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Humoral response to SARS-CoV-2 after vaccination and booster effect in patients undergoing dialysis

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ABSTRACT

Objective: The aim of this study was to determine and evaluate the postvaccination variation in immunoglobulin G (IgG) receptor-binding domain (RBD) produced in non-SARS-CoV-2–infected patients with nephropathy and renal replacement therapy.
Methods: This is a follow-up study of the humoral response to the BNT162b2 messenger ribonucleic acid COVID-19 vaccine in patients with nephropathy, comparing it with itself at different times and with the healthy population.
Results: In patients with nephropathy, a very striking decrease in IgG RBD was observed compared with the healthy population ($P<0.001$) at three months after the second dose. In patients with nephropathy, the response rate ≥590 binding antibody units/ml (4154 AU/ml) was detected in 45% of patients, 15 days after the second dose, whereas at 3 months, this decreased to 9% ($P<0.05$) and then increased to 86% after the third dose ($P<0.001$).
Conclusion: In patients with nephropathy and renal replacement therapy, it is necessary to administer a third-dose vaccination within 3 months after the second dose. It is important to continue monitoring the humoral response to obtain a better SARS-CoV-2 vaccination schedule.

1. Introduction

The COVID-19 pandemic continues to spread worldwide and to be one of the main problems affecting public health around the world. In Spain, according to data published by the Ministry of Health on April 13, 2022, 92.5% of the population aged over 12 years residing in Spain has received a complete vaccination pattern, with 92.9% having received at least one dose, achieving a protective effect against transmission of the virus (Ministerio de Sanidad. Gobierno de España, 2022). The BNT162b2 messenger ribonucleic acid (mRNA) COVID-19 vaccine has shown optimal protection in the general population (Polack et al., 2020). However, the decrease of antibodies over time after vaccination, as well as after infection, has been reported by several authors (Shrotri et al., 2021; Ripperger et al., 2020). On the other hand, the effect of some drugs, especially immunosuppressants, has led to the administration of booster doses of vaccine in different population groups, especially in patients who receive immunosuppressive treatment (Grupper *et al.*, 2021; Mrak et al., 2021). Similarly, patients with nephropathy add other intrinsic factors that can contribute to a lower immune response, such as the effect of uremia on the immune system, among others.

The importance of detecting and quantifying the antibodies generated after vaccination and infection lies in the fact that these antibodies have the capacity to neutralize the receptor-binding domain (RBD) of the SARS-CoV-2 virus in the S1 subunit, thus preventing its binding to the cellular receptor angiotensin-converting enzyme 2 and avoiding the entry of the virus into the cell. The action of these antibodies has shown effective protection against reinfection through rapid immune control (Chandrashekar *et al.*, 2020), as well as therapeutic action in patients with severe COVID-

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19 who were given early plasma from convalescent patients with high titers of these antibodies (Maor et al., 2020; Rasheed et al., 2020).

Finally, assays that detect immunoglobulin G (IgG) against RBD are highly specific and sensitive, and their titer information can be used as surrogates for neutralization activity against SARS CoV-2 (Suthar *et al*., 2020). It is therefore of interest to determine the amount of such antibodies produced. However, the World Health Organization (WHO) has not yet established the threshold of antibodies needed to determine the efficacy of vaccines and their durability (World Health Organization, 2020).

The aim of the present study was to determine the postvaccination variation in the level of IgG RBD antibodies produced in non–SARS CoV-2-infected patients with nephropathy in need of renal replacement therapy and to evaluate the difference in this level with that of vaccinated subjects without an underlying pathology who were not infected with SARS CoV-2.

2. Material and Methods

2.1. Individuals

A total of 44 patients with nephropathy in need of renal replacement therapy and 145 healthcare workers met the inclusion criteria and gave their consent to participate in the study. All participants had a negative IgG value against nucleocapsid, so none of them suffered SARS-CoV-2 infection during the study.

2.2. Study design

This study was a follow-up study of the humoral response to the BNT162b2 mRNA COVID-19 vaccine in patients with nephropathy in need of renal replacement therapy who attended the Hemodialysis Unit of the Complejo Hospitalario Universitario de Canarias, comparing it with the response of a healthy population of vaccinated healthcare workers. The study period was from March to November 2021. The study was approved by the hospital's Ethics Committee under code MIC 001. All study participants initially received two doses of BNT162b2 mRNA COVID-19 vaccine (30 ug per dose) within 21 days of each other, following the dosing recommendations. The healthcare personnel completed their two-dose vaccination schedule during the month of February 2021; however, the schedule of the group of patients with nephropathy was delayed from February to June 2021. Pregnant patients and those who had not completed the full vaccination schedule, who had been vaccinated with vaccines other than BNT162b2 mRNA COVID-19, or who had been infected with COVID-19 before or during the study were excluded; likewise, those with comorbidities were excluded from the healthcare group. In patients with nephropathy who required renal replacement therapy, serum and blood samples were collected at three different time points: 15 days after the administration of the second dose of vaccination, three months after said vaccination, and finally, 15 days after the administration of the third dose of vaccination, which was implemented during the month of October 2021. The sample was always collected at the beginning of dialysis, before the blood came into contact with the dialyzer membrane. In the healthcare personnel, a single serum sample was extracted six months after the administration of the second dose of vaccination. Demographic variables were collected in both groups, and in the group of patients with nephropathy, the following variables were collected from the review of the clinical histories: high blood pressure, diabetes, percentage of lymphocytes in the leukocyte formula, number of lymphocytes/ml in the three time sections, and mean determination of albumin g/dl in blood.

2.3. Serology studies

The serum and plasma samples of the patients with nephropathy extracted at different times were analyzed in parallel to determine the level of IgG RBD, lymphocyte count, and albumin concentration. Determinations of IgG RBD antibodies were performed using the Abbott microparticle chemiluminescence technique (ARCHITECT i 2000 SR TM), with the SARS-CoV-2 IgG II Quant reagent, following the manufacturer's instructions. In the interpretation of results, values $\geq$ 50 arbitrary units (AU)/ml (7.1 binding antibody units (BAU)/ml) were considered positive. To obtain comparable results of anti-SARS-CoV-2 antibody quantification at the international level, we transformed the units of the results obtained in AU/ml to the WHO international standard, BAU/ml. For this purpose, we multiplied each value obtained by the 0.142 coefficient. To ensure that no participant had been subclinically infected, we determined the presence of nucleocapsid IgG antibodies by means of the SARS-CoV-2 IgG chemiluminescence assay, Abbott.

2.4. Statistical analysis

The characteristics of the samples of hemodialyzed patients and healthcare workers are presented by summarizing the nominal variables with the absolute and relative frequencies of their component categories and those on a numerical scale with mean (SD) or median (P5-P95) according to their normal or nonnormal distribution, verified with the Kolmogorov-Smirnov or Shapiro-Wilk test, depending on the sample size available. The balance in sex and age between patients with nephropathy and healthcare workers was verified with Pearson's chi^2 or Fisher's Exact and Student's *t*-tests. For each of the three study points according to the vaccination of the patients with nephropathy, the level of IgG RBD antibodies generated between the groups of patients with nephropathy and healthcare personnel was compared cross-sectionally using the Mann-Whitney U test. In the case of imbalances between groups by age and/or sex between the groups compared, multivariate linear regression models with a full model and backward steps were used, with the level of IgG RBD at each cutoff point as the effect with the group as the explanatory variable for the differences and sex and age as adjustment covariates.

The Spearman correlation coefficient between lymphocyte levels (% and ml) and IgG RBD antibodies in patients with nephropathy was estimated for each cutoff point. The Spearman correlation coefficient between mean albumin level and RBD IgG levels at each cutoff point was also estimated.

The longitudinal progression of RBD IgG levels and leukocyte concentrations across the three cutoff points for nephropathic patients was estimated with Friedman's tests and the general linear model for repeated measures, respectively, obtaining the significance of the intrapatient change.

All hypothesis contrast tests were bilateral at a $P \leq 0.05$ significance level, and the calculations involved were performed using the SPSS 25.0^{TM} statistical data processing package from IBM Co® on Windows NT Professional operating system.

3. Results

A total of 44 patients with nephropathy in need of renal replacement therapy and 145 healthcare workers met the inclusion criteria and none of the exclusion criteria and gave their consent to participate in the study. All participants had a negative IgG value against nucleocapsid, so none of them suffered SARS-CoV-2 infection during the study.

In the patients with nephropathy, 57% had type 2 diabetes mellitus, and 86% had arterial hypertension. In the healthcare sample, 81% were women compared with 27% in the nephropaths

Table 1
Results of cross-sectional comparisons between nephropathic patients and healthcare personnel of their IgG RBD concentrations (BAU/ml) at each of the three cutoff points of the determinations.

IgG RBD (BAU/mL) in hemodialyzed patients Median (P5-P95)	IgG RBD (BAU/mL) in healthcare workers at 6 months after vaccination Median (P5-P95)	*Bivariate p-Value*[d]	*Adjusted P-Value*[e]
437.1 (26.4-4500.8)[a]	164.6 (37.4-724.7)	<.001	<.001
95.3 (7.1-1036.7)[b]	164.6 (37.4-724.7)	.004	<.001
2466.0 (335.7-5680)[c]	164.6 (37.4-724.7)	<.001	.009

BAU: binding antibody units; IgG: immunoglobulin G; RBD: receptor binding domain.
[a] 15 days after second dose of vaccination.
[b] 3 months after second dose of vaccination.
[c] 15 days after third dose of vaccination.
[d] Significance of differences obtained with the Mann-Whitney U test.
[e] Significance of the linear regression coefficient of patients versus clinicians on the IgG RBD. level adjusted for age and sex (not included in the regression models).

Table 2
Correlations of IgG RBD levels (BAU/ml) and lymphocyte concentration (% lymphocytes in leukocyte formula and lymphocytes/ml) in patients with nephropathy.

Temporary cut-off. according to the vaccination period in hemodialyzed patients.	IgG RBD (BAU/mL) in nephropathic patients Median (P5-P95)	% Lymphocytes in blood leukocyte formula Mean (SD)	*Spearman's correlation coefficient (p-Value)*	Lymphocytes/mL in blood Mean (SD)	*Spearman's correlation coefficient (P-Value)*
1	437.1 (26.4-4500.8)	20.9(7.2)	.093 (.548)	1.4×10^3 ($.5 \times 10^3$)	.307 (.043)
2	95.3 (4.9-1035.7)	20.4(7)	.159 (.303)	1.3×10^3 ($.5 \times 10^3$)	.301 (.047)
3	2466.0 (335.7-5680)	20.3 (8.3)	.12 (.940)	1.3×10^3 ($.5 \times 10^3$)	.156 (.313)

BAU: binding antiboy units; IgG: immunoglobulin G; RBD: receptor binding domain.
1–15 days after second dose of vaccination.
2– 3 months after second dose of vaccination.
3–15 days after third dose of vaccination.

(P<.001), and the age of the healthcare workers was 45 (±10) years compared with 72 (±12) years in the patients with nephropathy (P<.001).

A comparison of the level of RBD IgG antibodies between patients with nephropathy and vaccinated healthcare personnel for each cutoff point is shown in Table 1. The table provides the statistical significance of the bivariate cross-sectional comparisons without considering the age and sex imbalances observed between the groups, as well as the significance of the regression coefficient estimated by the multivariable linear backward stepwise model for the group as an explanation of the differences adjusted for age and sex, both covariates being driven out by the models at all cutoff points.

The correlations between the level of IgG RBD antibodies and the concentration of lymphocytes in blood (measured in % and lymphocytes/ml) for each time cutoff in the sample of hemodialyzed patients are shown in Table 2. As can be seen in the first and second cutoff, the statistical significance of the correlation coefficient, direct but weak, is reached between the level of IgG RBD and the concentration of lymphocytes expressed in lymphocytes/ml.

We also analyzed the concentration of albumin in global serum for the three time sections in patients with nephropathy, with its mean concentration of 3.8 (.34) g/dl not presenting statistical significance in the correlation with respect to the IgG level (BAU/mL) in the three time points (P=.583 - rho=.087, P=.897-rho=.021, P=.854-rho=.029).

Statistical significance tests of the evolution of IgG RBD levels and lymphocyte concentrations (in % and lymphocytes/ml) of Friedman and General Linear Model for repetitive measures yielded differences in the progression of the three indicators within patients with nephropathy (P<.0001 in the three cases).

A response rate of over 590 BAU/ml (4154 AU/ml) was detected in 45% of the patients 15 days after the second dose, whereas at 3 months, this percentage decreased to 9% (P<0.05), and 15 days after the third dose, it increased to 86% (P<0.001).

4. Discussion

This study reports the experience of a tertiary hospital on the humoral response to SARS-CoV-2 and its evolution in vaccinated nephropathic patients with nephropathy who required renal replacement therapy. For this purpose, we conducted a study in which the level of IgG RBD antibodies was analyzed at three different time points: first cutoff (at 15 days after the administration of the second dose), second cutoff (at 3 months after vaccination), and third cutoff (at 15 days after the administration of the third dose).

At the first cutoff point, we obtained a similar level of IgG RBD antibodies to that obtained in other series, such as that of Grupper *et al.* (2021), which analyzed the humoral response at the same time (median of 437.1 BAU/ml (3077 AU/ml) vs 2900 AU/ml). On the other hand, we detected that only 45% presented a threshold above 590 BAU/ml (4154 AU/ml), which could imply an initial deprotection in 55% of the patients, given the level of IgG RBD corresponding to a high titer of neutralizing antibodies *in vitro* was not reached (Ebinger et al., 2021). We used this conservative threshold of >590 BAU/ml (> 4154 AU/ml) because it correlates with a 95% probability of high neutralizing antibody titer (Ebinger et al., 2021).

However, we must consider that the humoral response in this type of patients is delayed, as described by Van Praet *et al.*, (2021), when it reflects the increase in synthesized antibodies from 4-5 to 8-9 weeks after vaccination. On the other hand, although a strong correlation between the level of neutralizing antibodies and efficacy has been described (Khoury et al., 2021), it should not be forgotten that discrete levels of antibodies can be effective (Bartsch et al., 2021), as can be the role played by the cellular response in the control of SARS-CoV-2 infection (Laing et al., 2020; Sekine et al., 2020). In the second cutoff point, a very striking decrease in the antibody level was observed, which was statistically significant when compared with the level of antibodies of healthcare personnel reached at six months after vaccination. This is proba-

bly because the humoral response immediately after vaccination in hemodialyzed patients is substantial, but significantly lower than in healthy individuals (Simon et al., 2021). Moreover, 91% of patients with nephropathy had a threshold below 590 BAU/mL, being more vulnerable to acquiring a SARS-CoV-2 infection and being at the expense of their cellular response and functionality of their present antibodies.

In the third cutoff point, a large increase in the level of IgG RBD antibodies was registered, which was higher and significant both in the comparison with the level reached in healthcare workers six months after vaccination and in the intrasubject analysis.

In addition, 45% of patients showed a response of more than 590 BAU/ml (4154 AU/ml) 15 days after the second dose, whereas at 3 months, this percentage decreased to 9% and 15 days after the third dose, increased to 86%.

The latest studies describe how the administration of a third dose of BNT162b2 mRNA COVID-19 vaccine achieves a booster effect that results in decreased rates of infection and severe COVID-19 when compared with the population that did not show a booster effect (Bar-On et al., 2021).

Considering the decrease in antibodies that occurs over time and the appearance of new emerging variants that could affect the efficacy of the vaccination, it seems necessary to administer a third dose; however, there is no definitive evidence on when a third dose is necessary (The Lancet Infectious Diseases, 2021). According to our study in hemodialyzed patients with nephropathy, it seems to be necessary to administer it less than three months after receiving the second dose.

On the other hand, plasma albumin concentration is related to the nutritional status of the patient, and decreased levels could be associated with decreased humoral immune response (Agur et al., 2021; Santos-Araújo et al., 2022). In our study, we did not find this association in the different time sections, coinciding with Grupper et al., (2021) However, the albumin levels reached in our study were $>$ 3g/dl.

Finally, we highlight the intersubject evolution in the group of patients with nephropathy who required replacement therapy of IgG RBD antibody and lymphocyte levels, whereby as lymphocyte levels increased, so did the levels of IgG RBD antibodies.

Our study has several limitations: the first is that our study population was not ethnically diverse, which reduces the generalization of our results. On the other hand, we cannot be sure that the decrease in the level of antibodies observed in patients with nephropathy three months after the administration of the second dose is exclusive to this population, because it is possible that the same occurred in healthcare personnel who were not analyzed at the same cutoff point. Finally, we have not determined the cellular response in this group of patients, and it would be important to do so in those cases in which the level of humoral response is limited, because different studies describe a robust and efficient T lymphocyte cellular response in asymptomatic patients or those with moderate COVID-19 who presented an absence of humoral response (Sekine et al., 2020). On the other hand, antibody titers are not a surrogate indicator of the magnitude of memory T cells (Dan et al., 2021); a simple antibody serodiagnosis test will not be a robust indicator of protective immunity, and older individuals have a more limited naïve T cell repertoire.

5. Conclusion

Our study reflects the need to continue monitoring the humoral response in patients with nephropathy who receive renal replacement therapy, to achieve in them a better adaptation of the vaccination schedule against SARS-CoV-2, detecting the necessary moments for the administration of new doses of vaccine that produce a protective booster effect.

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Ethical Approval statement

The study was approved by the Ethical Committee with the code MIC 001.

Declaration of Competing Interest

The authors have no competing interests to declare.

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