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ORIGINAL ARTICLE

Antibody response to mRNA SARS-CoV-2 vaccines in haemodialysis patients

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ABSTRACT

Background. Some studies have shown an attenuated immune response in haemodialysis patients after vaccination. The present study examines the humoral response after mRNA vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in a large population of haemodialysis patients from different outpatient dialysis centres.

Methods. We retrospectively assessed antibodies against SARS-CoV-2 spike protein and nucleocapsid protein (chemiluminescence immunoassays, Roche diagnostics) 3–6 weeks after the second mRNA vaccine dose in 179 maintenance haemodialysis and 70 non-dialysis patients (control cohort). Differences in anti-SARS-CoV-2 spike protein titers were statistically analysed with respect to patient-relevant factors, including age, gender, previous coronavirus disease 2019 (COVID-19) infection, systemic immunosuppressive therapy and time on dialysis.

Results. We found a favourable, but profoundly lower SARS-CoV-2 spike protein antibody response in comparison with a non-dialysis cohort (median 253.5 versus 1756 U/mL, $P < 0.001$). In multivariate analysis, previous COVID-19 infection ($P < 0.001$) and female gender were associated with a significantly higher vaccine response ($P = 0.006$) in haemodialysis patients, while there was a significant inverse correlation with increasing patient age and systemic immunosuppression ($P < 0.001$). There was no statistically significant correlation between the antibody titer and time on dialysis. Immune response in haemodialysis patients with a previous COVID-19 infection led to substantially higher antibody titers that were equal to those of vaccinated non-dialysis individuals with previous infection.

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Conclusion. We strongly argue in favour of regular antibody testing after COVID-19 vaccination in haemodialysis patients. Further studies should elucidate the utility of booster vaccinations to foster a stronger and persistent antibody response.

Keywords: antibody response, haemodialysis, immunosuppression, SARS-CoV-2, vaccination

INTRODUCTION

Dialysis patients represent a particularly vulnerable population during the coronavirus disease 2019 (COVID-19) pandemic. Given that most patients receive in-centre dialysis, they are not able to self-isolate and are regularly exposed to potential contagious individuals, for example healthcare workers or other patients. This results in a higher seroprevalence rate in this cohort [1, 2]. Furthermore, a severe course and a potential lethal outcome are more likely in the event of an infection due to multimorbidity in immunocompromised dialysis patients [3, 4]. Thus, current vaccination strategies prioritize dialysis patients.

However, data on the safety and efficacy of COVID-19 vaccines in dialysis patients are scarce due to the exclusion of this specific cohort in the registration studies [5]. Although vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has proven to prevent severe COVID-19 infection in the general population [6, 7], the restricted immune response of dialysis patients in general might adversely affect efficacy of the vaccination against SARS-CoV-2. After COVID-19 infection, 10% of dialysis patients showed no antibody response [8], or a lack of neutralizing antibodies [9]. An altered and weaker immune response has also been shown for other vaccines like influenza or hepatitis B [10, 11], which in the case of hepatitis B led to strategies of identifying individuals at risk by regular measurement of antibody status and of using increased doses or booster vaccinations [12].

Therefore, measuring the immune response after vaccination against SARS-CoV-2 in dialysis patients is highly relevant for clinical management. In this study, we examined the immune response after vaccination with mRNA vaccines against SARS-CoV-2 in haemodialysis patients with and without previous COVID-19 infection in comparison with patients not requiring dialysis. To evaluate potential confounders, demographics, comorbidities and use of immunosuppressive medication were assessed.

MATERIALS AND METHODS

Study setting

The present study took place in five different outpatient dialysis centres. Individuals aged ≥18 years who received full COVID-19 mRNA vaccination according to the license between January and March 2021 and who had SARS-CoV-2 antibody response measured were retrospectively analysed. The local institutional review board of the LMU Munich approved the study (No. 21-0358).

Laboratory testing

SARS-CoV-2 antibody testing was performed 3–6 weeks after the second vaccine dose with chemiluminescence immunoassays designed to detect antibodies against the SARS-CoV-2 spike protein (Elecsys Anti-SARS-CoV-2 S, Roche Diagnostics, Mannheim, Germany) and antibodies against the SARS-CoV-2 nucleocapsid protein (Elecsys Anti-SARS-CoV-2 N, Roche Diagnostics). Seroconversion in SARS-CoV-2 infection yields antibodies targeting both the spike and nucleocapsid proteins, while SARS-CoV-2 vaccination (without previous infection) only leads to the presence of antibodies against the spike protein. Testing was performed in the Institute of Laboratory Medicine of the University Hospital Munich. According to the manufacturer's specifications, anti-SARS-CoV-2 S titers ≥0.8 U/L are considered reactive (sensitivity 98.8% and specificity 99.9%).

Data evaluation and statistical analysis

Due to the high rate of asymptomatic SARS-CoV-2 histories, patients with a previously positive PCR result as well as positive antibody reactions to the SARS-CoV-2 nucleocapsid protein were considered previously infected. Differences in anti-SARS-CoV-2 S titers were analysed using a Mann–Whitney *U*-test. Patients' characteristics were compared between groups using a Mann–Whitney *U*-test for numerical data and a Pearson's Chi-square test for categorical data. Univariate regression analyses with log10-transformed anti-SARS-CoV-2 S antibody titers as outcome were performed to calculate standardized effects of given covariates. Significance given by P-values was computed using Wald's test. Standardized effects of covariates on log10-transformed anti-SARS-CoV-2 S as dependent variables were computed by multivariate regression analyses with age, sex, previous COVID-19 infection, time on dialysis and use of systemic immunosuppressive therapy as independent variables. P-values were computed by using Wald's test. The R programming language was used for statistical analysis (Versions 4.0.2).

RESULTS

Demographic and clinical data

The study population consisted of 179 haemodialysis patients and 70 patients without dialysis (consisting of patients on low-density lipoprotein apheresis, kidney transplant patients and medical visits of healthcare workers, named control). Approximately 6% and 4% of the patients with and without dialysis, respectively, had laboratory-confirmed evidence of SARS-CoV-2 infection prior to vaccination. From a total of 249 vaccinated patients, 247 were immunized with the BNT162b2 vaccine from Pfizer–BioNTech (Mainz, Germany) and 2 with the mRNA-1273 vaccine from Moderna (Cambridge, MA, USA). Patients who received systemic immunosuppressive therapy (calcineurin inhibitor, $n = 9$; mycophenolic acid, $n = 4$; prednisolone, $n = 7$; everolimus, $n = 1$; rituximab; $n = 2$; and hydroxyurea, $n = 1$; usually as combination therapy) were equally prevalent among both groups. Vaccinated haemodialysis patients had been on dialysis treatment for a median of 42 months, the median age was 75 years and 64% of the haemodialysis patients were male. Detailed patients' characteristics can be found in Table 1.

Antibody response

The majority of haemodialysis patients (96.6%) and controls (97.1%) developed a detectable humoral antibody response

Table 1. Patient characteristics

	Patients without dialysis ($n = 70$)	Patients with haemodialysis ($n = 179$)	P-value[a]
Age, median (Q1–Q3) (years)	53 (42–60)	75 (64–82)	<0.001
Male gender, *n* (%)	15 (21.4)	114 (63.7)	<0.001
Previous SARS-CoV-2 infection, *n* (%)	3 (4.3)	11 (6.1)	0.567
Anti-SARS-CoV-2 nucleocapsid protein response	3 (4.3)	10 (5.6)	0.678
Anti-SARS-CoV-2 S response in females (≥0.8 U/mL), *n* (%)	54 (98.2)	63 (96.9)	0.660
Anti-SARS-CoV-2 S response in males (≥0.8 U/mL), *n* (%)	14 (93.3)	110 (96.5)	0.551
Anti-SARS-CoV-2 S response in uninfected female patients, median (Q1–Q3) (U/mL)	1832 (1082.8–2392.3)	302 (82.5–799.5)	<0.001
Anti-SARS-CoV-2 S response in previously infected female patients, median (Q1–Q3) (U/mL)	10 650 (6640–12 825)	51 475 (26 917.8–74 612.5)	0.024
Anti-SARS-CoV-2 S response in uninfected male patients, median (Q1–Q3) (U/mL)	1285 (706.5–2467.5)	233 (42–643)	<0.001
Anti-SARS-CoV-2 S response in previously infected male patients, median (Q1–Q3) (U/mL)	n.a.	1900 (240–15 400)	n.a.
History of organ transplantation, *n* (%)	4 (5.7)	13 (7.3)	0.663
History of cancer, *n* (%)	n.d.	37 (20.7)	n.a.
Diabetes, *n* (%)	n.d.	54 (30.2)	n.a.
Systemic immunosuppression, *n* (%)	4 (5.7)	9 (5.0)	0.827
Cumulative time on haemodialysis, median (Q1–Q3) (months)	n.a.	42 (20.0–69.5)	n.a.

[a]Significance given by P-values was computed using Mann–Whitney *U*-test for numeric data and Pearson's chi-square test for categorical data. Q1, lower quartile; Q3, upper quartile; n.a., not applicable; n.d., not determined.

(anti-SARS-CoV-2 S titer ≥0.8 U/mL) measured 3–6 weeks after completion of vaccination. We observed significant differences in SARS-CoV-2 S subunit antibody response between the subgroups. Previously uninfected control patients had significantly higher anti-SARS-CoV-2 S titers when compared with uninfected haemodialysis patients [median (Q1–Q3) 1756 (971.5–2436.5) versus 253.5 (64.2–679.0) U/mL, $P < 0.001$]. Overall, 54% of the haemodialysis patients had a titer below the lowest anti-SARS-CoV-2 S titer of 299 U/L in the group of control patients (excluding immunosuppressed patients). The median anti-SARS-CoV-2 S titer in patients with systemic immunosuppressive therapy was 114 U/L for non-dialysis patients and 8 U/L in the haemodialysis group. In contrast, the highest antibody response was observed in patients receiving vaccination after previous SARS-CoV-2 infection. Figure 1 and Supplementary data, Figure S1 show the anti-SARS-CoV-2 S titers in the different subgroups using boxplots. An increase of anti-SARS-CoV-2 S titers was not observed with time after vaccination within the selected time period (Supplementary data, Figure S2).

On multivariate analysis, female gender and previous COVID-19 infection were associated with a significantly higher vaccine response, while there was a significant inverse correlation with increasing patients' age and systemic immunosuppressive therapy. Time on dialysis was not associated with the antibody response (Table 2).

DISCUSSION

Dialysis patients are generally immunocompromised, resulting also in an impaired response to vaccinations, such as hepatitis B. Additional risk factors for a low antibody response in these patients are immunosuppressive therapy and previous chemotherapy. Our data demonstrate that mRNA-based COVID-19 vaccines, unlike hepatitis B and influenza vaccination, elicit a substantial antibody response in the dialysis population. However, their humoral response is significantly lower than in non-dialysis patients or healthcare workers, which has been also shown in other studies [13–15].

Furthermore, haemodialysis patients with prior COVID-19 infection showed a more pronounced vaccine response than their previously uninfected counterparts—leading to antibody titers equal to non-dialysis vaccinated individuals. Such a booster effect of the vaccination has also been described in healthcare workers with past infection [16], where higher titers in neutralizing antibodies were observed after a single dose of vaccine in contrast to healthcare workers without prior infection who had received the second dose of the vaccine [17]. In contrast, patients on immunosuppressive therapy are less likely to mount adequate antibody titers, as it has been observed in patients with solid organ transplants [18]. However, we did not measure baseline antibody levels for comparison.

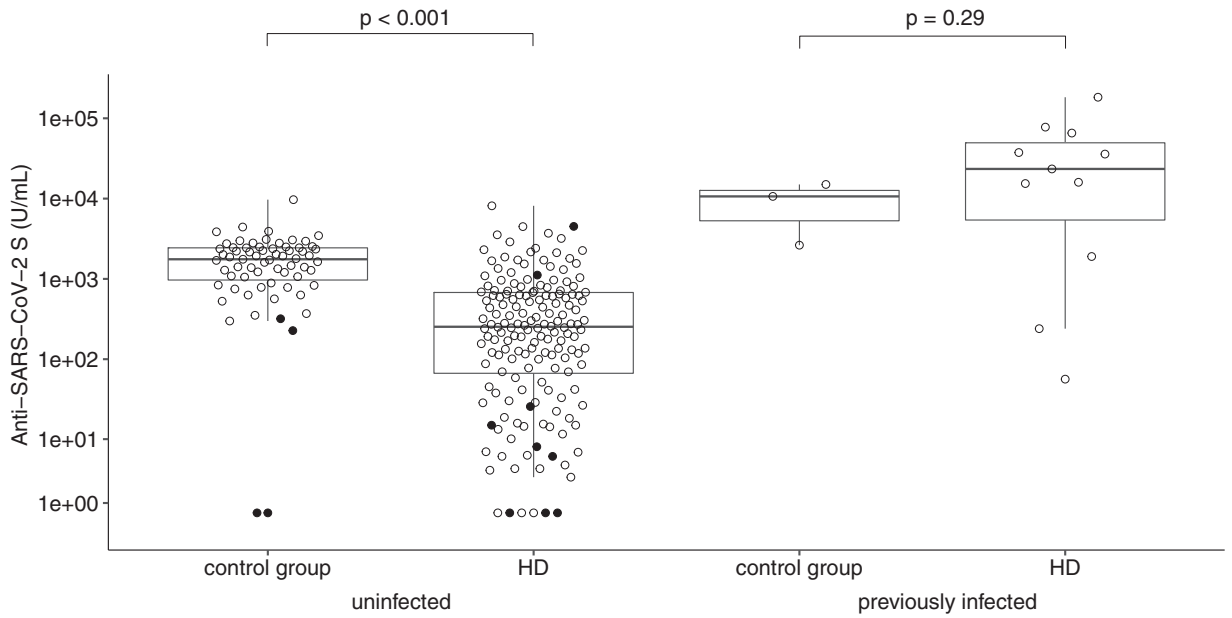

FIGURE 1: Antibody response in individuals previously vaccinated with mRNA-based COVID-19 vaccines. Shown are anti-SARS-CoV-2 S antibody titers in uninfected patients and with previous laboratory-confirmed SARS-CoV-2 infection. The box shows the interquartile range, the horizontal line inside the box represents the median values, whiskers represent minimum and maximum range of points within 1.5 times the interquartile range in the box. Antibody titers in samples obtained from individual patients receiving systemic immunosuppressant therapy are presented as solid circles. HD, haemodialysis patients.

Table 2. Univariate and multivariate analyses of factors influencing the mRNA-based COVID-19 vaccination anti-SARS-CoV-2 S response in haemodialysis patients ($n = 179$)

	Univariate			Multivariate		
Parameters	Standardized beta	95% CI	P-value[a]	Standardized beta	95% CI	P-value[a]
Age (years)	−0.18	−0.32, −0.03	0.017	−0.19	−0.32, −0.07	0.003
Female gender	0.34	0.03, 0.64	0.031	0.37	0.10, 0.63	0.006
Previous SARS-CoV-2 infection	1.79	1.23, 2.34	<0.001	0.94	0.54, 1.34	<0.001
Systemic immunosuppression	−1.31	−1.96, −0.66	<0.001	−1.63	−2.19, −1.07	<0.001
Cumulative time on haemodialysis (months)	−0.07	−0.22, 0.08	0.489	−0.02	−0.15, 0.11	0.759

[a]Significance given by P-values was computed using Wald's test. CI, confidence interval.

In our study, age and male gender were associated with a lower SARS-CoV-2 antibody response, supporting the findings of three recently published smaller studies [13–15]. Larger studies may address this question in greater detail.

A limitation of the study is that we could not evaluate cellular immunity (especially memory T cells), which contributes importantly to the longevity of immunity against SARS-CoV-2. A recent study by Sattler *et al.* [19] suggests that in addition to the humoral response, the T cell response is also compromised. Furthermore, there are no data on the duration of the SARS-CoV-2 seroconversion in dialysis patients or the rate of SARS-CoV-2 infection after vaccination.

However, in analogy to the general population, decreasing antibody titers, decreasing protection from SARS-CoV-2 infection and the need for subsequent booster vaccinations may be expected. Due to the high risk dialysis patients face in case of a COVID-19 infection, we argue in favour of regular assessment of quantitative antibody titers over time. Further investigation is needed to determine whether dialysis patients with a lower immune response might benefit from an additional booster vaccination. This would be in line with our finding that dialysis patients with a prior infection had a much higher antibody response than their naïve companions. Our data are supported by the recent work of Krammer *et al.* [20] showing stable and high antibody titers after a single-shot vaccination in seropositive individuals. Further studies should link antibody response and cellular immunity in order to broaden our understanding of the efficacy of the vaccination in the future [21].

In summary, in this study, we report a favourable antibody response after mRNA vaccination against SARS-CoV-2 in haemodialysis patients. However, the immune response of haemodialysis patients is lower compared with healthy individuals,

except for the immune response of haemodialysis patients with prior COVID-19 infection.

This argues in favour of a booster effect and suggests that measurement of the antibody response may be of clinical utility. Further studies should clarify the role of booster vaccinations to foster a stronger and persistent antibody response in haemodialysis patients. In particular, patients with low or no response and therefore a high risk of an infection might benefit from regular antibody testing and intensified vaccine schedules.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

ETHICS APPROVAL

The Ethical Review Committee of the Ludwig-Maximilians-University Munich approved the study (document number KB 21-0358).

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

M.F. and U.S. provided conceptualization, writing—review and editing and supervision. M.P., F.M.A., S.H. and B.N. contributed the methodology. M.P., F.M.A., T.L., S.H. and B.N. performed the formal analysis. T.L., J.K., D.S.-R., J.S.-O., W.B., M.T., G.v.G., N.T., S.R., D.T. and M.B. contributed resources. U.S., S.H., M.P. and M.F. were involved in writing—original draft preparation. F.M.A. and S.H. performed visualization.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest to declare. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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