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ORIGINAL ARTICLE

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Low-density lipoprotein apheresis is associated with removal of SARS-CoV-2 antibodies

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Abstract

Background: Low-density lipoprotein apheresis is not specific to lipoproteins but removes immunoglobulins as well. It remains elusive, whether protective SARS-CoV-2 antibodies after vaccination from COVID-19 are eliminated as well.

Methods: A cross-sectional case–control study on 55 patients undergoing weekly lipoprotein apheresis and 21 patients with comparable comorbidities and epidemiology not undergoing apheresis. SARS-CoV-2 IgG was assessed in all patients prior to apheresis and in 38 patients both before and after apheresis.

Results: SARS-CoV-2 IgG concentrations before a session of lipoprotein apheresis were comparable to control patients not undergoing apheresis (1727 IU/ml, IQR 365–2500) vs. 1652 IU/ml,(IQR408.8–2500), $p = 0.78$). SARS-CoV-2 IgG concentrations were reduced by lipoprotein apheresis from 1656 IU/ml(IQR 540.5–2500) prior to 1305 IU/ml (IQR 449–2500) afterwards ($p < 0.0001$).

Conclusion: Lipoprotein apheresis removes SARS-CoV-2 IgG. The average elimination rate was 21.2%. In the present population of patients undergoing apheresis once weekly, however, the elimination did not lead to inferior concentrations compared to patients not undergoing lipoprotein apheresis.

KEYWORDS

coronavirus disease 2019, low-density lipoprotein apheresis, SARS-CoV-2, vaccination, antibodies

1 | INTRODUCTION

Low-density lipoprotein apheresis is an extracorporeal therapy that removes apolipoprotein B-containing lipoproteins from circulation. It is approved for the treatment of refractory hypercholesterolemia and hyperlipoproteinemia (a) in several countries, for example, Germany. There are different apheresis techniques on the market, among them double filtration plasmapheresis (DFPP, lipid filtration), a hemoperfusion system directly absorbing lipoproteins (DALI), ApoB100 immunoadsorption, and heparin-induced extracorporeal LDL-precipitation (HELP). None of these approaches is completely selective for lipoproteins. Due to their particular physicochemical and structural characteristics, they also eliminate different quantities of various other plasma proteins, including fibrinogen, and immunoglobulins. (1–3) Whereas fibrinogen is removed by up to 50%, the immunoglobulin extinction is lower. Thus, IgG is removed during an individual session of DFPP by 14%, HELP by 16%, DALI by 15%–20%, and immunoadsorption by 25%. (2)

In times of SARS-CoV-2 pandemic, it is of special interest, whether lipoprotein apheresis removes

TABLE 1 Characterization of study population including epidemiology, apheresis modality, comorbidities, SARS-CoV-2 vaccination status, and antibodies

	Patients undergoing apheresis ($n = 55$)	**Control ($n = 21$)**	***p***
Age (years)	61.1 ± 9.4	67 ± 8.2	0.49
Body mass index (kg/m^2)	27.6 ± 4.6	28.6 ± 5.7	0.45
Apheresis indication:		/	
hypercholesterolemia and hyperlipoproteinemia (a) (*n*, %)	−33, 60%		
hypercholesterolemia (*n*, %)	−11, 20%		
hyperlipoproteinemia (a) (*n*, %)	−11, 20%		
Apheresis modality (*n*, %)		/	
Lipid filtration	−38, 69.1%		
DALI	−13, 23.6%		
HELP	−4, 7.3%		
Lipid-lowering medication (*n*, %)			
Statins	−37, 65.5%	−24, 85.7%	0.08
Ezetimibe	−25, 45.5%	−2, 9.5%	0.0034
PCSK9-inhibitors	−8, 12.7%	−0, 0%	0.09
Comorbidities			
Coronary artery disease (*n*, %)	47, 85.5%	15, 71.4%	0.16
Cerebrovascular disease (*n*, %)	19, 34.6%	9, 42.9%	0.5
Peripheral artery disease (*n*, %)	13, 23.6%	5, 23.8%	0.98
Hypertension (*n*, %)	29, 52.7%	19, 90.5%	0.0023
Diabetes (*n*, %)	14, 25.5%	7, 33.3%	0.49
Chronic kidney disease (*n*, %)	14, 25.5%	7,33.3%	0.49
SARS-CoV-2			
Patients with complete vaccination (*n*, %)	55, 100%	21, 100%	
SARS-CoV-2 vaccine (*n*, %)			0.41
BNT162b2	−46, 80%	−25, 90.4%	
mRNA-1273	−2, 16.4%	−1, 4.8%	
AZD1222	−10, 3.6%	−1, 4.8%	
Time after the second dose (weeks)	5 ± 2.5	6.1 ± 1.8	0.07
SARS-CoV-2 IgG concentration	1727 (IQR 365–2500)	1652 (IQR 408.8–2500)	0.78

TABLE 2 Detailed description of apheresis modalities

	Lipid filtration $n = 38$	DALI $n = 13$	HELP $n = 4$
Treatment time (minutes)	100 (IQR 90–110)	120 (IQR 120–155)	140 (IQR 135–150)
Treated serum/blood volume (ml)	3500 (IQR 3000–3825)	8000 (IQR 6250–9000)	2550 (IQR 1925–3700)
Blood purification equipment			
DALI Adsorber 750		4, 30.7%	
DALI Adsorber 1000		6, 46.2%	
DALI Adsorber 1250		3, 23.1%	
HELP/Cascades, Haemoselect M 0.5, HELP precipitate filter			4, 100%
Membrane blood			
OP08W (n, %)	−35, 92.1%	/	/
OP05W	−3, 7.9%		
Membrane lipid			
EC 50 W	−38, 100%	/	/
Vascular access			
Peripheral vein	18, 88.2%	5, 71.4%	2, 50%
Shunt	6, 11.8%	2, 28.6%	2, 50%
Medicines related to lipoproteins apheresis therapy			
Heparin	34, 89.5%	4, 30.7%	2, 50%
Tinzaparin	3, 7.9%	0, 0%	0, 0%
Dalteparin	1, 2.6%	1, 7.8%	2, 50%
Citrate	0, 0%	8, 61.5%	0, 0%
Plasma flow (ml/min)	30 (IQR 30–30)	/	21 (IQR 18–24.8)
Blood flow (ml/min)	90 (IQR 90–100)	70 (IQR 60–80)	75 (IQR 67.5–78.6)
Volume replacement solution (ml)	0 (IQR 0–100)	0 (0–250)	/

Note: Data are presented as provided by each center, no imputation for missing data.

protective antibodies to the virus as well. If so, does lipoprotein apheresis remove antibodies to a clinically relevant extent? In a cross-sectional case–control study, we analyzed SARS-CoV-2 IgG in 55 vaccinated patients who routinely undergo lipoprotein apheresis once weekly. Patients with comparable comorbidities and age served as control.

2 | METHODS

2.1 | Patients and design

Patients were recruited at the Dialysis Unit of a University Hospital and three outpatient dialysis centers. There are no specifications for a particular procedure in Germany. Lipid filtration was the standard procedure in all the centers in this analysis. In case of clinical problems (e.g., hypotension, failure to achieve the predefined LDL-C/Lp(a) reduction), the procedure was changed to either DALI or HELP.

Inclusion criteria were an application of the second dose of a SARS-CoV-2 vaccine at least 2 weeks prior to inclusion in the study, lipoprotein apheresis on a regular basis starting before SARS-CoV-2 vaccination. Exclusion criteria were a time > 10 weeks after application of the second dose of a SARS-CoV-2 vaccine and antibody-depleting therapies, for example, rituximab or bortezomib. Vaccinated outpatients of a German University not undergoing lipoprotein apheresis served as control and were matched for age, comorbidities, and time after the second vaccination. Blood samples for SARS-CoV-2 antibody measurement were drawn right before the start of the apheresis session. In all but one dialysis unit, additional blood samples were obtained at the end of lipoprotein apheresis. This study was conducted in accordance with the declaration of Helsinki and was approved by the local ethic

TABLE 3 Description of blood purification machines as blood purification equipment

Blood purification machines:	
DFPP	Octo Nova, DIAMED, Cologne, Germany
DALI	Hemoadsorption device 4008 ADS, Fresenius Medical Care Germany GmbH, Bad Homburg, Germany
HELP	Plasmat Futura, B. Braun Avitum AG, Melsungen, Germany
Blood purification equipment	
DALI Adsorber 750	Fresenius Medical Care Germany GmbH, Bad Homburg, Germany
DALI Adsorber 1000	Fresenius Medical Care Germany GmbH, Bad Homburg, Germany
DALI Adsorber 1250	Fresenius Medical Care Germany GmbH, Bad Homburg, Germany
HELP/Cascades, Haemoselect M 0.5, HELP precipitate filter	Braun Avitum AG, Melsungen, Germany
Membrane blood and lipid	
OP08W (*n*, %)	Asahi Kasei Medical, Tokyo, Japan
OP05W	Asahi Kasei Medical, Tokyo, Japan
EC 50 W	Asahi Kasei Medical, Tokyo, Japan

committee. Informed consent was obtained from all participants.

2.2 | Measurement of SARS-CoV-2 antibodies

The Elecsys Anti-SARS-CoV-2 S (Roche Diagnostics International Ltd, Rotkreuz, Switzerland) immunoassay was used for measurement of IgG to SARS-CoV-2 spike protein having a linear detection range of up to 2500 IU/ml.

2.3 | Statistics

Numeric data were tested for normal distribution (D'Agostino & Pearson test). In case of normal distribution, data are presented as mean ± standard deviation, otherwise as median and interquartile range (IQR). Numeric epidemiological data of the two groups were compared by unpaired two-tailed t-tests, dichotomic data by chi-squared tests. Antibody concentrations were compared between groups by Mann–Whitney test, concentrations before and after apheresis by Wilcoxon test. $p < 0.05$ was regarded significant. Statistical analysis was performed with GraphPad Prism (Version 9.12, GraphPad Software, La Jolla California USA).

3 | RESULTS

Fifty-five patients undergoing lipoprotein apheresis were included in the study. Eleven patients (20%) were on apheresis for familial hypercholesterolemia, 11 patients (20%) for hyperlipoproteinemia (a), 33 patients (60%) were on apheresis for both indications. Mean age was 61.1 ± 9.4 years. As presented in Table 1, all these patients underwent apheresis as a secondary prevention strategy, thus having manifest cardiovascular disease. The most frequently used apheresis modality was lipid filtration ($n = 38$, 69.1%), followed by DALI ($n = 13$, 23.6%) and HELP ($n = 4$, 7.3%). 65.46% of the patients were on statins, 45.7% on ezetimibe and 12.7% received PCSK9-inhibitors. A detailed description of apheresis modalities, blood purification machines, and equipment are shown in Tables 2 and 3. The control group was comparable to the apheresis group regarding age, body mass index, and the time after the second dose of the SARS-CoV-2 vaccine.

All of the apheresis patients and the patients not undergoing apheresis were fully vaccinated. The majority of patients received an mRNA vaccine. Table 1 presents the individual vaccine utilization in the two groups.

Pre-session SARS-CoV-2 IgG concentrations in patients undergoing lipoprotein apheresis were comparable to those of control patients not undergoing apheresis (Figure 1A, 1727 IU/ml (IQR 365–2500) vs. 1652 IU/ml (IQR 408.8–2500), $p = 0.78$). Time since the administration of the second dose did not significantly differ between groups (5.0 ± 2.5 vs. 6.1 ± 1.8 weeks, $p > 0.05$). Lipoprotein apheresis sessions significantly reduced SARS-CoV-2 IgG concentrations (Figure 1B) from 1656 IU/ml (IQR 540.5–2500) prior to the procedure to 1305 IU/ml (IQR 449–2500) afterward ($p < 0.0001$).

Overall, the percentage removal rate of SARS-CoV-2 IgG was 21.2% (Figure 1B). The highest removal rate was observed in HELP (52.73%), followed by DALI (32.4%) and lipid filtration (19.5%, Figure 1D).

Since the upper threshold of the linear detection range of the ELISA assay was 2.500 IU/ml, the true

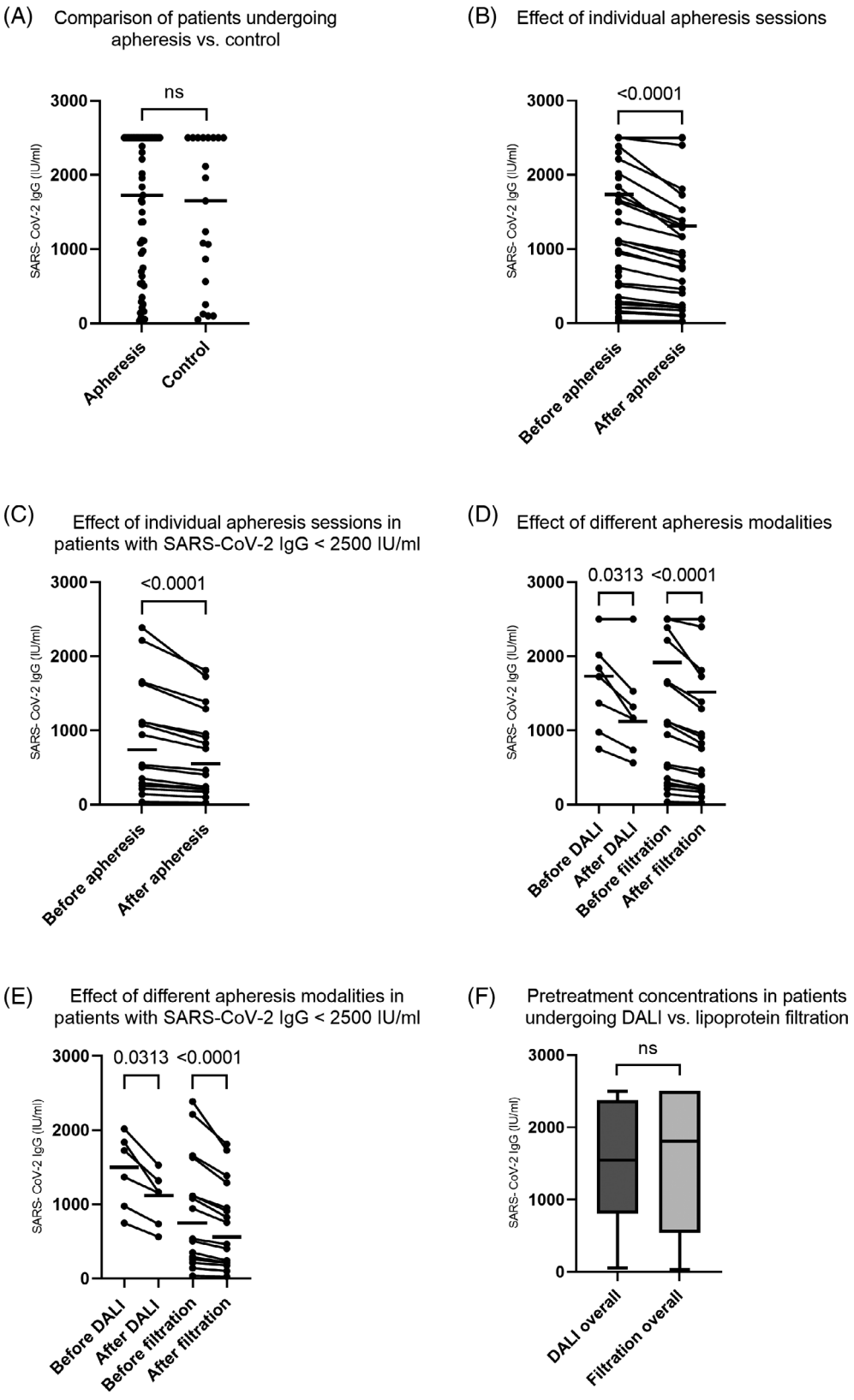

FIGURE 1 (A) SARS-CoV-2 IgG concentration in apheresis ($n = 55$) and control group. ($n = 21$). Black bars demonstrate median (B) SARS-CoV-2 IgG concentration before and after an individual apheresis session with any kind of lipoprotein apheresis. Black bars demonstrate median ($n = 38$) (C) SARS-CoV-2 IgG concentration before and after an individual apheresis session with any kind of lipoprotein apheresis without individuals, which reached a linear detection rate of >2500 IU/ml ($n = 16$). Black bars demonstrate median (D) SARS-CoV-2 IgG concentration before and after an individual apheresis session with lipid filtration ($n = 28$) and DALI ($n = 8$). Black bars demonstrate median (E) SARS-CoV-2 IgG concentration before and after an individual apheresis session with lipid filtration ($n = 16$), DALI ($n = 6$). Individuals, which reached a linear detection rate of >2500 IU/ml were excluded. Black bars demonstrate median (F) presentation SARS-CoV-2 IgG concentration with lipid filtration as boxplot ($n = 38$), DALI ($n = 12$). (A–F) antibody concentrations were compared between groups by Mann–Whitney test, concentrations before and after apheresis by Wilcoxon test. *$p < 0.05$ was regarded significant

elimination rate of SARS-CoV-2 IgG antibodies could be underestimated by the present analysis. Therefore, we performed a second analysis, in which those subjects with antibody concentrations of ≥2.500 IU/ml were excluded (Figure 1C, E). In this analysis of patients within the linear detection range, the elimination rate

was 20%, comparable to the overall analysis. The highest removal rate was also observed with DALI (25%), followed by lipid filtration (17.7%).

The pretreatment SARS-CoV2-IgG concentration was higher in the lipid filtration population 1808 (IQR 542.3–2500) compared to the DALI population 1548 (IQR 805.5–2380, $p > 0.05$, Figure 1F).

4 | DISCUSSION

Cerebrovascular and cardiovascular disease are associated with increased severity and mortality in COVID-19. (4, 5) Indication of chronic lipoprotein apheresis requires manifest and progressive cardiovascular disease.(6) Thus, patients undergoing lipoprotein apheresis mandatorily constitute a high-risk group for an adverse course of the disease. (7, 8) Thus, a sustained vaccine-induced immune response to SARS-CoV-2 is of crucial importance for these patients. The present cross-sectional study shows for the first time that an individual lipoprotein apheresis session reduces the vaccine-induced anti-spike SARS-CoV-2 IgG concentration by approximately 20%. This extinction largely corresponds to the lipoprotein apheresis-induced elimination rates of overall IgG concentrations in the literature. (2) The analysis excluding patients with antibody concentration 2500 IU/ml confirms the observed reduction rate and thereby excludes a falsely low finding.

The removal rate of DALI (32.4%) was higher than that of lipid filtration (19.5%). This finding matches with the literature as well: DALI is known to have a higher average elimination rate of IgG than lipid filtration. (2) Noteworthy, the number of patients with DALI was low in our study ($n = 9$).

Despite its well-described effect on IgG removal, lipoprotein apheresis does generally not lead to hypogammaglobulinemia since immunoglobulins are rapidly regenerated in non-immunocompromised subjects. (1, 3) Accordingly, we did not observe differences in pre-apheresis anti-SARS-CoV-2 IgG concentrations with anti-SARS-CoV-2 IgG concentrations of subjects not undergoing apheresis. This finding strongly suggests that regeneration of these antibodies take place in a sufficient manner to compensate for the removal by lipoprotein apheresis. Moreover, it indicates that the primary vaccine-induced immune response in patients undergoing lipoprotein apheresis is non-inferior to the general population. (9)

The study is limited by its cross-sectional character. Despite the comparable SARS-CoV-2 IgG concentrations in both groups, only a longitudinal study comparing pre-apheresis concentrations with concentrations of subjects without apheresis over several months will be able to finally exclude a clinically relevant long-term effect of lipoprotein apheresis on anti-SARS-CoV-2 IgG. The vaccine efficacy of BNT162b2 has recently been demonstrated to decrease by 3% per month after the second vaccination. (10) In this context, the longitudinal study will have to exclude an acceleration of this trend by lipoprotein apheresis.

In conclusion, the present study shows that lipoprotein apheresis indeed removes SARS-CoV-2 IgG. The average elimination rate of about 20% did not lead, however, to inferior concentrations compared to patients not undergoing lipoprotein apheresis. With regard to the extraordinarily high cardiovascular risk of patients undergoing lipoprotein apheresis and the consequently high risk for an adverse course of COVID-19, a longitudinal study on the continuous effects of lipoprotein apheresis on anti-SARS-CoV-2 IgG concentrations is highly desirable to finally exclude a clinically relevant effect.

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CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

FUNDING INFORMATION

No funding has been received for this study.

ETHICAL APPROVAL AND PATIENT CONSENT STATEMENT

This study was conducted in accordance with the declaration of Helsinki and was approved by the ethics committee of Ruhr-University Bochum (20–68 860). Informed consent was obtained from all participants. Clinical trial registration was not necessary, because of the retrospective design of the study.

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