CORONAVIRUS

Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients

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Patients with kidney failure are at increased risk of SARS-CoV-2 infection, making effective vaccinations a critical need. It is not known how well mRNA vaccines induce B and plasma cell responses in dialysis patients (DPs) or kidney transplant recipients (KTRs) compared with healthy controls (HCs). We studied humoral and B cell responses of 35 HCs, 44 DPs, and 40 KTRs. Markedly impaired anti-BNT162b2 responses were identified among KTRs and DPs compared with HCs. In DPs, the response was delayed (3 to 4 weeks after boost) and reduced with anti-S1 IgG and IgA positivity in 70.5 and 68.2%, respectively. In contrast, KTRs did not develop IgG responses except for one patient who had a previous unrecognized infection and developed anti-S1 IgG. Most antigen-specific B cells (RBD+) were identified in the plasmablast or post-switch memory B cell compartments in HCs, whereas RBD+ B cells were enriched among pre-switch and naïve B cells from DPs and KTRs. The frequency and absolute number of antigen-specific circulating plasmablasts in the cohort correlated with the Ig response, a characteristic not reported for other vaccinations. In conclusion, these data indicated that immunosuppression resulted in impaired protective immunity after mRNA vaccination, including Ig induction with corresponding generation of plasmablasts and memory B cells. Thus, there is an urgent need to improve vaccination protocols in patients after kidney transplantation or on chronic dialysis.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) leads to a high morbidity and mortality especially among patients with kidney failure (1). Dialysis patients (DPs) and kidney transplant recipients (KTRs) are at increased risk of developing COVID-19 and experiencing a severe infection because of exposure risk in the health care system, their comorbidities, and their impaired immune function from kidney failure or immunosuppressive medications. For this vulnerable population, vaccination is of the utmost importance.

The mRNA severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine BNT162b2 (BioNTech/Pfizer) has demonstrated efficacy in healthy individuals in a clinical study (2) and under real-world conditions (3). Recent data described a lower serological response to an mRNA vaccine in DPs (4) and KTRs (5), suggesting an overall diminished vaccine response. Whereas numerous studies have addressed the consequences of conventional vaccines on B and plasma cells (6–8) and corresponding immunoglobulin (Ig) levels, nothing is known yet about the B lineage consequences in response to an mRNA vaccine among healthy controls (HCs) and immunocompromised patients. The ongoing uremic state in patients with kidney failure leads to an immune dysfunction on various levels of innate and adaptive immunity. Restoring kidney function by kidney transplantation does not fully restore cellular and adaptive immunity, whereas immunosuppressive drugs impair protective immunity further. Thus, patients with kidney failure (with or without kidney transplant) show an increased susceptibility for infection and viral-associated cancers (9–11).

Previous studies in patients with kidney failure (with or without kidney transplant) report markedly diminished response to vaccinations. This has led to an adaption of vaccination protocols with either higher initial vaccine doses or more frequent booster doses (12, 13). Whether such adaptations of the protocol are required for the COVID-19 mRNA vaccines or whether alternate adjuvanted vaccines are necessary is not yet known.

The induction of B cell memory by mRNA vaccines and the relation to humoral immune response are largely under-investigated, especially studies of immunocompromised cohorts. Upon natural acute SARS-CoV-2 infection, immunological memory (antibodies and memory B cells) is shown to last for at least 8 months (14–16).
In patients with chronic kidney disease, such data are largely lacking, although prolonged time of viral shedding with impaired virus clearance is reported and likely related to impaired cell-mediated immunity (17).

In this study, we compared the characteristics of the humoral and antigen-specific B cell immune response against the mRNA vaccine BNT162b2 between HCs and patients with kidney failure treated by maintenance hemodialysis (HD) or kidney transplantation. We found a diminished humoral response to BNT162b2 and a lack of proper B lineage memory formation including receptor binding domain (RBD)–specific plasmablasts and post-switch memory B cells.

RESULTS
Cohorts and patient characteristics
For this study, we recruited 35 HCs, 41 patients on maintenance HD, 4 peritoneal DPs, and 40 KTRs. HD and peritoneal dialysis (PD) patients did not significantly differ in age and vaccine response and were therefore grouped together. After written informed consent, serum and peripheral blood mononuclear cells (PBMCs) were collected before vaccination (baseline) and 7 ± 2 days after boost vaccination (second dose), respectively. Serological follow-up was available in DPs and KTRs 3 to 4 weeks after boost. Because of local vaccination guidelines, HCs, who were mainly health care workers, were significantly younger than DPs (P < 0.01). DPs were significantly older than KTRs. As known for patients with kidney failure (18), most DPs and KTRs were male. The median time on dialysis was 5.5 years [interquartile range (IQR), 2.0 to 9.0]. Among KTRs, only one patient was transplanted less than 1 year ago, and median time after transplantation was 5.0 years (IQR, 2.0 to 10.0). KTRs were on a uniform immunosuppressive regimen with mycophenolate mofetil (MMF) in 39 of 40, steroid in 37 of 40, and calcineurin inhibitor (CNI) in 37 of 40 patients. Demographics are summarized in Table 1. To identify previously SARS-CoV-2–infected individuals, we measured antinucleocapsid protein (NCP) antibodies 7 ± 2 days after boost, which is not a component of BNT162b2. Therefore, positivity of NCP originated from natural infection. One HC, one DP, and one KTR were identified anti-NCP positive (Fig. S1).

Substantially impaired serological response upon mRNA vaccination with BNT162b2 in DP and even more pronounced in KTR patients
Antibody response to BNT162b2 was assessed in all individuals 7 ± 2 days after boost using the Euroimmun enzyme-linked immunosorbent assay (ELISA) for the detection of IgG and IgA against the S1 domain of the SARS-CoV-2 spike. All HCs seroconverted, were positive for both anti-S1 IgG and IgA (Fig. 1, A and B), and showed SARS-CoV-2 neutralization (Fig. 1C). Anti-S1 IgA and IgG titers were markedly diminished 7 ± 2 days after boost in DPs compared with HCs (Fig. 1, A and B). In the S1 IgG assay, 31 of 44 (70.5%) of the DPs were positive and 30 of 44 (68.2%) developed anti-S1 IgA antibodies.

Of particular interest, anti-S1 IgG and IgA responses were substantially diminished in KTRs compared with HCs and DPs, respectively. Only 1 of 40 patients (2.5%) was positive for IgG (apparently after previous unrecognized infection), and 4 patients were positive for IgA (10%). Virus neutralization was observed in 30 of 44 (68.2%) DPs (Fig. 1C), whereas 0 of 40 KTRs had inhibiting antiviral antibodies (Fig. 1C). The patient’s serum with IgG and previous infection did not achieve neutralizing effects. Previously infected individuals are indicated in red in Fig. 1 (A to C). Their levels of antibody and neutralization were in the range of other individuals of the respective group.

To further address the effect of age in our cohort, we divided the group into individuals <60 years and ≥60 years of age. HCs >60 years showed a lower anti-S1 IgG and IgA than HCs <60 years, whereas their neutralization capacity (NC) was unchanged (Fig. 1, D to F). DPs and KTRs did not show differences in anti-S1 IgG and IgA, but DPs >60 exhibited a lower NC compared with DPs <60 years (Fig. 1, D to F). DPs and KTRs <60 and ≥60 years of age showed an overall diminished anti-S1 IgG and IgA as well as NC compared with HCs <60 and ≥60 years of age, respectively (Fig. 1, D to F). Anti-S1 IgG and IgA correlated with age in HCs, whereas this correlation was weak in DPs and KTRs (fig. S2).

HCs showed no significant further increase of humoral response later than 28 days after initial vaccination with BNT162b2 (19). A delayed immune response might have explained the initial limited serologic response in immunocompromised individuals (DPs and KTRs) with mRNA vaccines. Therefore, we collected additional follow-up samples from KTRs and DPs 3 to 4 weeks after boost. Anti-S1 IgG increased significantly in DPs (Fig. 1G), whereas anti-S1 IgA and surrogate neutralization remained stable (Fig. 1H) during the additional observation. In contrast, KTRs did not develop additional anti-S1 IgG, anti-S1 IgA, and neutralizing antibodies until the second follow-up investigation 3 to 4 weeks after the boost (Fig. 1, G to I). In summary, KTRs showed a significantly reduced serological response, including lack of further increases up to 3 to 4 weeks after BNT162b2 boost.

DPs and KTRs showed reduced B cell numbers but similar distribution among memory subsets
B cell lymphopenia is described for DPs (20) and KTRs (21) and might affect proper humoral immune responses. To initially address the frequency, distribution, and phenotype of peripheral blood B cells in DPs and KTRs compared with HCs, we analyzed the distribution of B cell subsets at baseline (prevaccination) and 7 ± 2 days after boost (Fig. 2A). Of interest, the frequency of CD19+ B cells was significantly diminished only in KTRs compared with DPs at the assessment 7 ± 2 days after boost and compared with HCs at baseline, whereas no differences were otherwise observed (Fig. 2B). However, substantial reductions in absolute B cell counts were identified between KTRs and HCs at baseline as well as HC versus the DP and KTR cohorts 7 ± 2 days after boost, respectively (Fig. 2C).

The frequency of plasmablasts among total CD19+ B cells did not differ between groups (Fig. 2, D and E) at baseline and after boost. DPs and KTRs carried lower frequencies of pre-switch B cells, whereas KTRs had an increased frequency of naïve B cells before, but not after, vaccination. Post-switch memory B cells were higher in DPs before, but not after, vaccination. Double-negative (DN; CD27- IgD-) B cells did not differ significantly among groups (Fig. 2, D and E). Ig isotype distribution among B cell subsets was not different among study groups (Fig. 2, F and G). In summary, KTRs and DPs showed a characteristic reduction of absolute B cells with certain differences in the pre-memory (naïve and pre-switch) but no differences within B memory compartments.

Impaired induction of anti-BNT162b2 B cell and plasmablast responses in KTRs and HD patients
To better understand the underlying B and plasma cell differentiation upon vaccine challenge, we developed a flow cytometric method to...
identify and quantify RBD-specific B cells in human peripheral blood. B cells (CD3\(^{-}\) CD14\(^{-}\) CD19\(^{+}\)), which can simultaneously bind RBD–Alexa Fluor 488 (AF488) and RBD–AF647, were validated as antigen specific (Fig. 3A). The specificity of RBD binding was further confirmed by blocking with unlabeled RBD before staining (Fig. 3A). We identified an RBD-specific clone (CDRH3: ARDYGGNANYFHY, CDRL3: QQYDNLPIT) in three different vaccines (HCs) with highly identical amino acid sequence as reported before upon mRNA vaccinations (22). Subsequently, RBD\(^{+}\) B cells were further analyzed according to their distribution among subsets and isotypes (gated as shown for general B cells in Fig. 2AF).

Overall, an increased frequency of RBD-specific B cells among CD19\(^{+}\) B cells was found 7 ± 2 days after boost compared with baseline for HCs, DPs, and KTRs (Fig. 3B). The absolute number of antigen-specific B cells was significantly increased in HCs at 7 ± 2 days after boost only, in contrast to DPs and KTRs (Fig. 3C).

Subsequent analyses addressed the distribution of the RBD-specific B cells among B cell subsets (gating as seen in Fig. 2A). A large number

Table 1. Patient characteristics.

|                | HC (N = 35) | KTR (N = 40) | HD (N = 40) | PD (N = 4) |
|----------------|------------|-------------|------------|-----------|
| **Age**        |            |             |            |           |
| Median [IQR]   | 51.0 [34.0–80] | 62.4 [51.25–69.5] | 69.0 [81.575–63.0] | 70.5 [80.5–63.5] |
| <50            | 17         | 7           | 3          | 0         |
| 51–59          | 5          | 10          | 6          | 0         |
| 60–69          | 4          | 15          | 13         | 2         |
| >70            | 9          | 8           | 18         | 2         |
| **Sex**        |            |             |            |           |
| Male           | 20         | 28          | 25         | 3         |
| Female         | 15         | 12          | 15         | 1         |
| **Renal replacement therapy** |            |             |            |           |
| Years since renal replacement therapy | 5.5 |            |            |           |
| Median [IQR]   | [2.0–9.0]  |             |            |           |
| Years since kidney transplantation | 5.0 |            |            |           |
| Median [IQR]   | [2.0–10.0] |             |            |           |
| **Immunosuppression** |            |             |            |           |
| Steroid + Tacrolimus + MMF (%) | 22 |            |            |           |
| Steroid + CyA + Azathioprine (%) | 1 |            |            |           |
| Steroid + CyA + MMF (%) | 13 |            |            |           |
| mTORi + MMF ± Steroid (%) 3 (7.69) | 3 |            |            |           |
| mTORi + CyA + MMF (%) 1 (2.56) | 1 |            |            |           |
| MMF (total)    | 39         | 12          | 11         | 16        |
| 2 g            |            | 12          |            |           |
| >1 g and <2 g  |            | 11          |            |           |
| ≤1 g           |            | 16          |            |           |
| Cadaveric kidney donor | 34 |            |            |           |
| Living kidney donor | 6 |            |            |           |
| Retransplantation | 6 |            |            |           |
| **Comorbidities** |            |             |            |           |
| Hypertension   | 2          | 36          | 34         | 3         |
| Diabetes mellitus | 0 | 13          | 19         | 0         |
| Malignancy, recent or history of | 0 | 7           | 4          | 0         |
of RBD$^+$ B cells were found in the plasmablast compartment in HCs, which was significantly lower in DPs and KTRs (Fig. 3D and fig. S3). The very limited antigen-specific B cells in KTRs resided preferentially within the naïve and pre-switch compartment compared with HCs (Fig. 3D and fig. S3). In contrast, antigen-specific B cells from HCs were detected mainly within post-switch and DN B cells belonging largely to the memory compartment (Fig. 3D). Consistent with impaired (not completely executed) B memory induction, the frequency of IgM RBD$^+$ B cells (defined as IgG$^+$ IgA$^-$) was more frequently detected in KTRs and DPs compared with HCs in whom antigen-specific IgG$^+$ B cells dominated. The frequency of IgA$^+$ RBD$^+$ B cells was comparable across groups (Fig. 3E).

Fig. 1. Humoral immune response was delayed in DPs and markedly reduced in KTRs. (A to C) Humoral immune response against SARS-CoV-2 was assessed by Euroimmun ELISA for (A) spike protein S1 IgG, (B) spike protein S1 IgA, and (C) virus neutralization by a blocking ELISA in HC $(n=34)$, DP $(n=44)$, and KTR $(n=40)$ 7 ± 2 days after the second vaccination with BNT162b2 in the total cohort. OD, optical density. (D to F) Humoral immune response with each cohort divided according to age [≥60 $(n=71)$ (HC, $n=13$; DP, $n=35$; KTR, $n=23$) and <60 years $(n=47)$ (HC, $n=21$; DP, $n=9$; KTR, $n=17$)] into two subgroups, and the corresponding results are shown for (D) spike protein S1 IgG, (E) spike protein S1 IgA, and (F) virus neutralization by a blocking ELISA. (G to I) Follow-up sera were collected from 37 DPs and 26 KTRs, respectively, 3 to 4 weeks after the second vaccination and investigated for (G) spike protein S1 IgG, (H) spike protein S1 IgA, and (I) virus neutralization by a blocking ELISA. (A to I) Threshold of upper limit of normal is indicated as dotted lines. (A to F) Kruskal-Wallis with Dunn’s posttest. Previously infected individuals are indicated in red. (G to I) Two-way analysis of variance (ANOVA) with Šidák’s posttest. *$P<0.05$, **$P<0.01$, ***$P<0.001$, ****$P<0.0001$. 

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Fig. 2. B cells were reduced in DPs and KTRs but show a similar distribution after second BNT162b2 vaccination. (A) Representative pseudocolor plots of CD19+ B cell gating into plasmablasts and mature B cells and representative pseudocolor plots of IgD/CD27-based classification. (B) Frequency of CD19+ B cells [gates shown in (A)] in HC, DP, and KTR before vaccination (n = 46: HD, n = 11; DP, n = 21; and KTR, n = 14) and 7 ± 2 days after second vaccination (n = 119: HD, n = 35; DP, n = 44; and KTR, n = 40) with BNT162b2. (C) Corresponding absolute numbers (per microliter of blood) measured by BD Trucount. Frequencies of plasmablasts and mature B cells according to CD27/IgD [gates shown in (A)] at (D) baseline (n = 46: HD, n = 11; DP, n = 21; and KTR, n = 14) and (E) 7 ± 2 days after second vaccination (n = 119: HD, n = 35; DP, n = 44; and KTR, n = 40). (F) Representative pseudocolor plot of IgA and IgG expression in B cells from HC. (G) Distribution of surface Ig isotype expression among HC, DP, and KTR 7 ± 2 days after second vaccination (n = 119: HD, n = 35; DP, n = 44; and KTR, n = 40). Two-way ANOVA with Šidák’s posttest. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.
Two-dimensional (2D) t-distributed stochastic neighbor embedding (t-SNE) plots clustering all RBD+ B cells according to expression patterns, analyzed with a color axis for CD27, CD38, and IgG, illustrated the marked differences between groups, including the substantially reduced plasmablasts (CD27++, CD38++) and IgG-expressing RBD+ B cells in the KTR cohort (Fig. 3F). In summary, KTRs not only were characterized by a reduced overall number of antigen-specific B cells but also exhibited signatures of abnormal B cell memory formation.

Fig. 3. RBD-specific B cells were present in DPs and KTRs after BNT162b2 vaccination but populate different B cell subsets. (A) Representative dot plot of double-positive RBD-specific B cells before and after blocking with unlabeled RBD. (B) Frequencies and (C) absolute numbers of RBD+ cells among total CD19+ B cells measured before (n = 59: HD, n = 10; DP, n = 23; and KTR, n = 26) and 7 ± 2 days after second vaccination (n = 119: HD, n = 35; DP, n = 44; and KTR n = 40). (D) Frequencies of plasmablasts, naïve, pre-switch, post-switch, and DN B cells (bar) and Ig isotype distribution among subsets (cakes) (HD, n = 10; DP, n = 23; and KTR, n = 26). (E) Ig isotype expression among total RBD+ cells in HC, DP, and KTR and 7 ± 2 days after second vaccination (HD, n = 35; DP, n = 44; and KTR, n = 40). (F) 2D t-SNE of all RBD+ cells in HC (n = 21), DP (n = 23), and KTR (n = 34). Color code indicates expression of CD27 (top), CD38 (middle), and IgG (bottom). Previously infected individuals are marked in red (E). (B to D) Two-way ANOVA with Šidák's posttest. (E) Kruskal-Wallis with Dunn’s posttest. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.
Unique correlation of anti-BNT162b2 serological and B cell responses

Our earlier vaccination studies against tetanus, diphtheria, and KLH (keyhole limpet hemocyanin) do not reveal a typical relation between plasmablast/B cell responses and the serologic Ig outcome (6–8), in contrast to such relation for polysaccharides, such as meningococcal and pneumococcal vaccine (23, 24). Therefore, we wondered how the anti-BNT162b2 humoral immune and B cell–specific responses against an mRNA vaccine are interrelated. A correlation matrix including all groups and patients was carried out. As previously described (25, 26), the NC strongly correlates with anti-S IgG and IgA (Fig. 4A). The frequency of total RBD+ cells did not correlate with anti-S IgG, IgA, and NC, respectively. The frequency and total number of RBD+ plasmablasts correlated with all parameters of humoral response (anti-S IgG, IgA, and the NC). Age and the total number of RBD+ B cells correlated in HCs, whereas they did not in DPs and KTRs (fig. S2). Subsequent analyses addressed how nonresponders with a negative neutralization test (<30%) differed from responders (>30%). Responders and nonresponders were significantly different in the frequency and number of RBD+ plasmablasts (fig. S2). Only correlations with NC ≤ 30% showed a significant correlation in HCs, whereas they did not in responders (NC > 30%, n = 63). Each point represents a donor. Unpaired two-sided Mann-Whitney U test. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Diminished T cell and plasmablast response in KTRs

To further understand the lack of B cell memory induction, we sorted CD27+CD38+ plasmablasts, CD27+CD38low memory B cells, and human leukocyte antigen (HLA)–DR+CD38+ activated T cells of the peripheral blood as indicators of the ongoing immune response after vaccination (7, 27) and generated single-cell transcriptomes combined with cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq) (28) for selected surface markers (fig. S4) 7 ± 2 days after boost vaccination. After removal of doublets, we analyzed a total of 10,796 cells. According to their transcriptomes, these cells were categorized in seven different clusters as shown by uniform manifold approximation and projection for dimension reduction (UMAP) (fig. S4, A and B) (29). We focused on the most abundant clusters, four of which belong to the T cell compartment, with the most abundant cluster 0 having represented activated CD8+HLA-DR+MS4A1+ T cells, followed by cluster 1, which represented different types of the CD4+ T cells, including, e.g., FOXP3+CD25+ regulatory T cells (figs. S4C and S5). Cluster 2 contained different populations of CD8+ T cell expressing either CD45RA or CD45RO (fig. S4, B and C), and finally, cluster 5 represented TCF7+CD27+GZMK+ T cells. Cluster 6 contained proliferating memory cells expressing MKI67 (fig. S4, B and C). Memory B cells expressing high levels of MS4A1, HLA-DRA, and CD27 were located in cluster 3. Cluster 4 represented plasmablasts expressing CD27, CD38, PRDM1, and IRF4 (fig. S4, B and C). The protein expression of selected surface markers detected by CITE-seq supported the classification of the seven main clusters (fig. S5). In the selected cohort of four KTRs, three did not show a serological response to the vaccination (nonresponder), whereas one individual had not only detectable anti-S IgG antibodies but also a previously undetected infection (responder). Accordingly, the three nonresponders had reduced frequencies of clusters 4, 5, and 6 representing plasmablasts TCF7+CD27+GZMK+ T cells and proliferating MKI67-expressing

![Fig. 4. Correlation of anti-BNT162b2 serological and B cell responses.](http://immunology.sciencemag.org/)

(A) Spearman’s correlation matrix showing the correlation of frequency of RBD+ cells in each B cell subset in the cohort. Corresponding correlations are represented by red (negative) or blue (positive) circles; size and intensity of color refer to the strength of correlation (HD, n = 35; DP, n = 44; and KTR, n = 40). Only correlations with P ≤ 0.05 are indicated. (B) Frequency (top) and absolute numbers (bottom) of RBD+ plasmablasts (PB), naïve B cells, and post-switch B cells in nonresponders (surrogate virus NC < 30%, n = 55) and responders (NC > 30%, n = 63). Each point represents a donor. Unpaired two-sided Mann-Whitney U test. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.
lymphocytes (fig. S4, D and E). CD45RO+ follicular T helper (Tfh)-like cells expressing either IL21 or PDCD1+ could only be detected in the CD4+ T cell compartment (cluster 1) of nonresponder #3 and the responder (fig. S4F). Most memory B cells (cluster 3) of the responder expressed ITGAX (gene encoding for CD11c), whereas this subpopulation in cluster 3 was almost absent in the nonresponders (fig. S4F).

**DISCUSSION**

SARS-CoV-2 mRNA vaccines are highly protective against COVID-19 (2, 30), although it is not yet clear how these vaccines induce and maintain B cell memory responses among immunocompromised patients. Available data show a durable humoral response and B cell response (31, 32) in healthy individuals and elderly patients (2, 19). Moreover, mRNA vaccines are reported to induce germinal center (GC) responses in mice and are expected to result in lasting plasma cell responses (33). Here, we investigated the distribution of anti-BNT162b2 antigen-specific B cell responses among HCs in comparison with DPs and KTRs as prototypes for differentially immunocompromised patients. An assay for the detection of RBD-specific B lineage cells has been developed with high specificity based on our previous experiences for the detection of antigen-specific B cells and plasmablasts [i.e., tetanus, KLH, and penetratin (8, 34)]. Specificity was proven by appropriate blocking experiments and identification of an RBD-specific clone (CDRH3) among RBD+ B cells, which was found in three different vaccines (HCs) with highly identical amino acid sequence immunized as reported very recently upon mRNA vaccinations (22). Of particular interest, seroconversion and the induction of neutralizing antibodies upon BNT162b2 vaccination were very robust and similar in our cohort in HCs, as observed by a previous study (2). In these HCs, we also found a typical formation of antigen-specific plasmablasts and post-switch memory B cells upon vaccination boost, which was comparable with frequencies of tetanus-specific B cells after booster vaccination (35). Thus, the findings among HCs provide a valid comparison with the two patient cohorts.

Among DPs and KTRs, we observed a markedly diminished generation of antigen-specific B cells, especially within major effector compartments of protective B cell immunity, namely, plasmablasts and memory B cells. Consistently, lower IgG anti-RBD cells were found related to impaired induction of a vaccine response. This was accompanied by a low rate of seroconversion of DPs on days 7 ± 2 that somewhat improved 3 to 4 weeks after vaccination, although this could not be compared with HCs in our cohort because of a missing follow-up. In the KTR cohort, the rate of serological and cellular response was almost absent, with only one patient who developed specific anti-S1 IgG apparently based on a previous unrecognized infection and likely reflecting a further boost underlining the potential effectiveness of optimized vaccines or vaccination protocols. No KTR exhibited a positive neutralization at days 7 ± 2 after boost, including the patient with positive IgG titers. At a further follow-up 3 to 4 weeks after boost, no seroconversions were found in KTRs. These data are in contrast to recently published data of Boyarsky et al. (5) who described a seroconversion in 23 of 223 (10.35%) of KTRs vaccinated with BNT162b2 already after the first dose. As a limitation of our study, we only have a limited sample size and a very uniform immunosuppressive regimen of KTRs, which does not allow for a firm conclusion that immunosuppressant may cause the impaired immune response. For DPs, seroconversion rates of about 90% after two doses have been described, which is similar to the findings in our cohort (4, 36).

The large discrepancy of the serological response and impaired B cell response in our KTR cohort raises the question about which factors or mechanisms are involved. Incorrect handling of the sensitive mRNA vaccine can be excluded because the same mRNA vaccine of the same lot induced a favorable response among DPs. The major difference between KTRs and DPs/HCs appeared to be the almost uniform immunosuppressive therapy with MMF, CNI, and glucocorticoids among the KTRs, although the individual impact of MMF, cyclosporine versus tacrolimus, and glucocorticoids needs to be further delineated. CNI and MMF directly inhibit activation and proliferation of CD4+ T cells, Tfh cells, and B cells (37–41). In this regard, single-cell transcriptomes and CITE-seq analyses identified substantial differences between the vaccine responder and three nonresponders within the KTR cohort. Namely, plasmablasts, TCF7+CD27+GZMK+ T cells, and proliferating MKI67+expressing lymphocytes were increased in the responders, suggesting that these three subsets are key drivers of a successful BNT162b2 response.

Three individuals with likely previous asymptomatic virus exposure (each in HC, DP, and KTR cohorts) were identified by preexisting antibodies against viral NC. They did not show marked differences in vaccine response compared with their cohorts, with the exception of one seroconversion in the KTR. A number of recent studies report that the first vaccination in previously infected individuals acts as a boost that leads to higher antibody levels than individuals vaccinated twice with an mRNA vaccine. It further does not change isotype distribution among memory B cells (32, 42, 43). After a natural COVID-19 infection, the numbers of RBD-specific memory B cells of healthy individuals are similar to those of patients who recovered from natural COVID-19 infection, whereas levels of anti-S1 and anti-RBD IgG are significantly higher in vaccinated individuals (22). The clonality of IGLV genes among RBD+ is very comparable between natural infection and the mRNA vaccination (22). At the moment, it is not known whether the magnitude of antibody levels or the presence or magnitude of a T cell response, or both, correlates with the protection against symptomatic COVID-19. However, after natural COVID-19 infection, the presence of anti-spike antibodies protects from recurrent infection, whereas a previous infection without detectable antibodies does not (44). Initial observational data from Israel indicate that chronic kidney disease (CKD) and immunosuppression have a negative impact on vaccine efficacy (45), which indicates that impaired B cell memory also results in diminished protection.

We found a unique relationship between plasmablast response and Ig titer, which is not seen in tetanus and KLH vaccination (6–8) and is only described for polysaccharide and protein-polysaccharide conjugate vaccinations (46). Polysaccharide vaccines, in contrast to mRNA vaccines, induce certain serological responses after vaccination in KTRs (47), which possibly relates to T independent responses. In this context, our single-cell analysis confirmed a diminished plasmablast induction in the nonresponders (KTR) but importantly also lack of proper CD4 and CD8 T cell activation. In the responder, classical signs of vaccine response with simultaneous B and T cell activation occurred but insufficient to induce neutralizing antibody titers. KTRs have to be considered as a patient group who remains vulnerable to SARS-CoV-2 infection even if vaccinated with the currently established BNT162b2 vaccination scheme.
In summary, we described a diminished humoral response to BNT162b2 and lack of appropriate memory formation, including RBD-specific plasmablasts and post-switch memory B cells in DPs and KTRs. DPs were able to further mature their antibody response in contrast to KTRs. As such, optimized vaccination strategies especially for KTRs are needed to achieve adequate anti-

viral protection.

**MATERIALS AND METHODS**

**Study design**

The study was designed to investigate the sero-response (anti-S1 IgA, anti-S1 IgG levels, and neutralization test) and B cell memory formation in DPs and KTRs after vaccination with BNT162b2. HCs, KTRs, and DPs were vaccinated with BNT162b2 21 days apart. Baseline blood was drawn to identify previously infected individual (NCP ELISA, anti-S1 IgA, and anti-S1 IgG levels) and access baseline B cell phenotype of HCs, DPs, and KTRs (flow cytometry). To investigate the plasmablast response, peripheral blood samples were obtained 7 ± 2 days after boost vaccination. B cell subsets and antigen-specific B cells were analyzed by flow cytometry. Seroresponse was investigated 7 ± 2 days (HCs, DPs, and KTRs) and 3 to 4 weeks after the second dose (DPs and KTRs).

**Study participants**

Peripheral blood samples (EDTA anticoagulated or serum tubes, BD Vacutainer System, BD Diagnostics, Franklin Lakes, NJ, USA) from 35 HCs, 40 HD patients, 4 peritoneal DPs, and 40 KTRs were collected at 7 ± 2 days after the second dose of SARS-CoV-2 BNT162b2 vaccination. Individuals from the KTR and DP cohorts are, in part, also represented in published manuscripts (serological response only) (48, 49). Material before vaccination was available for 19 HCs, 21 HD patients, 2 peritoneal DPs, and 28 KTRs, whereas a follow-up at 3 to 4 weeks after boost is available currently for 26 KTRs and 37 DPs. Donor information is summarized in Table 1. All participants gave written informed consent according to the approval of the ethics committee at the Charité University Hospital Berlin (EA2/010/21, EA4/188/20), the ethics committee of Saxony-Anhalt (EA7/21), and the ethics committee of the University of Greifswald (BB019/21).

**Sample processing and isolation of PBMCs and staining**

Serum tubes were centrifuged at 3000 rpm for 10 min to separate plasma. Serum was stored at −20°C for antibody analysis. PBMCs were prepared by density gradient centrifugation using Ficoll–Paque PLUS (GE Healthcare Bio-Sciences, Chicago, IL, USA). For staining, 1 × 10^6 to 3 × 10^6 cells were suspended in 50 µl of phosphate-buffered saline (PBS)/0.5% bovine serum albumin/EDTA and 10 µl of Brilliant Buffer (BD Horizon, San Jose, CA, USA). Cells were stained for 15 min on ice and washed afterwards with Dulbecco’s PBS containing 1% fetal calf serum (Biowest, Nuaillé, France) (810g; 8 min, 4°C). Flow cytometric analysis was performed as indicated in Figs. 1 to 4.

**Flow cytometry**

All flow cytometry analyses were performed using a BD FACS Fortessa (BD Biosciences, Franklin Lakes, NJ, USA). To ensure comparable mean fluorescence intensities over time of the analyses, cytometer setup and tracking beads (BD Biosciences, Franklin Lakes, NJ, USA) and rainbow calibration particles (BD Biosciences, Franklin Lakes, NJ, USA) were used. For flow cytometric analysis, the following fluorochrome-labeled antibodies were used: BV737 anti-CD11c (clone B-ly6, 1:50; BD Biosciences), BVU359 anti-CD14 (clone M5E2, 1:50; BD Biosciences), BVU359 anti-CD3 (clone UCHT1, 1:50; BD Biosciences), BVU786 anti-CD27 (clone L128, 1:50; BD Biosciences), BVU711 anti-CD19 (clone SJ25C1, 1:25; BD Biosciences), BVU605 anti-CD24 (clone ML5, 1:50; BD Biosciences), BVU510 anti-CD10 (clone H110A, 1:20; BD Biosciences), BVU421 anti-CDXCR5 (clone RF8B2, 1:20; BD Biosciences), phycoerythrin (PE)–Cy7 anti-CD95 (clone APO-1/Fas, 1:100; Thermo Fisher Scientific, Waltham, MA, USA), PE-CF594 anti-IgD (clone IA6-2, 1:5000; BioLegend, San Diego, CA, USA), allophycocyanin (APC)–Cy7 anti-CD38 (clone HIT2, 1:1000; BioLegend), PE–Cy7 anti-IgG (clone G18-145, 1:1000; BD Biosciences), anti-IgA–biotin (clone G20-359, 1:50; BD Biosciences), BV650 anti-IgM (clone MHM-88, 1:50; BD Biosciences), fluorescein isothiocyanate (FITC) anti–HLA-DR (clone L234, 1:25; BioLegend), PE anti-CD21 (clone B-ly4, 1:25; BD Biosciences), and APC anti-CD22 (clone S-HCL-1, 1:25; BD Biosciences). Siglec-1 (CD169, 1:25) expression analysis on CD14+ monocytes was performed at baseline and at the follow-up time point as previously described (11). The number of absolute B cells was measured with Trucount (BD Biosciences), and samples were processed according to the manufacturer’s instruction.

**Staining of antigen-specific B cells**

To identify RBD-specific B cells, recombinant purified RBD (DAGC149, Creative Diagnostics, New York, USA) was labeled with either AF647 or AF488. Double-positive cells were considered as antigen specific (Fig. 3). Antigens were labeled at the German Rheumatism Research Centre (DRFZ), Berlin, with N-hydroxysuccinimide (NHS) ester conjugation for AF647 and AF488. A blocking experiment using unlabeled RBD in 100-fold concentration was used to ensure specificity of the staining (Fig. 3A). The number of recorded antigen-specific events ranged from 0 to 422 events. To ensure the specificity of our RBD-specific flow cytometric staining, we labeled memory B cells with fluorescent RBDs and isolated them cytometrically. The isolated B cells were analyzed for their transcriptome and B cell receptor sequence using Dropseq (10X Genomics). We were able to intercept and examine 168 cells from eight vaccinated individuals 7 days after secondary immunization. This population of RBD-specific memory B cells was found to use VDJ gene rearrangements using preferentially certain IgHV segments (IGHV3-30, IGHV3-53, and IGH3-23) and IGK genes (IGKV1-39, IGKV1-33, IGKV1-9, and IGKV3-29) after mRNA inoculation, as described by Wang et al. (22). We even identified an RBD-specific clone (CDRH3: ARDY-GGNANYFYH, CDR3L: QQYDNLPIPT), which was found in three different vaccines with highly identical amino acid sequence immunized as reported very recently upon BioNTech or Moderna vaccinations (22).

**ELISA (Euroimmun)**

The Euroimmun anti–SARS-CoV-2 assay is a classical ELISA for the detection of IgG to the S1 domain of the SARS-CoV-2 spike (S) protein, IgA to the S1 domain of the SARS-CoV-2 spike protein, and IgG to the SARS-CoV-2 NCP protein. The assay was performed according to the manufacturer’s instructions and as described previously (25, 26).
Surrogate SARS-CoV-2 neutralization test (GenScript)
This blocking ELISA qualitatively detects anti–SARS-CoV-2 antibodies suppressing the interaction between the RBD of the viral spike glycoprotein (S) and the angiotensin-converting enzyme 2 (ACE2) protein on the surface of cells. The assay was performed according to the manufacturer’s instructions and as described previously (25, 26).

Single-cell RNA sequencing
Peripheral blood cells were enriched from peripheral blood using StraightFrom Whole Blood CD19, CD3, and CD138 MicroBeads (Miltenyi Biotec) according to the manufacturer’s instructions. Afterward, cells were stained, incubated with TotalSeq oligomer-conjugated hashtag antibodies (TotalSeq-C anti-human Hashtag antibody 1 to 4), and sorted with the MA900 Multi-Application Cell Sorter (Sunny Biotechnology).

Sorted populations were identified as plasmablasts (DAPI−CD3−CD14−CD16+CD38+CD27−), memory B cells (DAPI−CD3−CD14−CD16+CD38−CD27−), and activated T cells (DAPI+CD3+CD14−CD16+CD38−HLA-DR+) The three sorted populations were pooled in equal proportions and further processed for single-cell RNA sequencing. Single-cell RNA library preparation and sequencing, single-cell transcriptome sequencing, as well as data analysis and statistics have been performed as previously described (50). All details can additionally be found in the Supplementary Materials.

Data analysis and statistics
All details can be found in the Supplementary Materials.

SUPPLEMENTARY MATERIALS
immunology.sciencemag.org/cgi/content/full/6/60/eabj1031/DC1
Materials and Methods
FIGS. S1 TO S5
Table S1
View request a protocol for this paper from Bio-protocol.

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Impaired humoral immunity to SARS-CoV-2 BNT162b2 vaccine in kidney transplant recipients and dialysis patients

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COVID-19 vaccines produce poor B cell responses in transplant patients

COVID-19 vaccinations have shown remarkable protection against SARS-CoV-2 infection in patients around the world. However, recent evidence has suggested that immunocompromised and organ transplant patients have poor immune responses to COVID-19 vaccines. Here, Rincon-Arevalo et al. looked at antibody, plasmablast, and memory B cell responses in healthy, dialysis, and kidney transplant patients before and after the COVID-19 mRNA BNT162b2 vaccine. They found that dialysis and kidney transplant patients had poor antibody and B cell responses to the vaccine, suggesting that these patients may not be sufficiently protected against SARS-CoV-2 infection. Thus, different vaccine strategies need to be developed to sufficiently protect dialysis and kidney transplant patients against COVID-19.