Equivalent humoral and cellular immune response but different side effect rates following SARS-CoV-2 vaccination in peritoneal and hemodialysis patients using mRNA vaccines

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Successful SARS-CoV-2 vaccination is especially critical to the vulnerable dialysis patient population. To date, no SARS-CoV-2 vaccination related immune response data directly comparing hemodialysis (HD) with peritoneal dialysis (PD) patients are available.

We report a subanalysis of the observational, multicenter cohort Dia-Vacc study (NCT04799808) comparing COVID-19 vaccination related humoral as well as T-cellular immune responses as well as clinical side effects at 8 weeks after two vaccinations using BNT162b2 mRNA or mRNA-1273 vaccines.

SARS-CoV-2 specific IgG- or IgA-antibody reactions against the Spike protein subunit S1 and IgG-antibodies against the nucleocapsid protein subunit as well as the receptor binding domain (RBD) antibody formation suggesting virus neutralizing activity were analyzed before and eight weeks after start of vaccination. In a predefined subgroup, also the cellular immune response was measured using a SARS-CoV-2 specific interferon-γ release assay (IGRA).

Since vaccine type distribution was relevant for the immune response and not balanced in the 58 PD and 1168 HD patient cohort, we matched the 58 PD with 232 HD patients by propensity scores. Logistic regression analysis indicated no significant difference in humoral (anti-Spike or RBD antibodies) or T-cellular response (IGRA) after vaccination between matched PD and HD participants. In contrast, vaccination related clinical side effects such as fever and arm pain occurred more often in PD than in HD patients (OR = 3.45, 95%CI[1.95;6.16]).

In conclusion, no difference in COVID-19 mRNA vaccination related adaptive immune responses can be observed in PD and HD patients, while typical clinical side effects appear reduced in HD patients.

Significance Statement

Increased rates of vaccination failure have been reported in “immunocompromised” dialysis patients (DP) being likely related to uremia, inadequate dialysis, use of low biocompatibility dialysis material, hyperparathyroidism, anemia, iron overload and malnutrition. While seroconversion rates to COVID-19 mRNA vaccination appeared in the range of 95% after two vaccinations, many procedural differences between hemo- (HD) and peritoneal dialysis (PD) could differentially influence immune response or clinical side effect rates. In our study, development of a positive seroconversion response to vaccination did not depend on the type of dialysis. In contrast, development of typical vaccination side effects was markedly decreased in HD compared to PD patients, which may potentially be related to pain reception and/or differences in pain-/pyresis-related immune responses.

Dialysis patients (DP) are an especially vulnerable population experiencing a high percentage of complicated COVID-19 disease course with a mortality of about 20%[1]. In the general population, modern COVID-19 vaccines such as BNT162b2 mRNA (Pfizer/BioNTech) or mRNA-1273 (Moderna) have demonstrated COVID-19 related protection rates up to 95% after two vaccinations. While vaccination success rates against other diseases, such as hepatitis B, are known to be markedly reduced in DP compared to the general population[2], we[3] and others[4, 5] demonstrated high seroconversion rates around 90% after two vaccinations with COVID-19 mRNA vaccines. Most likely referring to severe procedural differences, immune reactivity differences between hemodialysis (HD) and peritoneal dialysis (PD) patients have been described after hepatitis B vaccination[6]. We present here a subanalysis of the German, observational, multicenter cohort Dia-Vacc study (NCT04799808) comparing COVID-19 vaccination related humoral and T-cellular immune responses as well as clinical side effects at 8 weeks after two vaccinations using BNT162b2 mRNA or mRNA-1273 vaccines.

The Dia-Vacc study enrolled 3101 participants from medical personnel, kidney transplant recipients, and dialysis patients. Besides clinical characteristics such as vaccination side effects, the study primarily observed the humoral and cellular immune responses of the participants after COVID-19 disease and/or vaccination with either of Pfizer/BioNTech - BNT162b2 mRNA or Moderna - mRNA-1273 vaccines[3]. In all study participants, COVID-19 specific IgG- or IgA-antibodies against the Spike protein subunit S1 and IgG-antibodies against the nucleocapsid protein subunit (NCP, to exclude previous and current infection) as well as the receptor binding domain (RBD) antibody formation (all by Euroimmun) were analyzed before and eight weeks after the start of vaccination[3]. The primary study end point was a positive serologic response as defined by either *de novo* IgG- or IgA antibody development (seroconversion) against the Spike protein. In a predefined subgroup, also the cellular immune response was measured using a COVID-19 specific interferon-γ release assay (IGRA, Euroimmun[3]). A more detailed description of the study design and methodology can be viewed in the original manuscript[3] and supplementary material.

Our vaccination-related dialysis cohort with a complete data set consisted of 58 PD and 1168 HD patients (baseline characteristics are provided in Tables 1A, S1). Hereby, we analyze the humoral and cellular immune response and incidence of vaccination side effects in these two groups. In the sequel, the significance level of 5% (two-sided) is used. In the main study, the humoral response was found to be positive in 88% of PD and 96% of HD patients (Tables 1B, S1). Although this difference is statistically significant ($\chi^2(1)$ = 5.39, p = 0.02), the association between humoral response and type of dialysis becomes non-significant after the vaccine type is taken into account (Table S2). This confounding is clearly captured by a good fit of the log-linear model of conditional independence[7] of the humoral response and type of dialysis given the vaccine type (Table S2). To account for a non-balanced vaccine distribution between HD and PD groups ($\chi^2(1)$ = 43.555, p < 0.001), and a strong association of vaccine type and humoral response [3], we, therefore, matched 58 PD with 232 HD patients by propensity scores (Table 1A). Based on the logistic regression model with type of dialysis and propensity score as predictors, the type of dialysis effect estimate indicates no significant difference in the humoral response between matched HD and PD participants (Table 1B). The analysis of association between RBD antibodies and type of dialysis and between IGRA and type of dialysis was conducted in the same manner, and no significant differences between the two types of dialysis in the matched cohorts were detected (Table 1B).

In the DiaVacc study, the vaccination side effects were recorded following each of the two vaccinations (Table 1B, S2, second followed first vaccination after three weeks for BNT162b2 mRNA and four weeks for 1273 mRNA). Overall, side effects occurred more often in PD patients than in HD patients (OR = 3.45, 95%CI [1.95;6.16]). The side effect frequency in PD patients was similar to the rate in the medical personnel in our original study[3] ($\chi^2(1)$ = 0.828, p = 0.363) and to the rate of 70% in the general population[8] (p = 0.044). The HD patients seem to experience typical symptoms such as fever, shivering or arm pain less frequently, and their overall incidence of side effects was much lower than 70% (p < 0.001). This difference in the incidence of side effects remained considerable between matching PD/HD sub-cohorts (Table 1B). These profound differences in vaccination side effects between HD and PD patients were unexpected, but may relate to the many procedural differences, where for example HD but not PD patients are used to repetitive puncture-related pain and to blood-membrane contact related chronic microinflammation. Whether these microinflammatory differences as described between PD and HD patients[9] may cause acquired hyporeactivity/tolerance of pyresis-related mediation systems specifically in HD patients is unclear. Further controlled studies will be needed to test these challenging hypotheses.

While our results are limited by the observational, non-randomized character of our study, no evidence for a difference in both humoral and cellular immune response rates between hemo- and

peritoneal dialysis patients was found after COVID-19 mRNA vaccination. In contrast, the incidence of typical vaccination side effects was lower in HD than in PD patients.

CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORS' CONTRIBUTIONS

JS and CH contributed to study design, recruitment, data collection, data interpretation, and drafting of the manuscript. AS, FG, HM, KF and TT were involved in data acquisition and collection or study organization. AK, RM were involved in statistical analysis and data management of the study. All authors have approved the final version for submission.

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Table 1A. Baseline characteristics of SARS-CoV-2 and -vaccine unexposed dialysis patients of the DIA-Vacc pure vaccination cohort before / after matching

Variable	*PD (N =58)*	*HD (all; N = 1168)*	*HD (matched; N = 232)*	*SMD (all data)*	*SMD (matched data)*
Vaccine type ("mRNA-1273")	29/58 (50%)	986/1168 (84%)	115/232 (50%)	-0.69	0.01
Taking IS drugs ("yes")	4/58 (7%)	56/1168 (5%)	20/232 (9%)	0.08	-0.07
Sex ("male")	38/58 (66%)	759/1168 (65%)	150/232 (65%)	0.01	0.02
Age (years)	60·84 ± 13.20	68.05 ± 13·88	63.64 ±13.02	-0.55	-0.21
BMI (kg/m^2)	27·08 ± 4·93	27·52 ± 5·72	26.82 ± 5.80	-0.09	0.05
Hepatitis B failure ("yes")	4/58 (7%)	259/1168 (22%)	15/232 (6%)	-0.60	0.02

Table 1B. Observed humoral, RBD, T-cell responses to vaccination, together with the odds ratios estimated using the logistic regression model for the matched data (with dialysis type and propensity score as predictors)

Variable	*PD (N = 58)*	*HD (all; N = 1168)*	*HD (matched; N = 232)*	*OR, 95%CI (matched data, ref=HD)*
Humoral response	43/49 (88%)	1018/1062 (96%)	200/217 (92%)	0.63 [0.23; 1.70]
IGG response	43/49 (88%)	1009/1062 (95%)	199/217 (92%)	0.67 [0.24; 1.80]
IGA response	40/49 (82%)	959/1062 (90%)	182/217 (84%)	0.88 [0.38; 1.99]
RBD response	38/41 (93%)	893/959 (93%)	147/160 (92%)	1.13 [0.30; 4.18]
IGRA response	13/16 (81%)	79/102 (77%)	27/36 (75%)	1.68 [0.36; 7.71]
Clinical side effects, T1	19/58 (33%)	96/1168 (8%)	34/232 (15%)	2.77 [1.40; 5.47]
Clinical side effects, T2	28/58 (48%)	274/1168 (23%)	53/232 (23%)	3.15 [1.72; 5.75]
Clinical side effects, either T1 or T2	33/58 (57%)	323/1168 (28%)	70/232 (30%)	3.01 [1.66; 5.45]

PD = peritoneal dialysis; HD = hemodialysis; SMD = standardized mean difference. OR = odds ratios. IS = immunosuppressive; Hepatitis B vaccination failure definition - patients with unsuccessful vaccination after at least four attempts. Humoral vaccination responses were assessed as positive, when de novo production of the antibody to the Spike S1 (IgA or IgG) protein (humoral response) or receptor binding domain (IgG) subunit (RBD response) was measured. IGRA response = positive vaccination-related T-cellular reactivity using Interferon-*γ* release assay (cut off value above 100 mIU/ml); T1 = 3-4 weeks after first and immediately before second vaccination; T2 = 8 weeks after first vaccination. The data analysis was performed using R version 4.0.1[10]. The propensity score matching was carried out using the R-package *MatchIt*[11]