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Assessment of Immune Response to the COVID-19 Vaccination in Egyptian Patients Undergoing Maintenance Hemodialysis

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ABSTRACT

Background: COVID-19 is a global health crisis caused by SARS-CoV-2 and associated with higher morbidity and mortality in patients on maintenance Haemodialysis (HD). Patients with chronic kidney disease (CKD), but especially those with End-stage renal disease (ESRD), treated with maintenance HD tend to have a reduced immune response to infection or vaccination.

Objective: The present study aimed to evaluate the immune response following vaccination with the COVID-19 vaccines in patients with maintenance HD and the factors associated with it.

Patients and methods: This prospective observational comparative study included 44 patients with ESRD on maintenance HD had been done in the Internal Medicine and Clinical Pathology Departments, Zagazig University Hospital. Another 20 vaccinated non-renal patients were considered controls. SARS-COV2 IgG was estimated using an ELISA assay.

Results: There is a lower significant value of SARS COVID igG in renal dialysis patients compared to the control group regarding sex, smoking habit, and obesity. Also, there is a lower significant value of SARS COVID IgG in renal dialysis patients compared to the control group regarding the history of COVID19 infection before vaccination and occurrence of post-vaccine adverse effects. There is a higher significant SARS COVID igG value for males and smokers in the control group.

Conclusion: Hemodialysis patients demonstrate a hyporesponsiveness to vaccination against COVID-19. Although most patients on maintenance hemodialysis developed a substantial humoral response following the COVID vaccine, it was significantly lower than controls.

Keywords: COVID-19 Vaccination; immune response; Hemodialysis.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is a worldwide health emergency brought on by coronavirus 2 that causes severe acute respiratory illness (SARS-CoV-2). Children tend to have much milder clinical traits, illness progression, and outcomes as compared to older people. Diabetes, chronic lung illness, and heart pathology are risk factors. Given the disease's progression and the possibility that acute respiratory distress syndrome (ARDS) will develop one week following the beginning of symptoms, quick detection is essential [(1)].

The five stages of kidney damage that make up chronic kidney disease (CKD) range from very minor damage in Stage 1 to full kidney failure in Stage 5. The ability of the kidneys to filter waste and excess fluid from the blood determines the stages of renal disease. The patient's kidneys can still filter waste from the blood in the early stages of renal disease. In the latter stages, the patient's kidneys may stop functioning entirely or require more effort to remove waste [(2)].

In patients receiving continuous hemodialysis, COVID-19 is linked to increased morbidity and death (HD). Prioritizing patients on dialysis for vaccination has been at the forefront of SARS-CoV-2 vaccination programs internationally. Patients with chronic kidney disease (CKD), but especially those with kidney failure, treated with maintenance HD tend to have a reduced immune response to infection or vaccination, as demonstrated with the hepatitis B virus vaccine. Consequently, there is often a need for higher vaccine dosage or scheduling changes in these patients [(3)].

According to a recent study, third Pfizer vaccination doses significantly raised antibody levels in dialysis patients, especially in those with unsatisfactory antibody levels after receiving the second dosage [(4)].

The high-risk groups for SARS-CoV-2 -mediated critical illness include those with obesity, diabetes mellitus, advanced age, and CKD. Among the patients with CKD, the percentage of patients with critical illness was higher than that in the other groups because of the multiple comorbidities and the impaired immune system in CKD patients with varying CKD stages [(5)].

Therefore, this study aimed to evaluate the immune response following vaccination with the COVID-19 vaccines in patients with maintenance HD and the factors associated with it.

PATIENTS AND METHODS

This prospective observational comparative study had been done in the Internal Medicine and Clinical Pathology Departments, Zagazig University Hospital.

The study included 44 patients with ESRD on maintenance HD (dialysis group"1" n=44). ESRD was diagnosed based on eGFR (≤15 mL/min per 1.73 m2) by CKD-epi (kidney disease epidemiology collaboration) equations [(6)]. In addition, 20 vaccinated non-renal patients (control group 2) were included in this study.

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Inclusion criteria:
End-stage renal disease (ESRD) on maintenance HD who had received two doses of the COVID-19 vaccine.

Exclusion criteria: CKD patients on conservative treatment, patients with acute kidney injury, and non-vaccinated patients.

Clinical Assessment:

Each studied patient underwent a thorough medical history taking and clinical examination including age, sex, smoking, obesity, history of comorbid diseases, dialysis venage, type of HD vascular access, history of covid19 infection before vaccination, side effects of vaccination, and underlying cause of ESRD.

I. Laboratory investigations:

All patients were subjected to the following investigation as complete blood count (CBC) on an automated cell counter (XN330-Sysmex, Japan); Liver function tests: serum albumin and total protein; Kidney function tests: urea and creatinine , calcium (Ca), Phosphorus and uric acid using Cobas8000Roch diagnost; eGFR using the CKD-epi equation; C-reactive protein (CRP) by turbidimetry on Roche Cobas C 501; Sodium (Na), Potassium(k), done on Sensacore ST200 plus., serum ferritin and PTH done on Roche Cobas 6000.

II. SARS COV2 IgG assay:

SARS-COV2 IgG ELISA assay detects antibodies against an epitope in Nucleocapsid (N) and the spike (S) region of SARS-CoV-2 proteins. Testing was done 30 days after receipt of the second dose of the vaccine. The positive cut-off value is more than 50 Au ml.

Ethical Consideration:

The study was approved by the Local Ethical Committee of Zagazig University. Written consent was obtained from every patient before the procedures. This study has been carried out following the code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All data were analyzed using IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp. Quantitative data were expressed as the mean ± SD & median (range), and qualitative data were expressed as numbers & percentages. Mann Whitney u test, t-test; Kruskal Wallis test, Chi-square test or Fisher exact test, Spearman correlation coefficient were used. P-value < 0.05 was considered statistically significant, p-value<0.001 was considered statistically highly significant, and p-value ≥ 0.05 was considered statistically insignificant.

RESULTS

The present study showed no statistical difference between renal dialysis patients and the control group regarding age, sex, smoking habit, and obesity (p>0.05) **(Table 1)**.

Table (1): Demographic characteristics of studied groups; renal dialysis group and control group :

Variables	Renal dialysis patients n.44		Control group n.20		χ 2	p-value
	No.	%	No.	%		
Age per years Means ±SD	53.9±13.4		56.75±8.3		t 0.86	0.39
Males	29	65.9	8	40.0	3.8	0.052
smokers	17	38.6	6	30.0	0.44	0.504
Obese	7	15.9	8	40.0	f	0.055

St deviation**, t=** test of significance**, χ 2=**chi square test of significance**, f:** Fisher exact test**, p**>0.05 insignificant

Regarding clinical parameters, the median duration of hemodialysis per year was 7.5 with a range from 2 months to 25 years. The main cause of renal failure was hypertension (38.6), followed by diabetes mellitus (18.6%), and interstitial glomerulonephritis (18.6%). Polycystic kidney disease &focal segmental glomerulosclerosis represent 6.8% for each. 2 patients have associated comorbidities **(Table 2)**.

Laboratory findings of renal hemodialysis patients were shown in **Table (3)**.

Table (2): Clinical parameters of studied renal dialysis group

Variables	Renal dialysis patients(n.44)	
Duration of Hemodialysis per years Median (range)	7.5 (2 months-25)	
The underlying disease of renal dialysis	No.	%
interstitial glomerulonephritis	8	18.2
Polycystic kidney disease	3	6.8
Diabetes Mellitus	8	18.2
Hypertension	17	38.6
Hypertension and Diabetes Mellitus	1	2.3
Lupus nephritis	1	2.3
Preeclampsia	2	4.5
Focal segmental glomerulosclerosis	3	6.8
Obstructive Uropathy	1	2.3
Long term use of immunosuppressive drugs	1	2.3
Co morbidity(1Strok&1cancer)	2	4.5

Table (3): Laboratory findings of studied renal dialysis group

Laboratory findings	Renal dialysis patients(n.44)
kt/v %	1.3±0.11
Hemoglobin (gm/dl)	10.4±01.8
WBC (mcL)	6.5±1.2
Lymphocyte	1.7±0.26
Platelet (150:450/mm^3)	234.8±8
Blood urea nitrogen (mg/dl)	66.4±4.8
Serum creatinine (mg/dl)	11.4±2.1
Serum sodium (mmol/l)	132.2±2.7
Serum potassium (mmol/l)	4.5±0.58
Serum calcium (mg/dl)	8.7±0.97
Serum phosphorus (mg/dl)	5.2±1.3
Serum uric acid (mg/dl)	7.1±1.2
Serum total proteins (mg/dl)	7.01±0.62
Serum albumin (mg/dl)	3.9±0.49
Serum ferritin (ng/ml)	204.5± 49.63
Parathyroid hormone (pg/ml)	309.7±73.81
C-reactive protein (mg/l)	5 ± 0.96

Data expressed as mean ±SD, or median (range), SD=standard deviation

There was no statistical difference between renal dialysis patients and the control group regarding COVID vaccine side effects. History of Covid19 infection before or after vaccination p>0.05 **(Table 4)**.

Table (5): Comparison between renal dialysis patients & control group regarding COVID vaccine side effects, history of Covid19 infection before or after vaccination with Sinopharm vaccine

Variables	Renal dialysis patients group (n.44)		Control group (n.20)		χ 2	p-value
	No.	%	No.	%		
History of Covid19 infection before vaccination	10	22.7	7	35.0	1.1	0.303
Adverse effect	19	43.2	12	60.0	1.6	0.21
Fatigue	11	25.0	8	40.0	1.5	0.22
Fever	13	29.5	10	50.0	2.5	0.11
Pain	3	6.8	0	.0	f	0.55
Headache	1	2.3	0	.0	f	0.99
Arthralgia	1	2.3	0	.0	f	0.99
History of Covid19 infection post-vaccination	0	0	0	0		

χ 2:chi square test of significance**, f:** Fisher exact test**, p**>0.05 insignificant

There was lower serum SARS COVID IgG Au/ml value among renal dialysis patients compared to the control group (p<0.001) **(Figure 1)**.

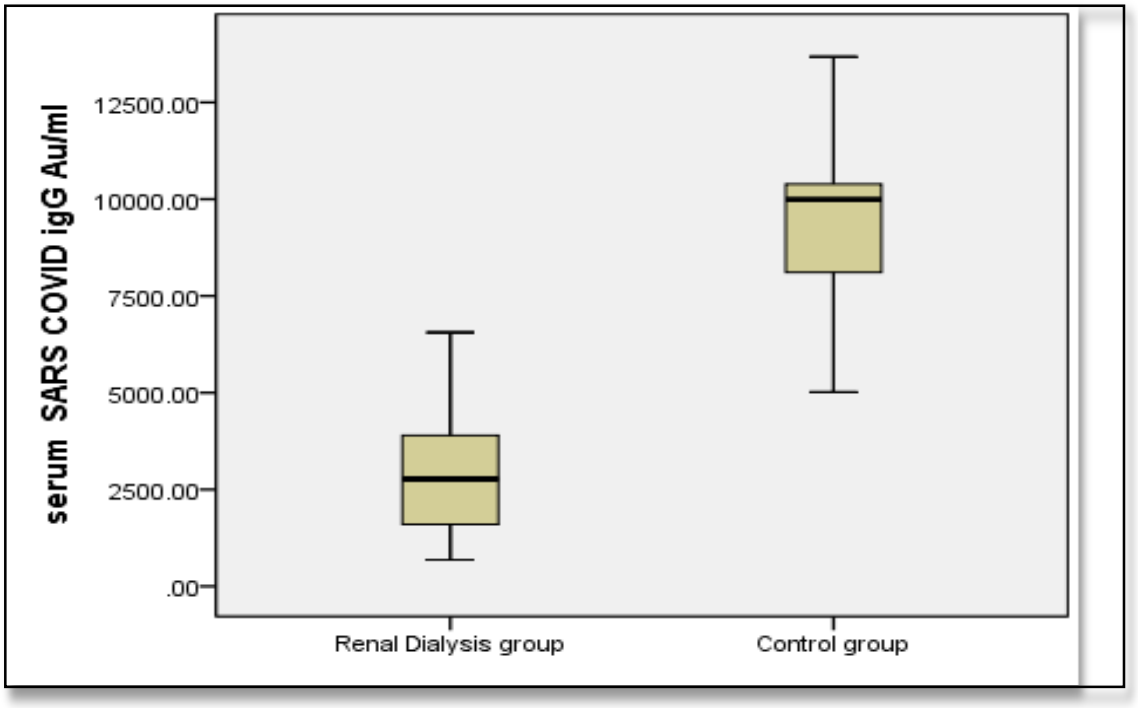

Figure (1): Median and range of serum SARS COVID IgG for renal dialysis patients and control group.

There was no significant difference in the SARS COVID igG value of renal dialysis patients regarding their underlying cause of renal failure (p>0.05) **(Table 5)**.

Table (5): Serum SARS COVID igG according to the underlying cause of renal failure (n=44):

Underlying causes of renal failure	Median(range)	kw	p
interstitial glomerulonephritis	2919(1046-6558)	**4.6**	**0.79**
Polycystic kidney disease	3214(2889-4187)		
Diabetes Mellitus	2374(1198-5194)		
Hypertension	1963(682-5784)		
Hypertension and Diabetes Mellitus	3635(3635-3635)		
Lupus nephritis	3896(3896-3896)		
Preeclampsia	3663(3565-3761)		
Focal segmental glomerulosclerosis	5375(1105-5697)		
Obstructive Uropathy	2108(2108-2108)		

Kw: Kruskal Wallis Test- p>0.05 non-significant

There was a lower significant value of SARS COVID IgG in renal dialysis patients compared to the control group regarding sex, smoking habit, and obesity p<0.001. Also, there was a lower significant value of SARS COVID IgG in renal dialysis patients compared to the control group regarding the history of COVID19 infection before vaccination and occurrence of post-vaccine adverse effects. There was no significant difference in SARS COVID IgG value of renal dialysis patients regarding their demographic parameters (p>0.05). There was a higher significant SARS COVID IgG value of males, and smokers in the control group (p<0.05**) (Table 6)**.

Table (6): SARS COVID IgG value of renal dialysis patients and control group regarding their demographic characteristics

Variables	Renal dialysis patients n.44	Control group n.20	u	p
Sex				
Males	2216(682-6558)	10292.5(7384-13680)	4.2	0.0001
Females	3214(1046-5697)	8905.5(5018-13680)	4.3	0.0001
U	0.02	2.04		
P	0.99	0.041*		
smoking				
Smoker	3165(682-6558)	10545.5(9289-13680)	3.6	0.0001
Non smoker	2722(1046-5697	8905.5(5018-13680)	5.1	0.0001
U	0.807	2.6		
P	0.91	0.023*		
Obesity				
Obese	2216(1227-3761)	9405(6178-13680)	3.2	0.001
Normal	2808(682-6558)	9994.5(5018-12216)	4.9	0.0001
U	0.21	0.23		
P	0.83	0.83		
Long-term use of immunosuppressive drugs				
Yes	3896(3896-3896)	-		
No	2734(682-6558)	-		
U	0.83	-		
P	0.41	-		
History of Covid19 infection before vaccination				
Yes	2882(878-5784)	9924(7384-13680)	3.4	0.001
No	2512(682-6558)	10060(5018-12216)	5.1	0.0001
U	0.41	0.19		
P	0.68	0.84		
Adverse effect				
Yes	2026(1046-5697)	9992(6877-13680)	4.6	0.0001
No	3165(682-6558)	9730.5(5018-12216)	3.9	0.0001

u= Mann-Whitney U**, p**>0.05 insignificant**, p**<0.05 significant**, p**<0.001 highly significant (**p:** comparison between renal dialysis patients and control group) Significant (**p1:** comparison within the group)

DISCUSSION

COVID-19 was associated with higher morbidity and mortality in patients on maintenance (HD [(4)]. Patients with renal illness, especially those on long-term dialysis, have an increased risk of developing severe COVID-19 infection-related complications and having a poor prognosis, which includes an increased risk of hospitalization, ICU admission, mechanical ventilation, and death [(7)].

Even if patients on in-center chronic HD are not infected with COVID-19, the pandemic may nevertheless have indirect consequences on their mental health in addition to these direct effects. In a patient population where symptoms like despair and anxiety already carry a disproportionately high burden, these consequences might be especially overpowering [(8)].

Prioritizing patients on dialysis for vaccination has been at the forefront of SARS-CoV-2 vaccination programs internationally. Patients with CKD, especially those with kidney failure, treated with maintenance HD tend to have a reduced immune response to infection or vaccination, as demonstrated with the hepatitis B virus vaccine. Consequently, there is often a need for higher vaccine dosage or scheduling changes in these patients [(9)].

Several vaccines have been approved for SARS-CoV-2 infection. Live attenuated vaccines generally should be avoided in patients on maintenance HD due to their dysregulated immune system. Both the mRNA vaccines BNT162b2 (Pfizer- BioNTech) and mRNA-1273 (Moderna) and the replication-defective viral-vectored vaccines, such as ChAdOx1 nCoV-19 (Oxford-AstraZeneca), are considered safe for use in patients treated with maintenance HD [(10)].

However, there have been very few studies assessing immune response to the COVID-19 vaccination in patients undergoing maintenance HD. So, this study aimed to assess the immune response following vaccination with the COVID-19 vaccine in patients with maintenance HD and the factors

associated with it. To achieve this target, 44 patients under maintenance hemodialysis (group 1) and 20 vaccinated non-renal patients (group 2) were included in the study.

In our study, the mean age of the studied groups was 53.9±13.4 and 56.75±8.3 for dialysis group 1 and the control group, respectively. Males represented 65.9 % and 40.0%, respectively. There is no statistical difference between renal dialysis patients and the control group regarding age, sex, smoking habit, and obesity.

These findings are similar to **Oguz *et al.*** [11] found that out of 50 patients included in the study group with a mean age of 55 ± 16 years, 32 (64%) were female and 18 (36%) were male. Out of 35 healthy controls with a mean age of 49 ± 14 years, 22 (62.9%) were female and 13 (37.1%) were male. The two groups did not differ in terms of age and gender.

In our study, the median duration of hemodialysis per year was 7.5. The main cause of renal failure was hypertension (38.6), followed by diabetes mellitus (18.6%), and interstitial glomerulonephritis (18.6%). Polycystic kidney disease &focal segmental glomerulosclerosis represent 6.8% for each.2 patients have associated comorbidities.

Piscitani *et al.* [12] included 21 hemodialysis patients (61.9% males) and 16 controls without chronic kidney disease (26.7% males). Briefly, their hemodialysis patients were older than controls (mean age 67.5 ± 13.4 years); 57.1% had hypertension, 23.8% had a history of diabetes, 42.9% had documented peripheral vascular disease and 38.1% had established cardiovascular disease including previous ischaemic heart disease, stroke, TIA). Among controls, 38.5% had a history of hypertension; no comorbidities were reported.

In our study, there was no statistical difference between renal dialysis patients and the control group regarding COVID vaccine side effects. History of Covid19 infection before or after vaccination (p>0.05). There was lower serum SARS COVID IgG Au/ml value among renal dialysis patients compared to the control group p<0.001.

Razzaghi *et al.* [13] documented that approximately 20% of hemodialysis patients were positive for COVID-19 with frequent clustering of cases among hemodialysis patients and the medical staff. On the other hand, patients performing peritoneal dialysis and home hemodialysis were relatively protected during this pandemic [14].

Piscitani *et al.* [12] reported hemodialysis patients had lower mean titers of serum antibodies to the SARS-CoV-2 spike antigen compared with controls (492.39 vs 1901.20 IU/mL, respectively; p < 0.001). Antibody titers were not affected by the duration of hemodialysis in the examined sample.

In our study, there was a significant negative correlation between, SARS COVID IgG Au/ml & age per year, duration of hemodialysis per year, and parathyroid hormone. Whereas, there is a significant positive correlation between SARS COVID IgG Au/ml and kt/v % of renal hemodialysis dialysis patients. Otherwise, there is no significant relation between, SARS COVID IgG Au/ml and other laboratory findings of studied patients p >0.05. There is no significant difference in SARS COVID IgG value of renal dialysis patients regarding their underlying cause of renal failure p>0.05.

Kato *et al.* [15] revealed that risk factors that seem to take part in the reduction of defense capabilities are older age, diabetes, time since the first dialysis, and malnutrition.

Krueger *et al.* [16] vaccination has been declared of primary importance in hemodialysis patients. Emergency Use Authorization (EUA) was based on clinical trials that did not include hemodialysis or transplant patients. The hyporesponsiveness of these patients to vaccination is well known. It has been reported that post-influenza vaccine seroprotection rates range from 33 to 80%.

Piscitani *et al.* [12] revealed to age-matched analysis on 18 participants, equally distributed between cases and controls (mean age 55.3 ± 10.5 years and 55.3 ± 6.9 years, respectively; p = 1.000), confirmed the observation of lower antibody titers among those on hemodialysis (580.8 vs 1836.4 IU/mL, respectively; p < 0.001). Also, **Kato *et al.*** [15] reported that uremic syndrome and extracorporeal circulation seem to play a role in disrupting the innate and adaptive immune response through reduced neutrophil and monocyte function, as well as reduced cell-mediated and antibody responses.

In our study, there is a lower significant value of SARS COVID igG in renal dialysis patients compared to the control group regarding the history of COVID19 infection before vaccination and occurrence of post-vaccine adverse effects.

Numerous studies, including those by **Piscitani *et al.*** [12], **Jahn *et al.*** [17], **and Janay *et al.*** [18] seem to confirm our finding that hemodialysis patients developed a specific humoral response post-vaccination, but the level of antibody production was lower than in control patients without renal disease. In addition, **Marion *et al.*** [19] showed similar results among renal transplant patients.

CONCLUSION

Hemodialysis patients demonstrate a hyporesponsiveness to vaccination against COVID-19. Although most patients on maintenance hemodialysis developed a substantial humoral response following the COVID vaccine, it was significantly lower than controls.

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