Renal Replacement Therapy

RESEARCH

Open Access

Robust antibody response after the third mRNA coronavirus vaccination in Japanese hemodialysis patients

Ryoichi Miyazaki[1*], Kyoko Miyagi[1], Misaki Yoshida[1], Yasunori Suzuki[1] and Shinya Hibino[1]

Abstract

Background Hemodialysis patients have chronic kidney disease, are often elderly, and have many complications such as hypertension, type 2 diabetes, cardiac disease, and cerebrovascular disease. Therefore, hemodialysis patients infected with COVID-19 are prone to severe disease. Vaccination is the most promising means of preventing the onset and reducing the severity of COVID-19. However, many reports have found that anti-spike antibody titers after two doses of mRNA vaccine are lower in hemodialysis patients than in healthy controls. For this reason, a third vaccination is recommended for hemodialysis patients. In Japan, there are several reports of a third vaccination, especially for hemodialysis patients. In this study, we also examined the antibody response to COVID-19 vaccine in Japanese hemodialysis patients who received the third dose of the vaccine.

Methods Study participants received a third vaccination (257 with BNT162b2 vaccine and 5 with mRNA-1273 vaccine) approximately 7–9 months after the second (BNT162b2 vaccine). Anti-SARS-CoV-2 spike IgG antibody titers were measured (Abbott SARS-CoV-2 IgG II Quan) in 185 hemodialysis patients and 109 healthcare workers approximately 2 weeks after the second vaccination and in 162 hemodialysis patients and 100 healthcare workers approximately 2 weeks after the third.

Results Following the second vaccination, 97.6% of the hemodialysis group and 100% of the control group were positive for the anti-spike antibody. The median level of the anti-spike antibody was 2728.7 AU/mL (IQR, 1024.2–7688.2 AU/mL) in the hemodialysis group and 10,500 AU/ml (IQR, 9346.1–2,4500 AU/mL) in the controls. Following the third vaccination, 99.4% of the hemodialysis group (only one person tested negative for the antibody) and 100% of the control group were positive for the anti-spike antibody. The median level of the anti-spike antibody was 20,000 AU/mL (IQR, 7729–37,000 AU/mL) in the hemodialysis group and 21,500 AU/ml (IQR, 14,000–32,250 AU/mL) in the control group. The factors involved in the low response to the BNT152b2 vaccine after the second vaccination included old age, low BMI, low Cr index, low nPCR, low GNRI, low lymphocyte count, steroid administration, and complications related to blood disorders. However, in hemodialysis patients, the response after the third vaccination was excellent, and all factors associated with the suppressed response to these vaccines were no longer significant.

Conclusions The humoral response of hemodialysis patients to two doses of mRNA vaccine was weaker than that of healthy controls. However, a third vaccination eliminated that difference.

Keywords COVID-19 prevention, mRNA vaccine, Japanese hemodialysis patients

*Correspondence:
Ryoichi Miyazaki
ryoichi@mitene.or.jp
Full list of author information is available at the end of the article

Background

Hemodialysis (HD) patients are a high-risk population with much higher hospitalization and mortality rates due to COVID-19 than the general population [1, 2]. Vaccination of HD patients is recommended to prevent infection and severe disease [3]. However, a number of reports have confirmed that after the usual two doses of COVID-19 vaccine, the antibody responses in HD patients are significantly weaker than in the general population [3–12]. Moreover, the elevated antibody titers decay over time [9]. We therefore believe that a COVID-19 booster vaccination for populations at high risk for severe disease, including HD patients, is justified. For that reason, in Japan a third dose of the vaccine is administered to populations at high risk of severe disease, including HD patients, with the expectation of a booster effect. In addition, the omicron variant strain of SARS-CoV2 is now the predominant strain in many countries, including Japan. With the omicron variant, immune escape is often seen, making breakthrough infection after vaccination an important issue [13]. And while the omicron variant appears to cause mild disease in the general population, there are reports of more severe cases among HD patients, so caution should be exercised [14].

Study design, setting, and participants

This observational, prospective, single-center study to evaluate humoral responses after mRNA vaccination in Japanese HD patients was conducted at Fujita Memorial Hospital. Overall, 185 HD patients (HD group) and a control group composed of 109 healthcare workers without kidney failure from our hospital (HCW group) were included in the study (Fig. 1). All HD patients over 18 years of age in our dialysis facility were considered for inclusion. Exclusion criteria were vaccination refusal (only one HD patient and two HCWs), a history of SARS-CoV-2 infection prior to vaccination, and positivity for anti-S IgG antibodies (>50 AU/mL) prior to vaccination. The characteristics of the participants at the beginning of the study are detailed in reference [4]. Between the second and third vaccinations, 18 patients dropped out of the HD group (9 died, 4 were transferred, 1 had a COVID-19 infection after the second vaccination, and 1 refused the third vaccination) and 9 dropped out of the HCW group (8 retired and 1 had a moderate adverse reaction) (Fig. 1). The characteristics of the participants at the time of the third vaccination are shown in Table 1.

The mRNA vaccine was administered at our dialysis facility. Two doses of BNT162b2 vaccine (30 μg each) were administered between April 4 and May 22, 2021. As recommended by the manufacturer, there was a 21-day interval between the first and second vaccinations. The third vaccination was administered 7–8 months after the second. Among the remaining 167 HD patients, 162 received the BNT162b2 vaccine and 5 received the mRNA-1273 vaccine. The remaining 100 HCWs all received the BNT162b2 vaccine. Follow-up continued until September 5, 2022.

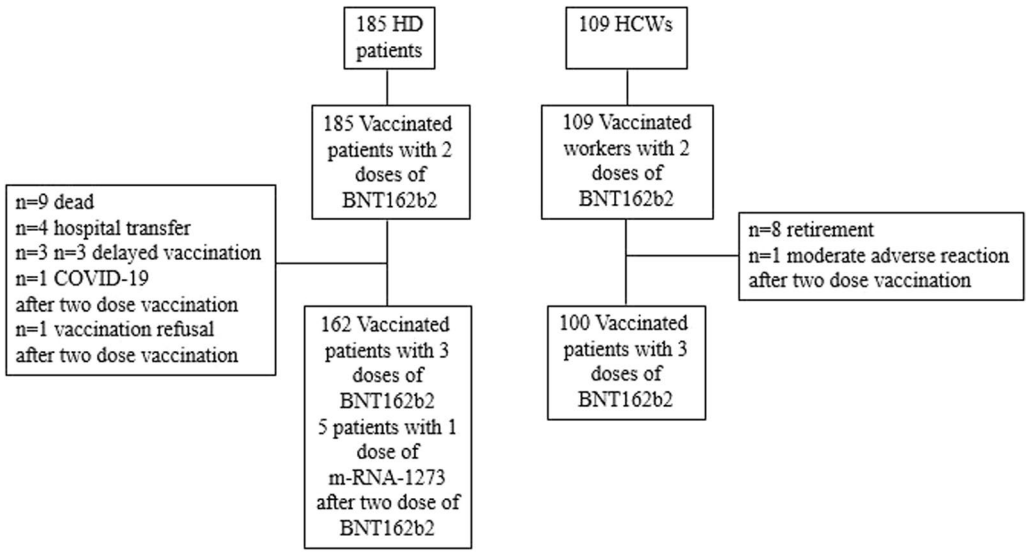

Fig. 1 Study flowchart. *HD* hemodialysis, *HCWs* healthcare workers

Table 1 Participant profile at the time of the third vaccination

	HD ($n=167$)	HCWs ($n=100$)	*P*
Age	70 [61–78]	54 [44–60]	< 0.001
Male/female	113/54	20/80	< 0.001
BMI kg/m^2	21.3 [19.4–24.2]	21.5 [19.2–23.5]	0.822
eGFR ml/min/1.73m^2	–	74.6 [66.2–81.5]	
Dialysis vintage, months	80 [35–158]	–	
DM/NDM	64/103	6/94	< 0.01
Hematologic disorder (yes/no)	8/159	0/100	0.027
Steroid (yes/no)	13/154	1/100	0.020
Current smoking (yes/no)	25/142	0/109	< 0.001

Results are shown as the median [interquartile range] for continuous variables. The Mann–Whitney test and Fisher exact test were used to compare continuous and categorical variables

BMI body mass index, *DM* diabetes mellitus, *eGFR* estimate glomerular filtration rate, *NDM* non-diabetes mellitus

Humoral response assessment

Postvaccination, serum levels of anti-SARS-CoV-2 spike protein IgG antibodies were assayed using a chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant assay on an ARCHITECT analyzer; Abbott). The assay detects antibodies against the receptor binding domain of the S1 subunit of the SARS-CoV-2 spike protein and presents a positive predictive agreement of 99.4% (95% confidence interval [95% CI], 96.50–99.97%) and a negative predictive agreement of 99.6% (95% CI, 99.15–99.37%). In addition, the results of this assay are consistent with those obtained using the neutralization method to wild-type SARS-CoV-2 (positive agreement, 100.0%; 95% CI, 95.72–100.00%) [15, 16]. Anti-SARS-CoV-2 spike IgG antibody assays have shown excellent correlation with neutralizing antibodies [17]. A value of 50 arbitrary units per milliliter (AU/ml) was considered evidence of a vaccination response [18]. Antibodies were measured before vaccination and a median of 17 (IQR: 16–19) days after the second and third vaccinations in both the HD and HCW groups. An anti-nucleocapsid IgG assay (Abbott) was also employed with 41 HD patients who had high spike antibody levels after the third vaccination.

Other variables

The Kt/V, protein catabolic rate (PCR), normalized protein catabolic rate (nPCR), creatinine (Cr) index, and geriatric nutritional risk index (GNRI) in the HD patients were calculated as described previously [19–21]. BMI was defined as dry weight in kilograms divided by height squared, in meters. We used recorded laboratory tests, which were routinely conducted for all HD patients at the beginning of the month prior to their first dose of SARS-CoV-2 vaccine. Details of the patients' maintenance were obtained from their medical charts.

Adverse events

Using a standardized questionnaire, vaccination-related adverse events were separately assessed in the HD and HCW groups. These included fever, malaise, headache, chills, vomiting, diarrhea, myalgia, and injection site pain. We questioned the HD patients and HCWs about the subjective severity of the adverse events after vaccine administration. The grading was divided into three levels (mild, moderate, and severe) established according to the Food and Drug Administration toxicity grading scale [22].

Breakthrough infection

Diagnosis of a breakthrough infection was made based on the clinical signs of COVID-19 and a positive PCR test for SARS-CoV-2 virus in nasopharyngeal swabs for patients who received 2 or 3 doses of m-RNA vaccination.

Statistical analyses

All data for continuous variables are summarized and displayed as the mean (SD) for each group. For categorical variables, the Chi-square statistic was used to assess the significance of differences between groups. Normally distributed parameters were compared using t tests. Parameters not normally distributed were compared using Kruskal–Wallis/Mann–Whitney *U* tests. Values of $P < 0.05$ were considered statistically significant for all analyses. EZR Statistics for Windows and R version 3.4.1 (The R Foundation for Statistical Computing, Japan) were used for all statistical analyses [23].

Results

Participants

The HD group was significantly older, more male-dominated, had a higher rate of diabetes and hematologic complications, and received more steroids than the HCW group (Table 1).

Humoral response

After two doses of mRNA vaccine, the anti-spike IgG level in the HD group (median, 2728.7; IQR, 1024.2–7,688.2) was significantly lower than in the HCW group (median, 10,500; IQR, 9346.1–24,500) (Fig. 2, left panel). However, after three doses of the vaccine, the difference between the anti-spike IgG titers in the HD (median, 20,000; interquartile range, 7729–37,000) and

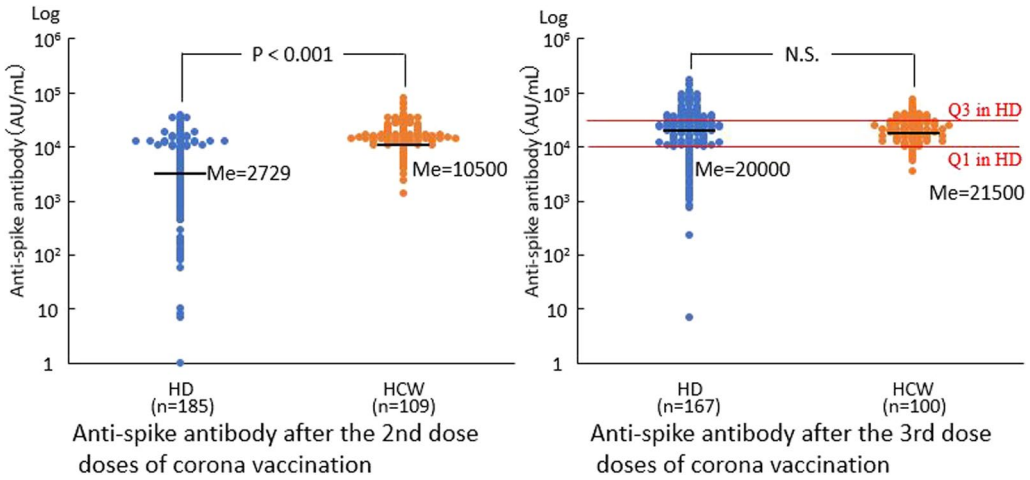

Fig. 2 Anti-spike antibody titers in HD patients and HCWs after the 2nd and 3rd vaccinations. *Me* median; *N.S.* not significant; *Q1 in HD* quartile 1 antibody level in the HD group, *Q3 in HD*, quartile 3 antibody level in the HD group

HCW (median, 21,500; IQR, 14,000–32,250) groups (Fig. 2, right panel) groups had disappeared. In the HD group, 164/167 (98.2%) patients showed antibody titers of ≥ 809 AU/mL, the neutralizing antibody titer for the delta variant, while 130/167 (77.8%) patients showed titers of ≥ 5889 AU/mL, the neutralizing antibody titer for the omicron variant [24]. In the HCW group, neutralizing antibody titers for the delta and omicron variants were attained in 100/100 (100%) and 98/100 (98.0%) of participants, respectively.

Table 2 shows the involvement of several factors in the low (< Q1) and high (> Q3) antibody responders after the 2-dose and 3-dose vaccinations. As we reported previously [3], factors associated with antibody hyporeactivity after 2 doses of vaccine in HD patients included advanced age, low nutrition (low nPCR, lymphocytes, and Cr index), current smoking, steroid medication, and complications of hematologic diseases. After 3 doses of vaccine, however, all of the factors related to a low antibody response were no longer significant, and even HD patients exhibited a robust antibody response.

Figure 3 shows the anti-spike antibody levels in HD patients and HCWs with high antibody titers after the third vaccination and the interval between the second and third vaccinations, which may be related to these titers. The median antibody titer in the HD patients was

Table 2 Comparison of the high (> Q3) and low (< Q1) responders in the HD group after 2 and 3 doses of m-RAN vaccine

	After 2nd doses			After 3rd doses		
	< Q1 (*n* = 46)	> Q3 (*n* = 46)	*P*	< Q1 (*n* = 41)	> Q3 (*n* = 41)	*P*
Age	71.5 [64.3–80.0]	67.5 [59.0–73.0]	< 0.05	72.0 [65.0–79.0]	72.0 [63.0–80.0]	N.S
Hemodialysis vintage (months)	77.5 [33.0–138.0]	83.5 [28.0–176.3]	N.S	75 [38–117]	60 [32–134]	N.S
DM/NDM	13/33	18/28	N.S	13/33	13/33	N.S
Serum albumin (g/dL)	3.6 [3.5–3.8]	3.7 [3.6–3.8]	N.S	3.7 [3.5–3.9]	3.6 [3.5–3.8]	N.S
nPCR (g/kg/day)	0.83 [0.74–0.94]	0.92 [0.79–1.09]	< 0.05	0.87 [0.77–1.02]	0.84 [0.75–1.00]	N.S
Lymphocytes (mm^3)	896 [729–1,067]	1,144 [849–1,443]	< 0.01	993 [752–1,170]	1,108 [752–1,410]	N.S
Cr index (mg/kg/day)	90.0 [66.5–105.5]	104.5 [81.7–116.8]	< 0.05	91.8 [78.7–101.2]	94.3 [69.2–107.8]	N.S
Current smoking (yes/no)	11/35	3/40	0.0405	10/31	3/38	N.S
Steroid (yes/no)	9/37	1/45	< 0.05	6/35	1/40	N.S
Immunosuppressant (yes/no)	1/45	0/45	N.S	4/37	2/39	N.S
Hematologic disorder (yes/no)	9/37	0/46	< 0.05	4/37	0/39	N.S

Results are shown as the median [interquartile range] for continuous variables or as numbers of patients (percentages) for categorical variables. The Mann–Whitney test and Fisher exact test were used to compare continuous and categorical variables

nPCR normalized protein catabolic rate, *Cr* creatinine

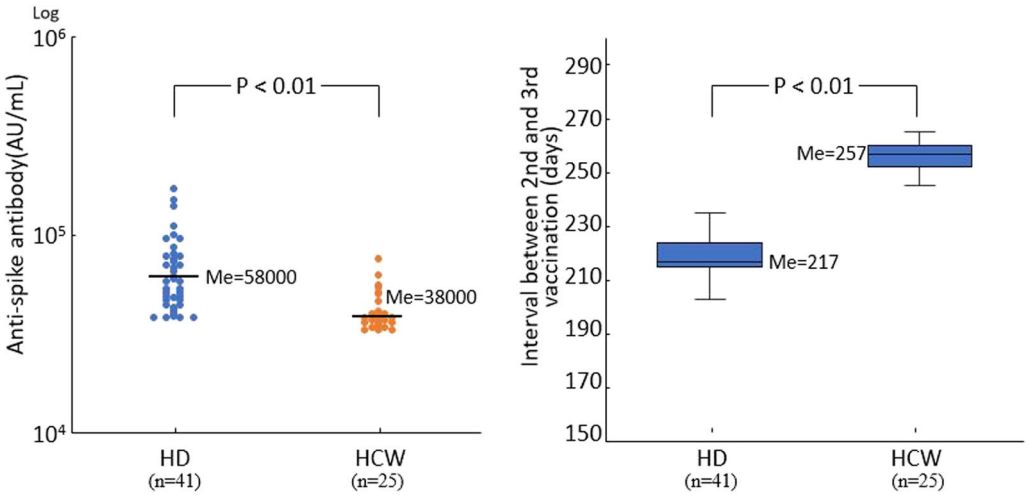

Fig. 3 Anti-spike antibody levels after 3 vaccinations in HD patients and HCWs with high antibody titers (left panel) and the interval (days) between the 2nd and 3rd vaccinations (right panel)

58,000 AU/mL with an IQR of 49,000–78,000 AU/mL, which was significantly higher than the median titer of 38,000 AU/mL and IQR of 36,000–46,000 AU/mL among HCWs (Fig. 3, left panel). The interval between the second and third vaccinations was significantly shorter in the HD group (median, 217 days; IQR, 215–225 days) than the HCW group (median, 257 days; IQR, 252–260 days) (Fig. 3, right panel). This difference in interval reflects the Japanese government's COVID-19 vaccine policy.

Figure 4 shows the anti-spike antibody titers in the HD patients and HCWs with low antibody titers after the third vaccination and the correlation between the anti-spike antibody titers after the second and third vaccinations. The median antibody titer for HD patients was 3233 AU/mL with an IQR of 1638–4919 AU/mL, which was significantly lower than that for HCWs (9950 AU/mL; IQR, 9031–12,000 AU/mL) (Fig. 4, left panel). In addition, there was a positive correlation between the anti-spike antibody titers after the second and third vaccinations (Fig. 4, right panel).

Adverse reactions to mRNA vaccine

As we previously reported, adverse events were generally milder in the HD group than in the HCW group [4].

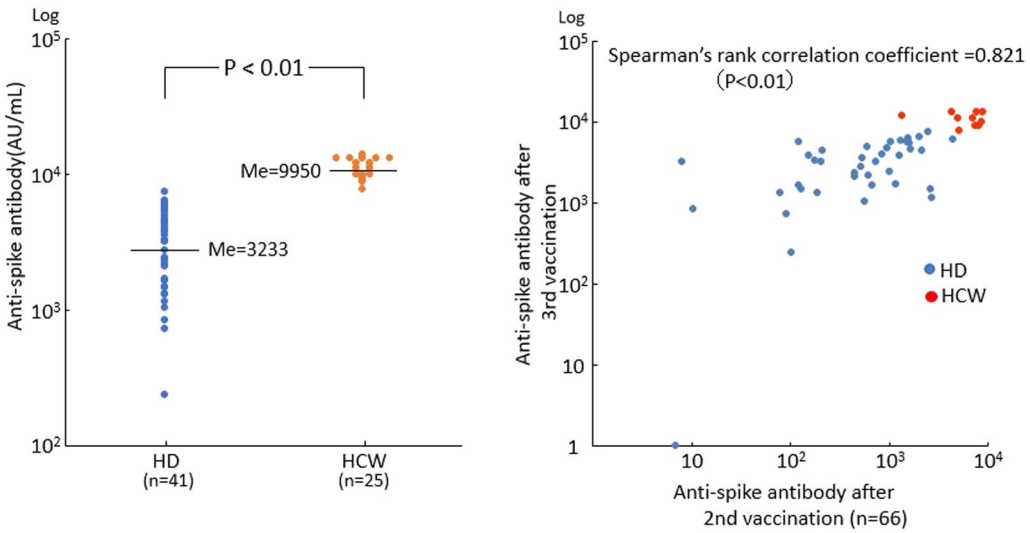

Fig. 4 Anti-spike antibody levels after 3 vaccinations in HD patients and HCWs with low antibody titers (left panel) and the correlation between anti-spike antibody titers after the 2nd and 3rd vaccinations (right panel)

Table 3 Breakthrough infections after mRNA vaccination

Patient	Age	Gender	Primary disease	Number of V	Days since last V (days)	Anti-spike antibody after 2 or 3 doses V (AU/mL)	Anti-spike antibody before BTI (AU/mL)	Severity of illness
1	73	F	DM	2	219	19,000	597.9	Mild·OP
2	75	M	DM	3	70	4,919	61,000	Mild·AD
3	50	F	NDM	3	91	11,000	14,000	Mild·OP
4	53	M	NDM	3	137	18,000	11,000	Mild·AD
5	58	M	NDM	3	141	11,000	6,424	Mild·OP
6	73	M	NDM	3	131	1,693	N.A	Mild·AD
7	68	M	NDM	3	164	62,000	10,000	Mild·AD

AD admission, *BTI* breakthrough infection, *F* female, *M* male, *OP* outpatient, *V* vaccination

Adverse events after the third vaccination were similar to those after the second, and adverse events were again milder in the HD than in the HCW group (Additional file 1: Fig S1, Additional file 1: Fig S2).

Breakthrough infections

Seven HD patients contracted COVID-19 after mRNA vaccination (Table 3). This included five males and two females ranging in age from 50 to 73 years. Two had diabetes as their primary disease, while five were not diabetic. The interval from their last vaccination to breakthrough infection ranged from 70 to 219 days. Their spike antibody titers after two of the three vaccinations ranged from 4919 to 62,000 AU/mL, and the titers just prior to breakthrough infection ranged from 597.9 to 61,000 AU/mL. The disease was mild in all seven patients, thought four required hospitalization; the other three patients were treated as outpatients. Based on the results of these seven cases of breakthrough infection, vaccination against the omicron variant is desirable in the future [25].

Discussion

HD patients with COVID-19 are reported to be at higher risk of severe illness, hospitalization, and death than the general population [1]. Vaccination is a promising means of preventing COVID-19 or reducing its severity. [3]. In our study, the vaccine positivity rate after two doses of BNT162b2 vaccine was 97.8% in the HD group and 100% in the HCW group. However, as in a number of earlier reports, the median antibody titer was significantly lower in the HD than in the HCW group [3–13]. Factors associated with the decreased humoral response after 2 doses of vaccine included older age, lower lymphocyte count, lower nPCR, lower GNRI, lower Cr index, lower BMI, steroid administration, and hematologic disease [4]. However, the HD group also showed a marked increase in anti-spike antibody titer after 3 doses of mRNA vaccine, and the difference from the HCW group disappeared. Our findings are consistent with previous reports, including several reports from Japan, that antibody production in HD patients after three doses of mRNA vaccine and loss of significance of the factors associated with the humoral hyporesponsiveness [26–34].

We previously (2003–2004) vaccinated (Bimmugen®) 106 HD patients for hepatitis B using a protocol that consisted of three doses of vaccine (10 μg 1 month and 6 months after the initial dose). This resulted in a 66.6% anti-hepatitis B antibody positivity rate after the first course and a 93.4% positivity rate after the second course (details of the data not presented). Those findings are consistent with a recent study showing the importance of repeated hepatitis B vaccinations in a group of HD patients [35]. We therefore hypothesized that booster vaccination would increase anti-SARS-CoV-2 antibody production in HD patients with impaired immune function.

Notably, in the present study, comparison between HD patients and HCWs with high anti-spike antibody titers after the third vaccination showed that antibody titers were significantly higher in the HD than in the HCW group.

Yoshifuji et al. reported that both cellular and humoral immunity were significantly higher in the HD group than in the control group at 3 weeks and 3 months after the booster dose, which was considered helpful for the prevention of severe disease. Panizo et al. [31] showed that most hemodialysis patients develop SARS-CoV-2-S antibody responses comparable to that of healthy controls at 15 days and 3 months after complete vaccination schedule (two doses) [36]. Also, Espi et al. found that the percentage of circulating spike-specific CD8 + T cells was more heterogeneous and slightly reduced in patients on maintenance hemodialysis patients as compared with in healthy volunteers

after the second vaccination [34]. One reason for this is likely the significantly shorter interval between the second and third vaccinations in the HD group (Fig. 3, left panel). Bensouna et al. reported that patients with a greater increase in anti-spike antibody titers after three doses of BNT162b2 vaccine had a shorter interval between the second and third doses [26]. When they divided their patients into three groups based on the ratio of anti-spike antibody titers after the second and third vaccinations, they found that the interval between the second and third doses was a factor involved in the ratio. They then examined groups with second and third vaccine antibody titer ratios of ≥ 43 and ≤ 7.3 and found that the interval between the second and third vaccinations was 74 [IQR, 72–79] days for the high antibody titer ratio group and 59 [IQR, 36–67] days for the low titer ratio group ($P < 0.001$). Our results show that the HD group, which had a shorter vaccination interval, had significantly higher antibody titers after the third vaccination than the HCW group, which had a longer interval. In the context of the abovementioned studies, this suggests the effect of the vaccination may be weakened if the vaccination interval is shorter or longer than optimal. On the other hand, Yoshifuji et al. reported that the hemodialysis group had significantly higher antibody titers than the control group, but there was no difference in the vaccination interval from the primary vaccine to the booster vaccine in the two groups [31].

Comparison between groups with low antibody titers after the third vaccination showed significantly lower titers in the HD than HCW group (Fig. 4, left panel), and a positive correlation was observed between the antibody titers after the second and third vaccinations (Fig. 4, right panel). Although the data are not shown, a positive correlation was also observed between the HD and HCW groups as a whole. The cause of this low antibody response may be a disorder of the genetic or acquired immune response. With regard to disorders of the genetic immune response, Higuchi et al. found a relationship between antibody titer and HLA polymorphism in Japanese rheumatoid arthritis patients after two doses of BNT162b2 vaccine [37]. We therefore suggest that a genetic factor may contribute to determining the magnitude of the increase in antibody titer after vaccination. As for acquired immune response disorders in hemodialysis patients, this is as previously reported.

Seven HD patients experienced COVID-19 breakthrough infections after the second or third vaccination. These breakthroughs occurred even when antibody titers measured just prior to COVID-19 infection were high. We suggest this may be due to the fact that the mRNA vaccine used was less compatible with the omicron variant or the exposure to SARS-CoV-2 virus was high.

This study has several limitations. First, the study was carried out at a single institution, and the number of participants in the study was relatively small. Second, the anti-spike antibodies measured in this study were not neutralizing antibodies, nor did we examine antibodies against the omicron variant, which is currently the dominant strain in Japan. Third, in this study, cellular immunity to the vaccine was not examined.

Conclusions

Anti-SARS-CoV-2 spike antibody titers were significantly lower in HD patients than in healthy controls after two doses of mRNA vaccine. However, after three doses, the HD patients also showed a very good increase in antibody titer, which no longer differed from that of healthy controls. The interval between the second and third vaccinations may have contributed to this result. Seven breakthrough infections occurred, and future vaccination against the omicron variant would be desirable.

Abbreviations

AD	Admission
AU	Arbitrary units
BMI	Body mass index
BTI	Breakthrough infection
CI	Confidence interval
COVID-19	Coronavirus disease 2019
Cr	Creatinine
DM	Diabetes mellitus
eGFR	Estimate glomerular filtration rate
F	Female
GNRI	Geriatric Nutritional Risk Index
HBV	Hepatitis B virus
HCWs	Healthcare
HD	Hemodialysis
IgG	Immunoglobulin G
IQR	Interquartile range
M	Male
Me	Median
mRNA	Messenger ribonucleic acid
NDM	Non-diabetes mellitus
nPCR	Normalized protein catabolic rate
N.S.	Not significant
OP	Outpatient
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
Q	Quadrant
V	Vaccination

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-023-00491-2.

Additional file 1. Figure S1. Adverse reactions to the second mRNA vaccination in the HD and HCW groups. Adverse events in the HD group were milder than in the HCW group, including injection site pain.

Additional file 2. Figure S2. Adverse reactions to the third mRNA vaccination in the HD and HCW groups. After the third dose of mRNA vaccine, as with the second dose, adverse events, including injection site pain, were milder in the HD group than in the HCW group.

Acknowledgements
None.

Author contributions
RM, KM, MY, YS, and SH took care of patients and participated in the decisions about treatment. RM prepared the manuscript. All authors have read and approved the final manuscript.

Funding
None.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
The study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee in the Fujita Memorial Hospital, Fukui, Japan (Approval Number: 58).

Consent for publication
Written informed consent was obtained from all participants. Written informed consent for the HD group was obtained at the time of rounds; that for the HCW group was obtained at the time of regular health checks.

Competing interests
No authors have conflicts to report.

Registration

Name of the registry: Robust antibody response after the third mRNA coronavirus vaccination in Japanese hemodialysis patients.
Trial registration number: R000053704
Date of registration: 2023/03/28
URL of trial registry record: Trial registration: UMIN, UMIN000047083. Registered March 28, 2023, https://center6.umin.ac.jp/cgi-bin/icdr/ctr_menu_form_reg.cgi?recptno=R000053704

Author details
[1]Department of Internal Medicine, Fujita Memorial Hospital, 4-15-7, Fukui, Fukui 910-00004, Japan.

Received: 2 April 2023 Accepted: 21 July 2023
Published online: 31 July 2023

References

1. Kikuchil K, Nangaku M, Ryuzaki M, Yamakawa T, Yoshihiro O, Hanafusa N, et al. Survival and predictive factors in dialysis patients with COVID-19 in Japan: a nationwide cohort study. Renal Replace Ther. 2020;6:55.
2. Hsu CM, Weiner DE, Aweh G, Miskulin DC, Manley HJ, Stewart C, Ladik V, et al. COVID-19 among US dialysis patients: risk factors and outcomes from a national dialysis provider. Am J Kidney Dis. 2021;77:748–56.
3. El Karoui K, De Vriese AS. COVID-19 in dialysis: clinical impact, immune response, prevention, and treatment. Kidney Int. 2022;101:883–94.
4. Miyazaki R, Miyagi K, Yoshida M, Suzuki Y. Humoral response after BNT162b2 vaccine in Japanese hemodialysis patients. Ren Replace Ther. 2023;9:13.
5. Ikizler TA, Coates PT, Rovin BH, Ronco P. Immune response to SARS-CoV-2 infection and vaccination in patients receiving kidney replacement therapy. Kidney Int. 2021;99:1275–9.
6. Toapanta N, Bestard O, Soler MJ. SARS-CoV-2 vaccination in patients receiving kidney replacement therapies: Where are we now with the protective immune response? Nephrol Dial Transplant. 2021;36:1950–4.
7. Carr EJ, Kronbichler A, Graham-Brown M, Abra G, Argyropoulos C, Harper L, et al. Review of early immune response to SARS-CoV-2 vaccination among patients with CKD. Kidney Int Rep. 2021;6:2292–304.
8. Toda M, Yoshifuji A, Kikuchi K, et al. Factors associated with SARS-CoV-2 antibody titers and prognosis of breakthrough infection in hemodialysis patients. Clin Exp Nephrol. 2022;26:571–80.
9. Kanai D, Wakui H, Haze T, et al. SARS-CoV-2 spike protein antibody titers 6 months after SARS-CoV-2 mRNA vaccination among patients undergoing hemodialysis in Japan. Clin Exp Nephrol. 2022;26:988–96.
10. Kitamura M, Takazono T, Yamamoto K, et al. Low humoral immune response to the BNT162b2 vaccine against COVID-19 in nursing home residents undergoing hemodialysis: a case–control observational study. Ren Replace Ther. 2022;8:8.
11. Matsunami M, Suzuki T, Fukuda J, et al. Comparison of antibody response following the second dose of SARS-CoV-2 mRNA vaccine in elderly patients with late-stage chronic kidney disease. Ren Replace Ther. 2022;8:13.
12. Hirai K, Shimotashiro M, Sonoda T, Okumura T, Ookawara S, Morishita Y. Factors associated with anti-SARS-CoV-2 spike antibody titers after a second BNT162b2 mRNA COVID-19 vaccination in Japanese hemodialysis patients. Clin Exp Nephrol. 2022;26:925–32.
13. Barouch DH. Covid-19 vaccines—immunity, variants. Boosters N Engl J Med. 2022;387:1011–20.
14. Haruta M, Otsubo S, Otsubo Y. Characteristics of the 6th Japanese wave of COVID-19 in hemodialysis patients. Ren Replace Ther. 2022;8:61.
15. Attias P, Sakhi H, Rieu P, Soorkia A, Assayag D, Bouhroum S, et al. Antibody response to the BNT162b2 vaccine in maintenance hemodialysis patients. Kidney Int. 2021;99:1490–2.
16. Yanay NB, Freiman S, Shapira M, Wishahi S, Hamze M, Elhaj M, et al. Experience with SARS-CoV-2 BNT162b2 mRNA vaccine in dialysis patients. Kidney Int. 2021;99:1496–8.
17. Perkmann T, Perkmann-Nagele N, Koller T, Mucher P, Radakovics A, Marculescu R, et al. Anti-spike protein assays to determine SARS-CoV-2 antibody levels: a head-to-head comparison of five quantitative assays. Microbiol Spectr. 2021;9(1):e0024721. https://doi.org/10.1128/Spectrum.00247-21.
18. Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol. 2021;16:1037–42.
19. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993;4:1205–13.
20. Borah MF, Schoenfeld PY, Gotch FA, Sargent JA, Wolfsen M, Humphreys MH, et al. Nitrogen balance during intermittent dialysis therapy of Uremia. Kidney Int. 1978;14(5):491–500.
21. Shinzato T, Nakai S, Miwa M, Iwayama N, Takai I, Matsumoto Y, et al. New method to calculate creatinine generation rate using pre- and post-dialysis creatinine concentrations. Artif Organs. 1997;21:864–72.
22. Food and Drug Administration. Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical. http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf. Accessed Dec 2011.
23. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. Bone Marrow Transplant. 2013;48:452–8.
24. Herman-Edelstein M, Ben-Dor N, Agur T, Guetta T, Raiter A, Meisel E, et al. BNT162b2 booster vaccination induced immunity against SARS-CoV-2 variants among hemodialysis patients. Vaccines. 2022;10:967.
25. Zou Y, Huang D, Jiang Q, Guo Y, Chen C. The vaccine efficacy against the SARS-CoV-2 Omicron: a systemic review and meta-analysis. Front Public Health. 2022;10:940956.
26. Momeni A. The best method of hepatitis B vaccination in hemodialysis patients? J Renal Inj Prev. 2013;2:125–6.

27. Bensouna I, Caudwell V, Kubab S, Acquaviva S, Pardon A, Vittoz N, et al. SARS-CoV-2 antibody response after a third dose of the BNT162b2 vaccine in patients receiving maintenance hemodialysis or peritoneal dialysis. Am J Kidney Dis. 2022;79:185–92.
28. Verdier JF, Boyer S, Chalmin F, Jeribi A, Egasse C, Maggi MF, et al. Response to three doses of the Pfizer/BioNTech BNT162b2 COVID-19 vaccine: a retrospective study of a cohort of haemodialysis patients in France. BMC Nephrol. 2022;23:189.
29. Agur T, Zingerman B, Ben-Dor N, Alkeesh W, Steinmetz T, Rachamimov R, et al. Humoral response to the third dose of BNT162b2 COVID-19 vaccine among hemodialysis patients. Nephron. 2022. https://doi.org/10.1159/000525519.
30. Garcia P, Han J, Montez-Rath ME, Sun S, Shang T, Parsonnet J, et al. SARS-CoV-2 booster vaccine response among patients receiving dialysis. Clin J Am Soc Nephrol. 2022;17:1036–8.
31. Yoshifuji A, Toda M, Ryuzaki M, Oyama E, Kikuchi K, Kawai T, et al. T-cell response and antibody production induced by the COVID-19 booster vaccine in Japanese chronic kidney disease patients treated with hemodialysis. Vaccines. 2023;11:653.
32. Kanai D, Wakui H, Haze T, Azushima K, Kinguchi S, Kanaoka T, et al. Improved immune response to the third COVID-19 mRNA vaccine dose in hemodialysis patients. Kidney Int Rep. 2022;7:2718–21.
33. Kawashima M, Saito H, Nishiuchi T, Yoshimura H, Wakui M, Tani Y, et al. Antibody and T-cell responses against SARS-CoV-2 after booster vaccination in patients on dialysis: a prospective observational study. Vaccines. 2023;11:260.
34. Espi M, Charmetant X, Barba T, Mathieu C, Pelletier C, Koppe L, et al. A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. Kidney Int. 2022;101:390–402.
35. Grzegorzewska AE. Hepatitis B vaccination in chronic kidney disease: review of evidence in non-dialyzed patients. Hepat Mon. 2012;12:e7359.
36. Panizo N, Albert E, Giménez-Civera E, Puchades MJ, D'Marco L, Gandía-Salmerón L, et al. Dynamics of SARS-CoV-2-Spike-reactive antibody and T-cell responses in chronic kidney disease patients within 3 months after COVID-19 full vaccination. Clin Kidney J. 2022;15:1562–73.
37. Higuchi T, Oka S, Furukawa H, Tohma S. Associations of HLA polymorphisms with Anti-SARS-CoV-2 spike and neutralizing antibody titers in Japanese rheumatoid arthritis patients vaccinated with BNT162b2. Vaccines. 2023;11:404.

Publisher's Note