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Inferior cellular and humoral immunity against Omicron and Delta variants of concern compared with SARS-CoV-2 wild type in hemodialysis patients immunized with 4 SARS-CoV-2 vaccine doses

To the editor: With the dominance of the most recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern Omicron (B.1.1.529), the question arises, what is the reason for its high contagiousness in coronavirus disease 2019 (COVID-19)–vaccinated dialysis patients compared with the previous SARS-CoV-2 variants Delta and wild type?

The objective of this study was, therefore, to analyze humoral and cellular immunity directed against the Omicron variant of concern compared with the wild-type or Delta variant of concern in hemodialysis patients ($n = 42$; Supplementary Table S1) immunized with 4 doses of mRNA COVID-19 vaccine. Titers of neutralizing antibodies (NAbs) against wild type, Delta, and Omicron were estimated by SARS-CoV-2 spike-protein (S-protein) pseudovirus assays. T-cell immunity reactive against wild-type, Delta-derived, and Omicron-derived S-protein was analyzed by multiparameter flow cytometry (Supplementary Figure S1). The analyses were performed 8 to 9 weeks following the fourth doses.

The hemodialysis patients had a clear seroconversion after 4 doses of SARS-CoV-2 vaccination, with a significantly higher titer of NAb against wild type compared with Delta or Omicron S-protein (median [interquartile range]-50% Neutralizing Dose [ND50] = 2117 [663–2560], 759 [276–2560], and 439 [160–1180], respectively). Interestingly, the NAb titer against Delta was significantly higher compared with Omicron-specific NAb (Figure 1a). Although the number of patients with a detectable S-protein–reactive CD4 T-cell response was nearly identical (40–41 of 42 patients; Supplementary Table S2), the magnitude of response was significantly lower against Omicron- and Delta-derived S-protein compared with wild type (Figure 1b). In contrast, significantly fewer patients showed a detectable S-protein–reactive CD8 T-cell response against Omicron but not Delta compared with wild type ($P = 0.0304$, Fisher exact test; Supplementary Table S2), although the magnitude of response was not different between all 3 SARS-CoV-2 variants (Figure 1c).

With regard to the functionality, the frequency of Omicron and Delta S-protein–reactive $CD4^+$ T cells producing T helper cell 1 cytokines interferon-γ and tumor necrosis factor was significantly lower compared with wild-type S-protein–reactive CD4+ T cells (Figure 1d and f).

In line with the results from the general populations,[1,2] hemodialysis patients show a clearly decreased humoral and cellular immune response against Omicron compared with SARS-CoV-2 wild type after 4 doses of vaccination. Of interest, Omicron-specific NAb titer was significantly lower compared with Delta-specific NAb, explaining the more efficient evasion of Omicron from neutralizing antibodies[3] and its efficient spread in vaccinated individuals.[4] Because the humoral immune response of dialysis patients strongly benefits from a fourth compared with a third vaccination,[5] an adjustment of the vaccination procedure should be recommended.

DATA STATEMENT

The data will be available on request.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Table S1. Cohort characteristics.

Table S2. Number of patients with CD4 or CD8 T-cell response.

Figure S1. Gating strategy to identify spike-protein (S-protein)–reactive T cells among $CD4^+$ T and $CD8^+$ T cells.

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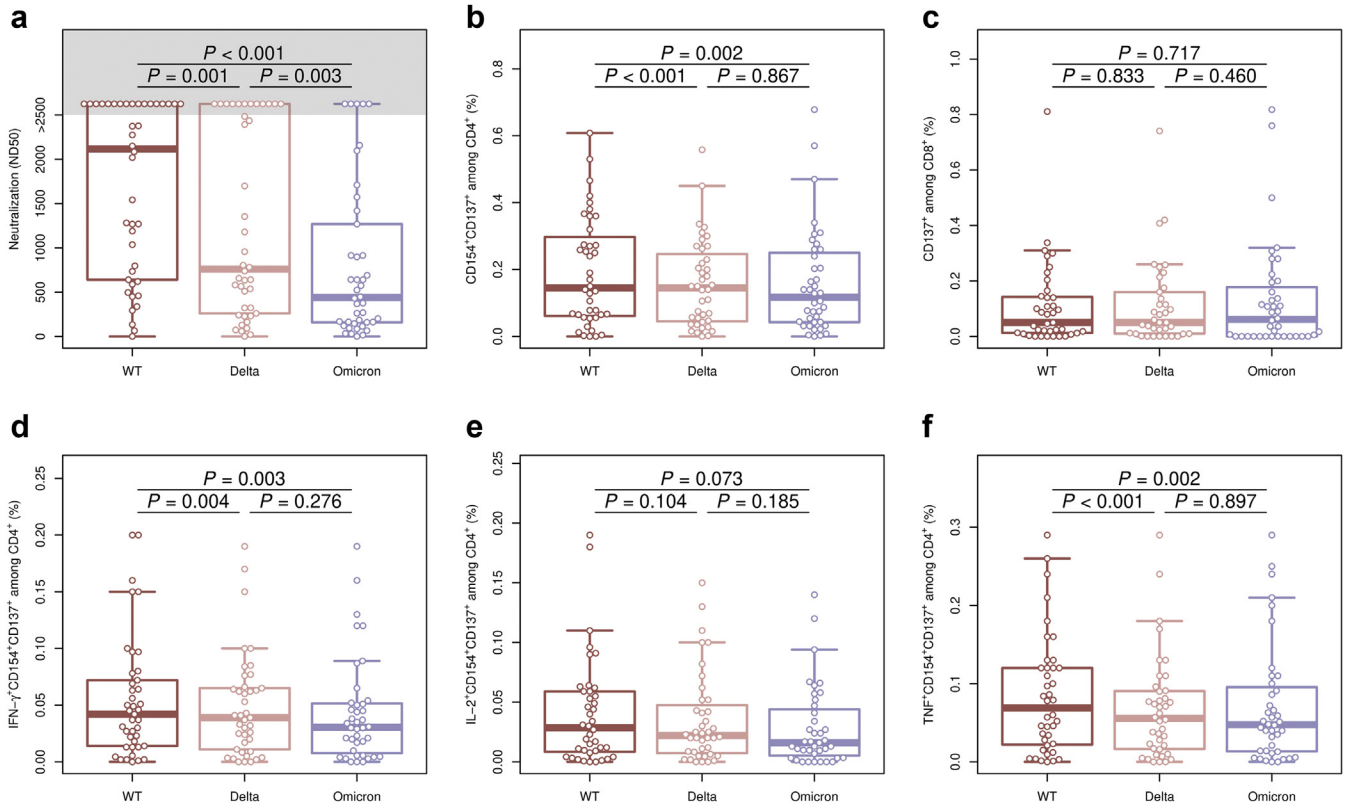

Figure 1 | Comparison of humoral and cellular immunity directed against spike protein (S-protein) derived from Omicron, Delta, and wild-type (WT) variants of concern in hemodialysis patients vaccinated with 4 mRNA coronavirus disease 2019 (COVID-19) vaccine doses. (**a**) Isolated serum from hemodialysis patients was analyzed for Omicron-, Delta-, and WT-specific neutralizing antibodies (50% Neutralizing Dose [ND50]). (**b**–**f**) Isolated peripheral blood mononuclear cells from hemodialysis patients were stimulated for 16 hours with 1 μg/ml severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) S-protein overlapping peptide pools from WT (dark red box plots), Delta (light red box plots), or Omicron (blue box plots). S-protein–reactive T helper cells were identified as life/dead-marker$^-$CD3$^+$CD4$^+$CD137$^+$CD154$^+$ (**b**), and S-protein–reactive cytotoxic T cells were identified as life/dead-marker$^-$CD3$^+$CD8$^+$CD137$^+$ (**c**). Within the S-protein–reactive CD4 T-cell population, antibodies against interferon-γ (IFN-γ) (**d**), interleukin-2 (IL-2) (**e**), and tumor necrosis factor (TNF) (**f**) were used to detect T helper cell 1 cytokine-producing T helper cells. Groups were compared using 2-sided, unpaired Mann-Whitney *U* test; $P \leq 0.050$ was defined as significant.

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Are randomized trials the best way to test different dialysis initiation regimens?

To the editor: We read with interest the randomized controlled trial by Vilar *et al.*, who compared standard thrice-weekly hemodialysis (sHD) with twice weekly dialysis (iHD) in patients initiating maintenance hemodialysis (MHD).[1]

The study enrolled 29 and 26 patients who were randomized to receive twice- versus thrice-weekly hemodialysis, respectively, and concluded that iHD is less costly and has similar 1-year outcomes compared with sHD, although no statistically significant benefit was observed in preserving residual kidney function. In line with previous reports,[2] about one-third of incident MHD patients were eligible for iHD. Randomization occurred within 3 months of initiation of MHD. Although we appreciate the finding that iHD is safe, we would like to raise some clinical and ethical issues.

First, only half the patients agreed to be randomized, although it is anticipated that patients with end-stage kidney disease starting on MHD are usually favorable to less frequent dialysis, unless they were accustomed to 3 sessions per week. Notably, 3 of the 26 patients in the sHD arm asked to be switched to less frequent hemodialysis, whereas no patient in the iHD arm asked to be moved to higher frequency during the short period of the study.

Although randomization within 3 months of initiation of dialysis is a reasonable strategy to differentiate between acute