a gap of about 6 months between the second and third dose. A study reported that antibody response wanes, particularly in older individuals, which explains lower antibody titer.[17] Moreover, the cutoff used in the current study was in accordance with previous studies.[18,19] This cutoff value may be validated through further studies. In this study, 13% of KTRs showed positive T cell response detected by IFGN secretion. Another study measured T cell response after second dose using IFNg secreting cells frequency and reported that 31- 61% of KTRs had positive T cell response.[8] Studies have reported that IFNg secreting cells in SOT recipients increased significantly after the third dose.[15,16] These studies used different assays thus it is difficult to compare results with our study. A study reported that in KTRs with humoral response levels of antigen reactive T cells is significantly higher compared to those without response.[16]

Previous studies on SOT recipients have reported various factors associated with response to a third dose of mRNA vaccine. Among KTRS, negative response to the second dose, low lymphocyte counts, and antimetabolite use were associated with negative response.[16] Among SOT recipients, eGFR, older age, and high level of immunosuppression were associated with absence of response to the vaccine.[12] A study on KTRs suggested a significant association between use of mycophenolatea and low seroconversion rates.[12] A study reported that only two individuals showed high positive antibody response, in one of those mycophenolate mofetil was discontinued at the time of immunization.[16] These findings suggest that immunosuppression reduction before vaccination yields a positive response. In our study, no acute rejection was

reported among patients in whom immunosuppression was reduced. Previous studies have also reported no acute rejection or adverse events following immunosuppression reduction.[20] There are a few limitations of our study. First, small sample size and limited multivariable analysis. Second, there was no record of cellular response after the second dose to be compared with a response after the third dose. Third, neutralizing antibodies were not assessed directly, cutoff value from the previous studies was used.

Conclusion

The third dose of Pfizer leads to improved immune response in KTRs. However, a major portion of these patients remain seronegative. There is a need to test and develop strategies for improved immunization in these patients.

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Conflict of Interest: The authors declare no conflict of interest.

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Authors Contribution

UA: Idea conception, manuscript writing and proofreading
MH: Data collection, data analysis, results and interpretation
AIK: Idea conception, study designing, data analysis, results and interpretation
MA: Study designing, data analysis, results and interpretation
MM: Data collection
IA: Study designing