Impaired immune response to SARS-CoV-2 vaccination in dialysis patients and in kidney transplant recipients

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KEY POINTS

- Immune response to COVID-19 vaccination is significantly reduced in kidney failure patients compared to controls without kidney failure.
- After 2 vaccinations, kidney transplant recipients show the lowest levels of SARS-CoV-2-specific IgGs with the lowest neutralizing capacity.
- These data suggest that vaccination strategies need modification in kidney transplant recipients and dialysis patients.

ABSTRACT

Background Kidney failure patients on dialysis or after renal transplantation have a high risk for severe COVID-19 infection and vaccination against SARS-CoV-2 is the only expedient prophylaxis. Generally, immune responses are attenuated in kidney failure patients, however, systematic analyses of immune responses to SARS-CoV-2 vaccination in dialysis patients and in kidney transplant recipients (KTR) are still missing.

Methods In this prospective multicentric cohort study, antibody responses COVID-19 mRNA vaccines (BNT162b2; Biontech/Pfizer or mRNA-1273; Moderna) were measured in 32 dialysis patients and in 28 KTRs. SARS-CoV-2-specific antibodies and neutralization capacity were evaluated and compared to controls (n=78) in a similar age-range.

Results After the first vaccination, SARS-CoV-2-specific antibodies were nearly undetectable in kidney failure patients. After the second vaccination, 93% of the controls and 88% of dialysis patients but only 37% of KTRs developed SARS-CoV-2-specific IgG above cut-off. Moreover, mean IgG levels were significantly lower in KTRs (54±93 BAU/ml) compared to dialysis patients (503±481 BAU/ml, p<0.01). Both KTRs as well as dialysis patients had significantly lower IgG levels compared to controls (1992±2485 BAU/ml; p<0.001 and p<0.01). Importantly, compared to controls, neutralizing antibody titers were significantly lower in KTRs and dialysis patients. After the second vaccination, 76% of KTRs did not show any neutralization capacity against SARS-CoV-2 suggesting impaired seroprotection.

Conclusions Kidney failure patients show a significantly weaker antibody response compared to controls. Most strikingly, only one out four KTRs developed neutralizing antibodies against SARS-CoV-2 after two doses of vaccine. These data suggest that vaccination strategies need modification in kidney transplant and dialysis patients.
Introduction

Although great effort has been made to develop effective strategies to prevent severe courses of COVID-19, the options to treat such patients are still disappointing. Prophylactic vaccination against acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) became the most effective protection against COVID-19. Patients with renal replacement therapy receiving dialysis or after renal transplantation belong to the highest risk group for a severe course of COVID-19 and consequently are dying from COVID-19. A general concept to protect these patients against COVID-19 is to prioritize dialysis patients and kidney transplant recipients (KTR) for vaccination. Until now, studies investigating immune responses to SARS-CoV-2 vaccination for patients with kidney failure are sparse. Moreover, these groups had been excluded from the main vaccine outcome studies. However, experience from other vaccination programs showed an impaired immune response in dialysis patients and in KTRs taking immunosuppressive therapy. Consequently, vaccination strategies against these infectious diseases have been modified by administering higher doses or changing the dosing interval to increase the immune response. Therefore, it is anticipated that the immune response to SARS-CoV-2 vaccination is also less robust in dialysis patients and in KTRs. In the present prospective, multicentric observational study, we measured the humoral immune response to SARS-CoV-2 vaccination in dialysis patients and in KTRs and compared them with a control group with no evidence of kidney failure. Time course and intensity of the immune response after SARS-CoV-2 vaccination needs to be known to develop future vaccination strategies for this particular patient group.
Methods

Study population

The study was approved by the ethics committee of the Medical Faculty at the Heinrich-Heine University Düsseldorf, Germany (study numbers 2020-1237 and 2021-1287) and in line with the Declaration of Helsinki, as revised in 2013. In this multicenter, prospective, observational study (NCT04743947), we consecutively enrolled 32 patients receiving dialysis, 28 renal transplant recipients (KTRs) and 78 volunteers (controls) with no evidence of kidney failure from a nursing home who had received a vaccination appointment between the 26th of December 2020 and the 15th of March 2021 according to the effective rules of prioritization defined by the German government at that time.10

Clinical data were obtained from medical records or medical questionnaires for the control group. Exclusion criteria were: age < 18 years, inability to give consent and former SARS-CoV-2 infection. All participants signed a written informed consent. 78 of the previously described group of 176 volunteers were selected and matched in the following manner 10. First, they should not have any evidence of kidney failure. Second, controls were selected by their date of birth. For each patient of the KTR and each patient of the dialysis group all available controls (1 to 6 controls) with a date of birth within 12 months of the date of birth of the dialysis or transplant patients were included in the analysis. Age-matched controls were not available for 7 of 28 KTRs and for one of 32 dialysis patients. None of the participants had a COVID-19 infection in the past as determined by patient history and measurement of SARS-CoV-2 antibodies prior to vaccination.

In dialysis patients and KTRs, we decided to perform five visits (one before, two after the first vaccination and two after the second vaccination) to detect the vaccination-induced immune response and to monitor potential adverse events. Blood samples were taken when regarded clinically necessary. Side-effects after vaccination were scored semi-quantitative according to the sum of symptoms: i) elevated temperature and fever, ii) chills, iii) pain at the injection site, iv) head/limb pain, v) fatigue/tiredness, vi) nausea/dizziness, vii) other complaints (unscored).

All participants were vaccinated between 12/27/2020 and 04/9/2021. For the control group, the dialysis patients and KTRs, SARS-CoV-2 samples for antibody levels and neutralization titers (NT) were taken 19 (17-19), 20 (19-21) and 20 (19-20) days (median; IQR) after the first vaccination and 17, 14 (13-15), 14 (14-15) days (median, IQR) after the second vaccination, respectively. All specimens were stored at 4°C.
Samples processing
All samples from the participants were sequentially tested for Anti-SARS-CoV-2 antibodies as well as for SARS-CoV-2 neutralization efficacy (NT) at the Institute of Virology, University Hospital Düsseldorf, Germany. Samples were tested for Anti-SARS-CoV-2 antibodies using the commercially available test system Anti-SARS-CoV-2-QuantiVac-ELISA from Euroimmun measuring IgG levels against SARS-CoV-2 spike S1 subunit. According to the manufacturer’s instruction results < 25.6 BAU/ml were considered as negative, ≥ 25.6 BAU/ml ≤ 35.2 BAU/ml as indeterminate, and > 35.2 BAU/ml as positive (BAU = Binding Antibody Units). The upper detection limit for undiluted samples was > 384 BAU/ml, the lower detection limit was < 3.2 BAU/ml. For samples above the detection limit, 1:10 or 1:100 dilutions were performed in IgG sample buffer according to the manufacturer's instruction. An immunoassay (Elecsys from Roche or Architect from Abbott) for detection of IgGs recognizing SARS-CoV-2 nucleocapsid (N) was used to detect a previous SARS-CoV-2 infection.

An endpoint dilution neutralization test with the infectious SARS-CoV-2 isolate (EPI_ISL_425126) at a TCID 50 of 100 was performed in a BSL-3 facility as described previously to determine the SARS-CoV-2 neutralization capacity of the serum samples after the first and second vaccination\textsuperscript{11}. The neutralization titer was determined as the highest serum dilution without virus induced cytopathic effect (CPE).

Statistical Analyses
The data were analyzed using GraphPad Prism 7.0 (GraphPad Software, San Diego, CA, USA). D'Agostino & Pearson omnibus normality test was performed to test normal distribution. In the case of normally distribution, student t-test or one-way ANOVA followed by Holm-Sidak for multiple comparisons was used as appropriate. For non-normally distributed samples, data were analyzed by the non-parametric Mann-Whitney test or Kruskal-Wallis Test with post hoc Dunn test. For categorical data, the Fisher's exact test and the Chi-Square test was used to assess the statistical significance between groups. Correlations were tested by the Spearman's rank correlation coefficient.
Results

Participants’ characteristics
Twenty-eight KTRs, 32 dialysis patients and 78 volunteers were enrolled in this prospective, multicenter observational study. The median age (IQR) in KTRs was 66 years (61-81) and lower compared to dialysis patients with a median age of 83 years (80-85, p<0.01) and to controls with a median age of 84 years (80-87, p<0.001). Male sex was less prevalent in controls (29%) compared to dialysis patients (69%) and KTRs (71%) groups (Table 1).

31 patients received haemodialysis and one patient peritoneal dialysis. The median time (IQR) on dialysis was 3 (2-6) years. Two patients had a history of a previous kidney transplantation and 5 patients were still taking a low dose of immunosuppressive therapy.

In KTRs, median time (IQR) after renal transplantation was 10 (3-12) years. The average estimated GFR at the beginning of the study was 46±20 ml/min/1.73m². Twenty-two out of 28 patients (79%) were treated with a triple immunosuppressive treatment (table 1). Participants of the control group were either residents of a nursing home or their caregivers as described previously (Table 1) 10.

**Reduced SARS-CoV-2 spike specific IgG levels in patients on dialysis and kidney transplant recipients after the first and second vaccination.**

After the first vaccination, mean vaccination-induced SARS-CoV-2 spike S1 specific IgG levels were significantly lower in dialysis patients (30±72 BAU/ml, p<0.05) and in KTRs (10±24 BAU/ml, p<0.001) compared to the controls (81±125 BAU/ml) but did not differ between dialysis patients and KTRs (Fig. 1A). IgG levels above the cut-off (>35.2 BAU/ml) were detected only in two out of 28 KTRs (7%) and in 3 out of 32 patients on dialysis (11%), but in 33 out of 78 controls (42%) after the first vaccination.

After the second vaccination, IgG levels increased significantly in all groups. Nevertheless, differences in the vaccination-induced immune response as determined by SARS-CoV-2 spike S1 specific IgG became even more evident between the three groups. IgG levels were still significantly lower in KTRs (54±93 BAU/ml) compared to the dialysis (503±481 BAU/ml p<0.001) and the control group (1922±2485 BAU/ml p<0.001), respectively (Figure 1B). Moreover, IgG levels were significantly lower in dialysis patients compared to controls (p<0.01). IgG levels were found to be positive (>35.2 BAU/ml) in 73 out of 78 controls (94%) and in 28 out of 32 dialysis patients (88%) but only in 10 out of 28 KTRs (36%).

In order to define co-factors influencing the immune response after SARS-CoV-2 vaccination, differences between KTRs with positive SARS-CoV-2- spike S1 specific IgGs and KTRs with lower SARS-CoV-2 levels were analyzed. As shown in table 2, KTRs with positive IgG levels had been transplanted for a longer median time and were more often treated with a dual
immunosuppressive therapy compared to KTRs with IgG levels lower than 35.2 BAU/ml. Furthermore, to test whether age affects the IgG response in patients with kidney failure, a correlation analysis was performed. We did not find any correlation between IgG levels and age in patients on dialysis ($r=-0.06$, $p<0.74$) or in KTRs ($r=0.07$, $p<0.73$). Estimated GFR did not correlate with the IgG response in KTRs ($r=-0.10$, $p<0.63$). Five out of 28 KTRs did not receive antimetabolite immunosuppression therapy (Table 1). Four of these 5 patients (80%) showed a positive immune response, whereas only 6 out of 23 (26%) KTRs treated with mycophenolate or azathioprine showed a positive immune response ($p<0.05$).

**Reduced SARS-CoV-2 neutralizing capacity in patients with kidney failure compared to controls.**

To further characterize the specific humoral immune response after COVID-19 vaccination in patients with kidney failure, neutralization capacity was determined in dialysis patients as well as in KTRs and compared to controls. After the first dose of vaccination, neutralizing antibodies were not detectable in dialysis patients or KTR and in only 4 out of 78 controls (4%). After the second vaccination, the frequency of detectable neutralizing capacity increased in all three groups. Median neutralization titers (IQR) were significantly lower in dialysis patients (1:10; 0 to 1:20, $p<0.01$) and KTRs (0; 0 to 1:10, $p<0.001$) compared to controls (1:40; 1:10 to 1:320) (Figure 2A). Importantly, neutralizing responses were detected in 60 out of 78 control (77%), in 20 out of 32 dialysis patients (63%) but only in 6 out 28 KTRs (21%) suggesting an impaired seroprotection in KTRs ($p<0.001$ vs. control; $p<0.01$ vs. dialysis) (Figure 2B). Based on the low numbers of KTRs with neutralizing antibodies, a clear correlation between any co-factors and the occurrence of neutralizing antibodies could not be determined.

**Post-vaccination reactions in dialysis patients and kidney transplant recipients**

To assess post vaccination reactions in kidney failure and to detect a potential impact of the COVID-19 vaccination on renal function in KTRs, patients were seen 2-4 days after each vaccination. Reactions to vaccination after first and second dose did not differ substantially (Figure 3A and B). In 19 KTRs, eGFR values were measured before vaccination (43±16 ml/min/1.73m$^2$) as well as after the first (42±16 ml/min/1.73m$^2$) and second (40±16 ml/min/1.73m$^2$) vaccination. Estimated GFR did not differ significantly between the three time points.
Discussion

In this prospective multicenter study, we showed an impaired immune-response to the mRNA COVID-19 vaccines BNT162b2 (Biontech/Pfizer) and mRNA-1273 (Moderna) in patients receiving renal replacement therapy compared to controls with a similar age range. To our knowledge, this is the first prospective study, which analyses the humoral immune response to COVID-19 vaccination by measuring IgG levels and their neutralizing capacity in dialysis and renal transplant patients in comparison to participants without kidney failure. It is well known, that patients on dialysis or after kidney transplantation show a reduced immune response to different vaccines such as hepatitis B or influenza A virus subtype H1N1. The impaired humoral and cellular immunity may be caused by accumulation of uremic toxins in kidney failure and by the chronic intake of immunosuppressive drugs.

Here, we clearly showed that the humoral immune response measured by SARS-CoV-2 spike specific IgG levels as well as the neutralizing capacity of the antibodies was almost undetectable in patients with kidney failure two to three weeks after the first vaccination and significantly reduced compared to controls. Although some studies showed protection against COVID-19 infection after the first injection, our results indicate that patients receiving renal replacement therapy by dialysis or renal transplantation are much less protected after the first vaccination.

Two weeks after the second vaccination, a time point when full protection can be assumed, mean SARS-CoV-2 spike specific IgG levels were significantly lower in dialysis and lowest in KTRs compared to controls. This is highlighted by our finding, that only 37% of KTRs had developed IgG levels above cut-off 2 weeks after the second vaccination. In addition to IgG levels as a classical parameter for assessing humoral immune response, we measured the neutralizing capacities of these antibodies. Recent studies have shown that neutralizing antibodies are crucial for the defense against viruses like SARS-CoV-2. High neutralizing antibody levels seem to be relevant for protection against novel circulating SARS-CoV-2 escape variants. 77% of controls and 63% of the dialysis patients developed neutralizing antibodies, whereas only 24% of the KTRs showed some neutralization capacity after the second vaccination. While the percentage of dialysis patients attaining neutralizing capacity was not statistically different to that of controls, the median neutralizing antibody titers were significantly lower suggesting less seroprotection against SARS-Cov-2.

The highly significant lower levels of SARS-CoV-2 spike specific IgGs and neutralizing antibodies in KTRs suggest specific explanations. Previous studies have addressed the role of immunosuppressive drugs, renal function, and age. Thus, two observational studies in transplant patients showed a correlation between a reduced immune response to SARS-COV-2 vaccination with the use of antimetabolite immunosuppression such as...
mycophenolate and azathioprine as well as with impaired renal function. In the present study, we also found a positive signal for a reduced immune response and use of antimetabolite immunosuppression. There was no correlation between IgG levels and kidney function or age in KTRs.

Post-vaccination reactions were assessed in all three groups. Both vaccinations were well tolerated, and kidney function was not affected in KTRs. Therefore, vaccination against SARS-CoV-2 by an mRNA vaccine appears to be safe in kidney failure patients.

There are several strengths of the present study. First, samples from all patients were analyzed in the same laboratory using an identical protocol for quantification of IgG levels and neutralizing capacity. Second, all three groups are in a similar age range, with the lowest median in the KTRs. Since KTRs had also the lowest immune response to vaccination, an age-dependent bias towards better immunity in this group can be excluded. Third, the study was performed in a controlled, prospective manner with a similar protocol including time points of sampling and analysis in dialysis and KTRs.

The limitations of the present study are the relative low number of KTRs and the lack of the exploration of the cellular immune response in the cohorts.

However, the present study offers enough evidence that the humoral immune response to SARS-CoV-2 vaccination is significantly impaired in dialysis patients and in KTRs compared to controls. This suggests the need for modification of vaccination strategies for patients with kidney failure. In line with this suggestion, a recent observational study reported an additional effect of a third vaccination in KTRs with markedly attenuated antibody response after the second vaccination. In this study 6 of 30 KTRs (20%) had low detectable SARS-CoV-2 antibodies levels whereas the others did not show any response. This immune response pattern is similar to that found in our case series of 28 KTRs (5 of 28 KTRs with low detectable SARS-CoV-2 antibodies levels <35.2BAU/ml). Interestingly, those KTRs with detectable SARS-CoV-2 antibodies levels after the second vaccination, showed an effective immune response after the third vaccination. In contrast, the majority of patients with no detectable antibodies after the second vaccination did not benefit from the third vaccination. Thus, it would be plausible to recommend a third vaccination at least in KTRs with detectable SARS-CoV-2 antibodies levels after the second vaccination. Furthermore, it will be essential to identify modifiable factors to enhance the chance of a sufficient immune response to vaccination in KTRs. Our findings underpin the recommendation to vaccinate all patients against SARS CoV-2 on the transplant waiting list.
Disclosures

M. Schmitz reports the following: Honoraria: Daiichi-Sankyo. L. Rump reports the following: Consultancy Agreements: Boehringer, Bayer, Medtronic, ReCor; Honoraria: Boehringer, Bayer, Medtronic, ReCor. J. Stegbauer reports the following: Research Funding: German Research Foundation; Honoraria: AstraZeneca, Boehringer, Bayer Life Science; Scientific Advisor or Membership: Editorial Board - Experimental and Clinical Endocrinology & Diabetes, Kidney360; Other Interests/Relationships: German Society of Nephrology, AHA High Blood Pressure, German Society of Hypertension. The remaining authors have nothing to disclose.

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M. Andree: Formal analysis; Methodology
M. Schmitz: Investigation; Writing - review and editing
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L. Weiland: Investigation; Writing - review and editing

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J. Stegbauer: Conceptualization; Data curation; Formal analysis; Writing - original draft; Writing - review and editing
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Table 1 Baseline characteristics of dialysis patients, kidney transplant recipients (KTR) and controls without evidence of kidney failure. Body mass index (BMI), hemodialysis (HD), peritoneal dialysis (PD), interquartile range (IQR), estimated glomerular filtration rate (eGFR).
Table 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SARS-CoV-2 spike S1 specific IgG &gt;35.2 BAU/ml</th>
<th>SARS-CoV-2 spike S1 specific IgG &lt;35.2 BAU/ml</th>
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<td>n= 18</td>
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<tr>
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<tr>
<td>Malignom (%)</td>
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<td>39</td>
</tr>
<tr>
<td><strong>Transplantation</strong></td>
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<tr>
<td>Time after transplantation (years); median (IQR)</td>
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<td>6 (3-11) *</td>
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<tr>
<td>History of previous transplantation</td>
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<td>1</td>
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<tr>
<td>Baseline eGFR (ml/min/1.73m²)</td>
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<td>47 ±18</td>
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<td>History of rejection within a year before vaccination</td>
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<td>0 (0%)</td>
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<tr>
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<td>Dual therapy</td>
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<td>1 (6%)*</td>
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<tr>
<td>Prednisolon</td>
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<td>18 (100%)</td>
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Table 2 Differences in baseline characteristics between KTRs with SARS-CoV-2 spike S1 specific IgG >35.2 BAU/ml and KTRs with SARS-CoV-2- spike S1 specific IgG < 35.2 BAU/ml. *represent significant difference between the groups (p< 0.05) using Mann-Whitney test.
Figure legends

**Figure 1** SARS-CoV-2 spike protein specific antibody titers were determined using Euroimmun Anti-SARS-CoV-2-QuantiVac-ELISA. Antibody titers > 35.2 BAU/ml were considered as positive immune response to vaccination. Antibody titers below the detection limit were set to 1.0. Antibody titers after first (A) and second (B) vaccination were significantly higher in controls compared to dialysis patients and KTRs. Moreover, mean antibody titers after the second vaccination were significantly lower in KTRs compared to the dialysis group. For comparison of three groups, data were analyzed by the non-parametric Kruskal-Wallis Test with post hoc Dunn test, *p<0.05, **p<0.01, ***p<0.001 are depicted in the figures.

**Figure 2** Median titer and Frequency of neutralizing antibodies in patients with kidney failure. (A) The mean titers of neutralizing antibodies were significantly lower in dialysis patients and KTRs compared to controls after the second vaccination. (B) Frequencies of neutralizing antibodies in controls, dialysis patients and KTRs after the second vaccination. For comparison of three groups, data were analyzed by the non-parametric Kruskal-Wallis Test with post hoc Dunn test, **p<0.01 are depicted in the figures.

**Figure 3** Frequency of side effects after the first (A) and second (B) vaccination were determined as the sum of cumulative reactions predefined in the method section.
Figure 2A

Second vaccination

**

***

Figure 2B

Frequency of NTs
Second vaccination

- **Control**
- **Dialysis**
- **KTR**

Neutralisation Titer [1:X]

Frequency (%)
Figure 3A
Frequency of side effects after first vaccination

- Control
- Dialysis
- KTR

Figure 3B
Frequency of side effects after second vaccination

- Control
- Dialysis
- KTR