Erratum
September 19, 2024. DOI: 10.1159/000541224

Blood Purification

Research Article

Blood Purif 2023;52(suppl 1):85–94
DOI: 10.1159/000540402

Received: April 12, 2023
Accepted: July 7, 2024
Published online: July 24, 2024

Protein-Bound Uremic Toxins and Inflammation Process in Hemodialysis Patients: Is There a Role for Adsorption Hemodiafiltration?

Paolo Fabbrini[a] Denise Vergani[b] Anna Malinverno[b] Federico Pieruzzi[b] Marita Marengo[c] Guido Merlotti[e] Claudio Medana[d] Alessandro Domenico Quercia[c] Vincenzo Cantaluppi[e]

[a]Nephrology Department, ASST-Nord milano, AO Bassini, Cinisello Balsamo-Milano, Italy; [b]Nephrology Department, Università degli Studi di Milano Bicocca, Monza, Italy; [c]Unit of Nephrology and Dialysis, Department of Medical Specialties, Cuneo, Italy; [d]Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy; [e]Nephrology and Kidney Transplantation Unit, Department of Translational Medicine (DIMET), University of Piemonte Orientale (UPO), "Maggiore della Carità" University Hospital, Novara, Italy

Keywords
Protein-bound uremic toxins · Inflammation · Adsorption · Hemodiafiltration

Abstract

Introduction: Despite major advances in the field of dialysis, there are still some unmet needs such as reducing inflammation through adequate depuration. It is well known that the wide spectrum of pro-inflammatory and pro-atherosclerotic uremic toxins are inefficiently removed by current dialysis techniques. Adsorption seems to be an extra tool to remove toxins, but its effect and optimization have not been widely studied. The aim of this report was to present preliminary results regarding the possibility of performing hemodiafiltration with a highly adsorptive polymethylmethacrylate membrane. ***Methods:*** The study was first conducted in 10 patients in which the safety and feasibility of hemodiafiltration with PMMA BG-U 2.1 membrane were tested through measurement of hemolysis indices, transmembrane pressures, and dialysis adequacy. Twenty patients were prospectively observed for 18-month period in which they consecutively underwent standard hemodialysis, standard post-dilution hemodiafiltration, and polymethylmethacrylate-based post-dilution hemodiafiltration. Protein-bound uremic toxins concentrations and inflammatory markers were measured throughout the observed period. ***Results:*** HDF-PMMA was inferior to HDF in convective volume, but KT/V was similar, and no differences were noted in operating pressures during the two treatments. During HDF-PMMA period of treatment, we observed a significant reduction of CPR levels, and HDF-PMMA was superior to all other treatments in hepcidin removal even if this did not significantly affect hemoglobin levels. HDF-PMMA could significantly reduce indoxyl sulfate (indoxyl) concentration over a period of 6 months but not for p-cresyl sulfate (p-cresyl). ***Conclusion:*** PMMA BG-U 2.1 membrane can be safely and efficiently used in hemodiafiltration. Moreover, as these preliminary results show, adding adsorption properties to convection and diffusion enabled an increased removal of indoxyl uremic toxin associated to a reduction in inflammation markers as CRP and hepcidin without any negative impact on albumin levels.

karger@karger.com
www.karger.com/bpu

Correspondence to:
Paolo Fabbrini, paolo.fabbrini@asst-nordmilano.it

Introduction

Dialysis techniques have evolved in recent years, new dialysis monitor technology has been introduced, and new dialyzers have been proposed to widen the spectrum of clinical opportunities for uremic patients. Diffusion and convection are the physical principles that, alone or combined, have represented the cornerstones of dialysis evolution, but not all depurative needs have been solved with hemodialysis (HD) and hemodiafiltration (HDF). Randomized controlled trials designed to show superiority of HDF in comparison to standard or high-flux HD in overall and cardiovascular mortality had shown contrasting results [1]. Recently CONVINCE study produced evidences that high-volume (23 lt) HDF seems to be favorable in terms of overall survival [2], but results were not confirmed on cardiovascular mortality leaving the debate on HDF superiority still open [3]. High doses of convection have the theoretical advantage of removing more toxins in the middle to the middle-high molecular range, but still, cannot efficiently remove protein-bound uremic toxins (PBUT) [4] that seem to have a great impact on the pro-inflammatory profile of the uremic milieu [5].CONTRAST study subanalysis, in fact, demonstrated that convection had a little impact on PBUT clearance [6] which plasma levels were mainly determined by residual kidney function due to residual tubular function. Between all the PBUTs, indoxyl and p-cresyl, have been shown to be associated, both in vitro and in vivo, with cardiovascular disease and to have a relationship with mortality.

Therefore, since convection and diffusion are not always the solution to improve toxins removal, several observations indicate implementation of adsorption as a possible implementation. Adsorption represents an adjunctive modality to remove solute but not all dialysis materials have this property [6], in particular, polysulfone (PS)-derived dialyzers exert only modest adsorption capacity due to their asymmetrical configuration in which the adsorptive component is just one-sixth of the entire capillary thickness. On the other hand, other types of membranes have different configurations, namely, polymethylmethacrylate (PMMA) membranes are highly symmetrical membranes in which all the capillary thickness is involved in the depuration process trapping molecules inside the capillary wall [7, 8]. There are various types of PMMA membranes with different properties, and their adsorptive characteristics have been studied in different clinical settings such as reduction of uremic pruritus [9, 10], better biocompatibility [11, 12], and serum-free light chain removal [13] In this selection of membranes, PMMA BG-U has a higher ultrafiltration coefficient (K-UF) and a more symmetric and uniform pore distribution which should make it suitable for HDF, adding to this conventional treatments the possibility to remove molecules through adsorption. Therefore, our hypothesis was that it should be possible to combine diffusion, convection, and adsorption in one treatment just by switching from a common PS-based membrane to PMMA BG-U membrane to perform online HDF. Adding adsorption should represent an advantage by removing a wider spectrum of toxins involved in the uremic mileau driven inflammation, including indoxyl and p-cresyl.

Table 1. Division in groups according to type of dialysis during the study observation periods

	T0–T6	T6–T12	T12–T18
Group 1	HD	HDF-PMMA	HDF
Group 2	HDF	HD	HDF-PMMA
Group 3	HDF-PMMA	HDF	HD

T0 to T18 represent 18 months of treatment. HD: standard HD with Helixone® FX Classix 80; HDF: post-dilution HDF with Helixone® FX CorDiax 100; HDF-PMMA: post-dilution HDF with Filtryzer® BG-U 2.1 – Toray Industries, Japan).

Materials and Methods

The study protocol was divided into two steps, an initial safety and feasibility test (10 test patients) followed by an 18-month crossover study (20 patients). We first evaluated the feasibility of performing HDF with PMMA BG-U 2.1 (Toray Industries, Inc. Tokyo, Japan). We selected 10 patients from a single institution who were already dialyzed using BG-U 2.1 in HD mode, and each of them was switched for a single session to post-dilution HDF treatment with the same dialyzer. We excluded patients who used a central venous catheter as dialysis access, patients with malfunctioning (Qb < 250 mL/min) native vascular access, or spontaneous (no EPO treatment) Hb levels greater than 12 g/dL, together with patients with active inflammatory disease (infectious or autoimmune disease). Inclusion criteria were age >18 years old and the ability to understand and sign an informed consent. HDF treatments were executed with Fresenius ©5008 monitor with post-dilution modality with automatic regulation of reinfusion volume (AutoSub Plus System). The monitor was connected to an electronic chart, and the following treatment parameters were registered every 5 min: aspiration (Pa, mm Hg), reinfusion (Pv, mm Hg), and transmembrane pressure (TMP, mm Hg) in the extracorporeal circuit, reinfusion volume (Qr, mL/min), blood flow (Qb, mL/min), ultrafiltration (UF, mL/min), blood pressure (BP, mm Hg), heart rate (HR, bpm), KT/V.

At the beginning and at the end of each PMMA post-dilution HDF session, we measured hemoglobin (Hb), hematocrit (Ht), total serum protein, β2-microglobulin, haptoglobin, and LDH. Results were compared with the *t* test for paired measures, $p < 0.05$ being considered statistically significant.

Table 2. Summary and schedule of tests performed during the study for each patient

	Monthly	T0	T3	T6	T9	T12	T15	T18
Standard routine	X							
CRP, mg/dL	X							
Albumin, g/dL	X							
IL-6, pg/mL		X	X	X	X	X	X	X
Hepcidin, pg/mL		X	X	X	X	X	X	X
p-cresyl, ppm		X	X	X	X	X	X	X
Indoxyl, ppm		X	X	X	X	X	X	X

The standard routine included iron panel, Hb levels, Ca-P balance, electrolytes, and acid-base test at the beginning of each month. Albumin and CRP levels were performed monthly, while beta-2 microglobulin and all the other tests were performed every 3 months, before and after the dialytic session to measure percentage removal (RR%).

According to the feasibility resulting from this analysis, we designed an observational crossover study in which 20 patients underwent 6 months of standard HD (Helixone® FX Classix 80 – Fresenius Medical Care, Germany), 6 months of post-dilution HDF (Helixone® FX CorDiax 100 – Fresenius Medical Care, Germany), and 6 months of PMMA-based post-dilution HDF (Filtryzer® BG-U 2.1 – Toray Industries, Japan). Every 6 months, a switch from one treatment to the other was randomly assigned.

Patients were therefore assigned to three groups according to the progressive switch from one treatment to the other as reported in Table 1. Patients were 7 in groups 1 and 2, while 6 in group 3 since 1 patient withdrew informed consent for personal reasons.

During the study period, at the middle week dialysis session, blood samples were collected, and analyses were performed according to Table 2. ELISA test was performed to test IL-6 and hepcidin concentrations, while HPLC analysis was used to determine PBUTs (indoxyl and p-cresyl) concentrations. Data are expressed as mean and minimum-maximum; *t* test and ANOVA for repeated measure were used to investigate statistical differences ($p < 0.05$).

All patients provided informed consents, the study was conducted in accordance with the World Medical Association Declaration of Helsinki, and the study was approved by the Local Ethical Committee Monza and Brianza (reference No. 459/4th May 2016).

Results

HDF-PMMA Efficacy

A prodromic test on HDF-PMMA efficacy was performed in 10 patients in a single session of post-dilution HDF. All the treatments were concluded without any complication, and every 5 min monitoring of the circuit pressures did not reveal a significant TMP rise, with an average of 210 mm Hg (min 75 mm Hg, max 320 mm Hg), the TMP pressures were stable during the 4-h treatment ranging from 200 (162–316) mm Hg for the first hour to 208 (170–322) mm Hg, 218 (170–320) mm Hg, 216 (75–319) mm Hg for the second, third, and fourth hour, respectively. Hemolysis indices (LDH and haptoglobin) were measured before and after every single session, LDH levels were 164 IU/L (100–185) before the session and 176 IU/L (97–195) with no significant differences ($p > 0.05$), haptoglobin levels rose from 140 mg/dL (125–152) to 159 mg/dL (135–167), indicating the absence of hemolysis ($p > 0.05$), Hb and Ht rose, as expected, secondary to hemoconcentration. Convective volume was measured every single hour, and it ranged from 5.4 lt/I hour to 4.0 L/IV hour, for a median value of 18.8 L (16.3–21.9) per session. As already mentioned, after this safety measure, 20 patients were assigned to the observational part of the study, allocated in three groups. Patients' basal characteristics are reported in Table 3, and there were no significant differences between groups. During the observation period, safety of HDF-PMMA was confirmed. We registered more than 750 PMMA-HDF sessions, on average 226 min long, in comparison to 225 and 227 min of HDF and HD treatment, respectively, with no significant difference, no events of hemolysis or other significant mechanical complications were registered. Convective volumes were reported for every HDF session: post-dilution volumes were significantly higher in standard HDF in comparison with HDF-PMMA with 25.8 L/treatment (7.1–35.7) and 19.4 L/treatment (5.1–32.8), respectively ($p < 0.05$). KT/V measures showed no differences between all the types of treatment with an average KT/V above 1.40 (1.46 for HD, 1.55 for HDF, 1.54 for BG-U HDF). Biochemical data, measured monthly before the dialysis sessions, were not different between HDF and HDF-PMMA groups, while both HDF showed a superiority in comparison to HD to reduce beta-2 microglobulin (79% HDF and 68% HDF-PMMA in comparison to 51% HD).

Albumin levels did not significantly change during the study in all study groups, HDF treatment started and ended with the same mean albumin value of 3.9 g/dL, and for HDF-PMMA treatment, levels were 3.9 g/dL at the beginning and after 6 months 3.8 g/dL ($p > 0.05$), while in HD, we observed a slight increase of albumin from 3.9 to 4.0 g/dL ($p > 0.05$).

Inflammation

The average value of all the monthly measured CRP levels during the 6 months of HDF-PMMA treatment were significantly lower in comparison to those measured both in 6 months of HDF or HD treatments (shown in Fig. 1a). Since CRP levels were obtained every month, we could also observe a trend toward CRP reduction during the 6 months of HDF-PMMA treatment and a tendency

Table 3. Baseline values of principal metabolic markers in all groups

	Group 1	Group 2	Group 3
Gender, M/F	4/3	4/3	4/2
Dialysis vintage, months	38 (26–66)	45 (36–69)	42 (29–88)
Age, years	71 (65–73)	72 (63–75)	73 (66–76)
KT/V	1.42 (1.27–1.52)	1.44 (1.19–1.6)	1.37 (1.21–1.54)
Hemoglobin, g/dL	9.8 (9–10.6)	10.03 (9.5–11)	9.9 (8.9–11.5)
BUN, mg/dL	65.6 (48–89.7)	54.7 (26–75.7)	57.4 (50–68)
Phosphate, mg/dL	5.2 (2.3–7.1)	4.4 (2.7–8.2)	3.8 (2.9–4.3)
Total calcium, mg/dL	9.0 (8.5–10)	9.1 (8.8–9.4)	8.9 (7.9–10.2)
CRP, mg/dL	0.49 (0.06–1.12)	0.62 (0.1–1.67)	0.20 (0.05–0.5)
Albumin, g/dL	3.9 (3.5–4.1)	3.9 (3.4–4.2)	3.9 (3.2–4.3)
Beta-2 microglobulin, mg/dL	31.1 (17–41)	26.8 (19.3–36.4)	31.5 (24–46.7)
Hepcidin, ng/mL	70.8 (63–81.8)	61.3 (25.9–75.6)	67.3 (47.0–77.8)
Ferritin, ng/mL	225.3 (187–289.3)	200.2 (165–350)	222.1 (150.7–400)

Data are reported as mean values (min–max), groups were compared with *t* test and no significant differences were found between groups ($p > 0.05$).

to an increase when patients were switched to other types of treatments (HDF and HD), even if there were no statistically significant differences (shown in Fig. 1b).

We measured hepcidin removal (ratio between pre- and post-dialytic values) every 3 months for all the different types of dialytic therapies and found on average, a more efficient reduction with HDF-PMMA (28.04%) compared to HDF and HD (12.81% and 14.05%, respectively) (shown in Fig. 2a). We then investigated if pre-dialytic hepcidin levels would have changed during the 6-month period with different treatments. Coherently, in all the three study groups, hepcidin levels were reduced after 6-month treatment with PMMA membrane, even this trend was not statistically significant (shown in Fig. 2b). In all groups, hemoglobin levels did not change significantly during the three different periods. Then we considered the average change of all Hb levels at the beginning and at the end of all different dialysis modalities (independently by patients' study groups allocation), we could observe a not significant trend in hemoglobin rise in all PMMA-HDF periods (shown in Fig. 3) in comparison to HD and HDF.

In this preliminary analysis, we could measure the erythropoietin resistance index (ERI) in 10 out of 20 patients. ERI was 10.19 ± 7.38 during HDF-PMMA, while it was 12.73 ± 10.71 and 12.62 ± 8.92 throughout HD and HDF periods, respectively ($p > 0.05$). In the same period, iron consumption was reported and expressed in mg of iron administrated per month (mg/month). Patients were treated with almost the same amount of iron, 149 mg/month, 153 mg/month, and 159 mg/month in HD, HDF, and HDF-PMMA periods, respectively, and we did not find any statistical differences between all groups. We found no significant correlation between CRP decline and ERI, hepcidin variations, and ferritin levels.

IL-6 levels were constantly low during all the study periods, and no differences were measured either in removal or trends over time between the different dialytic treatments in all three groups. IL-6 removal rate was 17% (1–58%) in HD, 25% (1–67%) in HDF, 20% (1–76%) in HDF-PMMA, and *p* values were 0.50 between HD and HDF, 0.47 between HDF-PMMA and HD, and 0.64 between HDF and HDF-PMMA.

Protein-Bound Toxins

p-cresyl and indoxyl were tested every 3 months, before and at the end of the dialytic sessions, to calculate single-session percentage removal and to measure the trend of pre-dialytic levels over time. No significant differences were found in the removal of p-cresyl, while for indoxyl, no differences were observed between standard HDF (30%; 0–62%) and HDF-PMMA (33%; 0–67%), but HDF-PMMA was superior to standard HD (12%; 0–55%). After 6 months of treatments, with different dialytic modalities, only PMMA-HDF was able to significantly reduce indoxyl, while no significant difference was found for p-cresyl (shown in Fig. 4).

Discussion

PMMA dialyzers are well known for their adsorption properties [8], which have been studied in several conditions to remove high molecular weight toxins, which

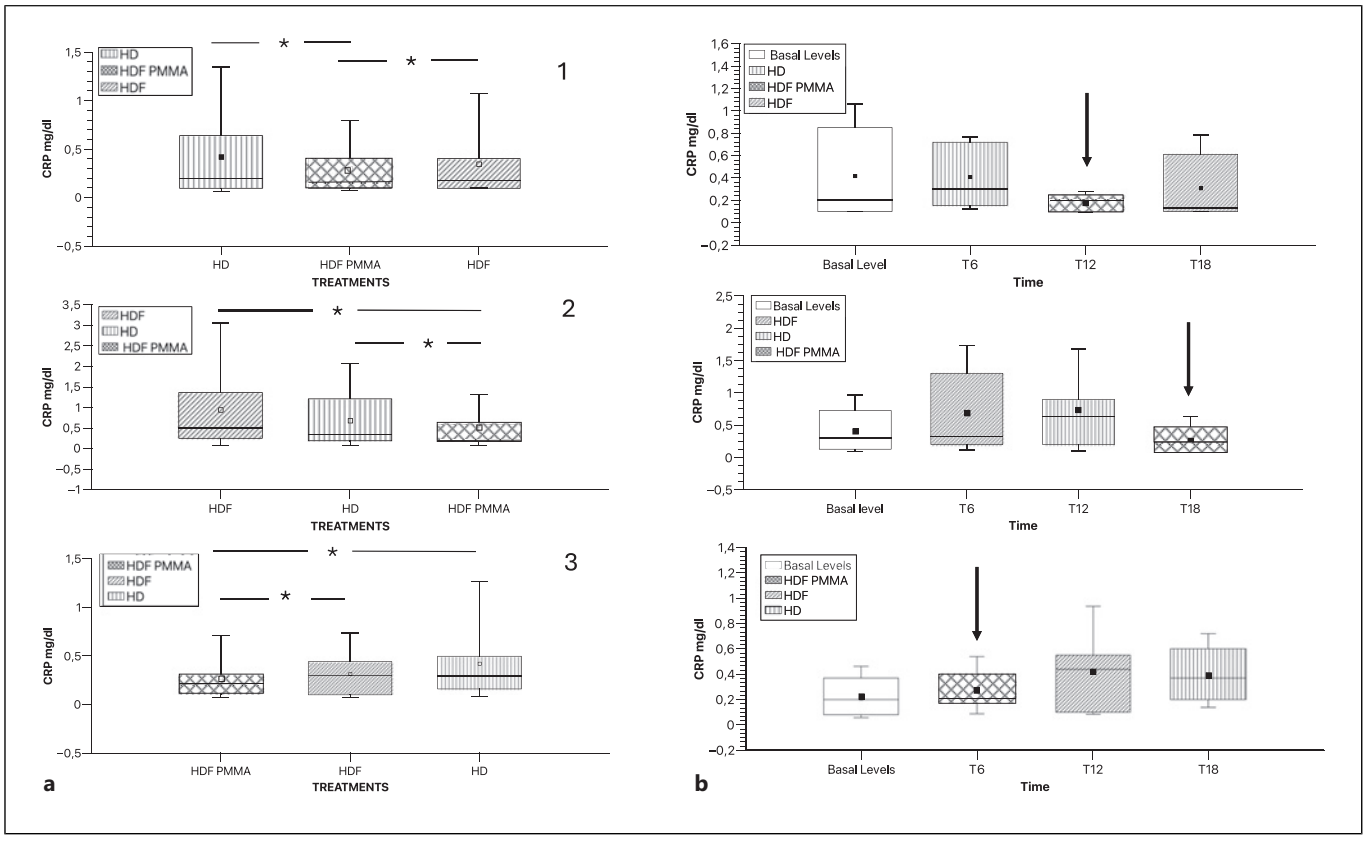

Fig. 1. Comparison of pre-dialysis CRP levels between HDF-PMMA, HDF, and HD. **a** Boxplot represents the average of all CRP values measured during different treatment types for the 6-month period (HD, HDF, HDF-PMMA). *between the lines indicates significant differences ($p < 0.05$) between groups. Groups 1, 2, and 3 indicate different study groups as reported in Table 1. **b** Boxplot represents average levels of CRP at different time points, being T6, T12 at the end of each treatment period before switching to the next treatment, and T18 at the end of the observation period. Arrows indicate boxplot of CRP in HDF-PMMA periods in all the study groups.

cannot be cleared by diffusion or high-dose convection. Since PMMA dialyzers have not been considered sufficiently performing in diffusive-convective therapies (i.e., HDF), they have been used only in standard HD, therefore adding adsorption to diffusion. Nevertheless, there is a large variety of PMMA membranes with differences in pore size, pore distribution, and ultrafiltration capacities, and between them, BG-U 2.1 membranes have technical characteristics compatible with HDF, but the clinical experience is limited [14]. In our study, we reported that BG-U 2.1 membranes can be safely used in HDF even if the amount of convection performed is below 23 lt/session, the volume that is now indicated as the threshold to be reached to reduce mortality. We, in fact, registered 18.8 L/session, confirming data from a recent analysis from Gomez et al. [8], in which they measured 20 lt/session with a Qb on average 50–70 mL/min higher than in our study (almost 400 mL/min in the Spanish study). This result was expected since the membrane water permeability is much lower than many of the modern polysulfone-based membranes, but aim of our study was to demonstrate that besides a lower performance in convection, using a membrane with high adsorption properties in diffusive-convective manner could enhance clearance of inflammatory molecules and, over a 6-month period, improve inflammation.

We measured that, even with a significant lower contribution of convection, we could reach the same level of solute removal than very high-volume HDF, including beta-2 microglobulin. In the past, some authors [12] demonstrated that PMMA membranes were superior to standard HD in removing inflammatory cytokines but only in comparison to standard high-flux dialyzers, which at the time were the reference for gold standard depuration. Therefore, in our report, the first in which effect of the long-term (6 months) use of PMMA in HDF have

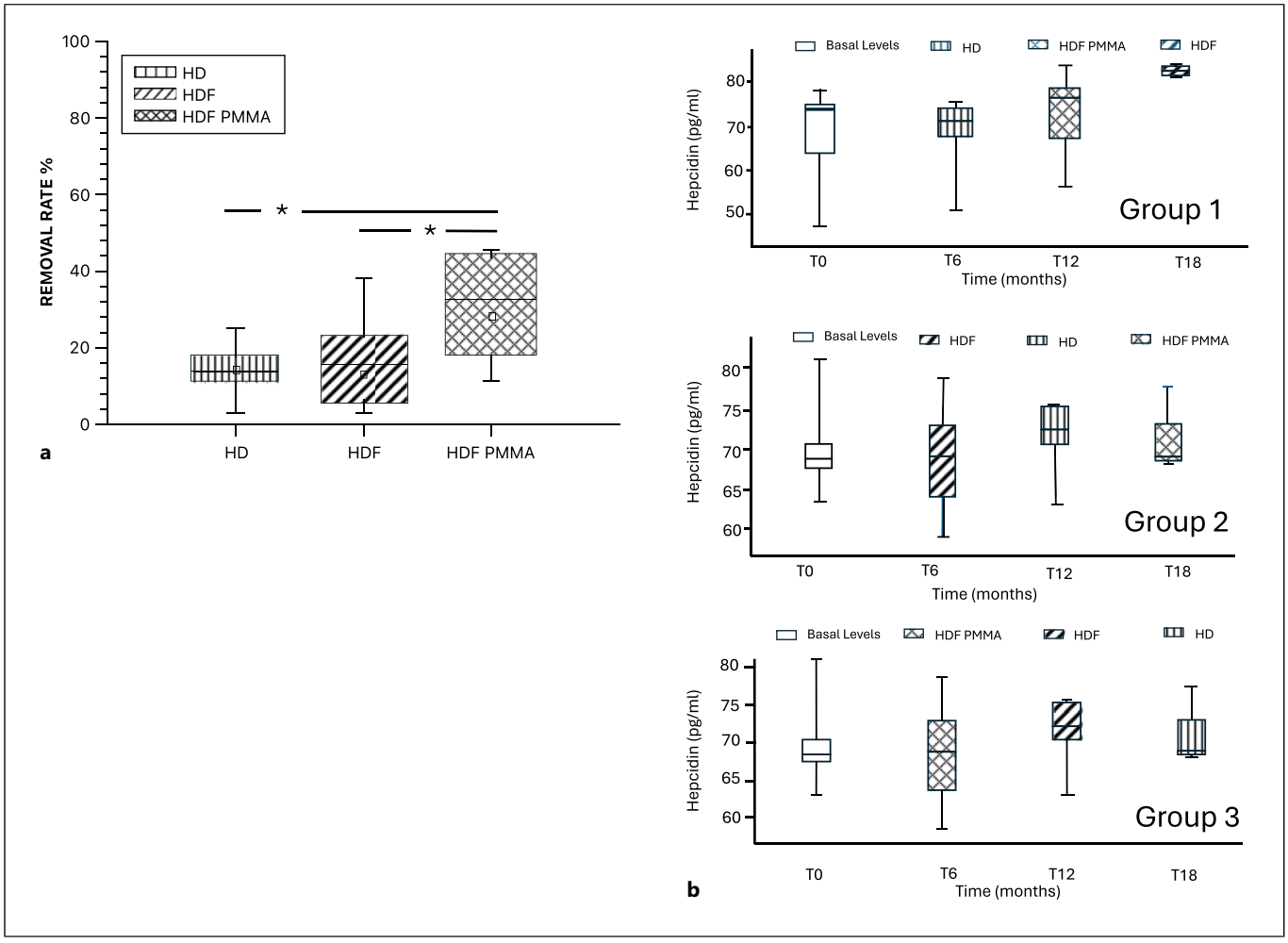

Fig. 2. Comparison of removal rates for hepcidin and predialysis hepcidin levels between HDF-PMMA, HDF, and HD. **a** Boxplot represents the percentage removal of hepcidin in all different types of treatments. *between the lines indicates significant differences ($p < 0.05$) between groups. In boxplot, line indicates median values, square average values. **b** Hepcidin levels with different treatments in different study groups. Groups 1, 2, and 3 indicate different study groups as reported in Table 1. HDF-PMMA periods always had a lower median value of hepcidin independently of the group observed, and no statistically significant differences were recorded.

been registered, we wanted to test that PMMA positive effects on inflammation are still valid even in comparison to nowadays available high-volume HDF.

The population examined was poorly inflamed (see exclusion criteria), but we observed a month by month reduction of CRP during PMMA-HDF treatment. The crossover design of the study allowed us to observe that CRP tendency toward reduction started when HDF-PMMA was introduced, independently of the previous treatments modalities (HD or high-dose HDF), indicating that convection was not the only drive to reduce pro-inflammatory molecules concentrations and eventually CRP levels. Moreover, delta between CRP levels at the beginning and the end of PMMA-HDF periods were statistically significant, while deltas did not significantly change during HD and HDF periods, confirming a specific positive effect of the studied dialysis modality.

To measure inflammation, we also tested IL-6 and Hepcidin levels every 3 months, either to measure percentage treatment removal (pre- and post-dialysis concentration) and to test impact of different treatments on basal levels. For IL-6, there were no differences either in single-session removal rate or in reduction through the observed period, but basal levels were very low, which probably reflected the inclusion for our study population. For hepcidin, we instead measure a better removal rate by

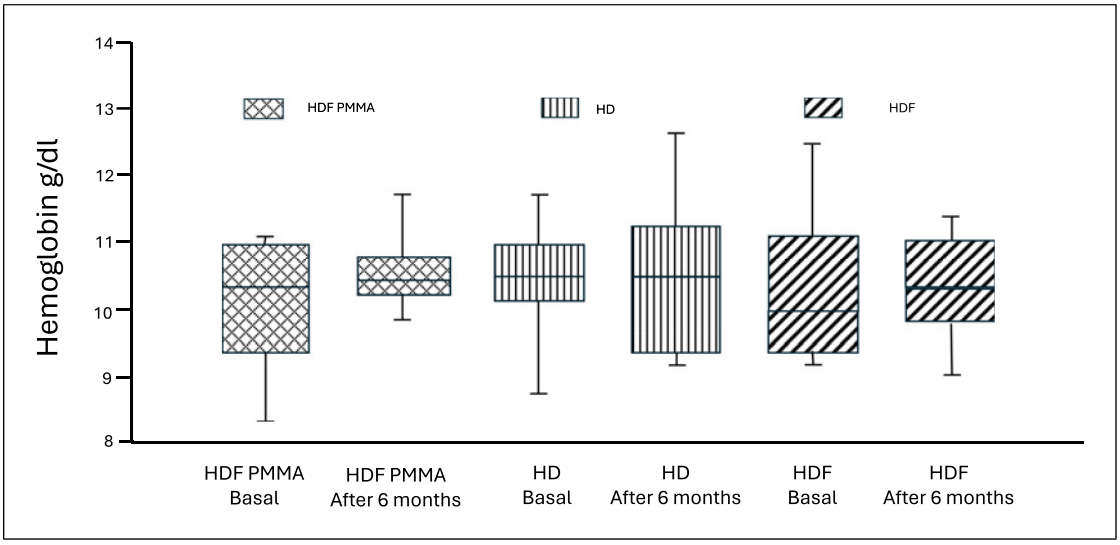

Fig. 3. Pre-dialysis hemoglobin levels at the beginning and at the end of 6 months of treatments for each dialysis period, data represents average of all Hb levels measured for single dialysis modalities regardless of patients' study group allocation. Boxplot represents pre-dialysis hemoglobin levels in all different types of treatments (n = 20). There were no statistical differences between each group.

PMMA-HDF, but we can only observe a trend toward reduction in the 6-month observation period without a statistical significance. Since hepcidin is increased in more inflamed patients [15], we can speculate that the reduction tendency observed in the long term was influenced by a better removal rate, but we cannot exclude a more general contribution of the PMMA-HDF in reducing inflammation and, as a consequence, hepcidin production. Even if hemoglobin levels were maintained in the therapeutic range (10.5–12 g/dL) according to local good clinical practice of dialysis physicians, we tested whether changes in the hepcidin profile had a clinical counterpart by measuring ERI index and we noticed its (not significant) reduction during PMMA treatment without any increase in iron supplementation. The study was not designed to determine a clinical advantage in anemia treatment, and clinicians' interventions were only driven by good clinical practice and personal experience, making difficult to correlate Hb changes just to hepcidin and CRP modifications. It is in fact well known that guidelines target are wide and different clinicians may have different attitudes to reach the higher or the lower Hb limit and iron supplementation in treating patients. We can speculate that for all these confounding factors, correlations between single markers and anemia management are not easy to establish, and to address this topic, there is the need for a specific designed study.

Moreover, PMMA treatment was the only one able to reduce indoxyl concentrations over time even if reduction rate of PBUT concentrations was not superior in comparison to HDF and HD. One possible explanation is related to the affinity of PMMA for albumin which has been demonstrated in several experimental conditions [16]. PMMA is in fact the only membrane which can adsorb albumin over all the dialysis period due to its peculiar configuration. The amount of albumin removed is not easily measured, the reduction rate is too small to see a drop of albumin levels before and after a single treatment, and no clearance can be calculated since adsorption is the main removal mechanism. Gomez et al. [8] showed, with very elegant and sophisticated analysis, that PMMA membranes either in HD mode were those with the highest adsorption of albumin and that adding convection in a single treatment raised this capacity even if not to a significant level. We can speculate that using PMMA over time and with the adjunction of convection (i.e., PMMA-HDF) can remove a significant amount of toxins related to the trapped albumin with a slow but continuous removal which cannot be adequately measured in a single treatment. Furthermore, in our study, albumin levels over time did not change significantly in comparison to HDF and HD, showing no arm in continuative use of PMMA in HDF modality. Our analysis showed significant results only for indoxyl, while p-cresyl did not change. Other studies showed that the two uremic compounds behave in

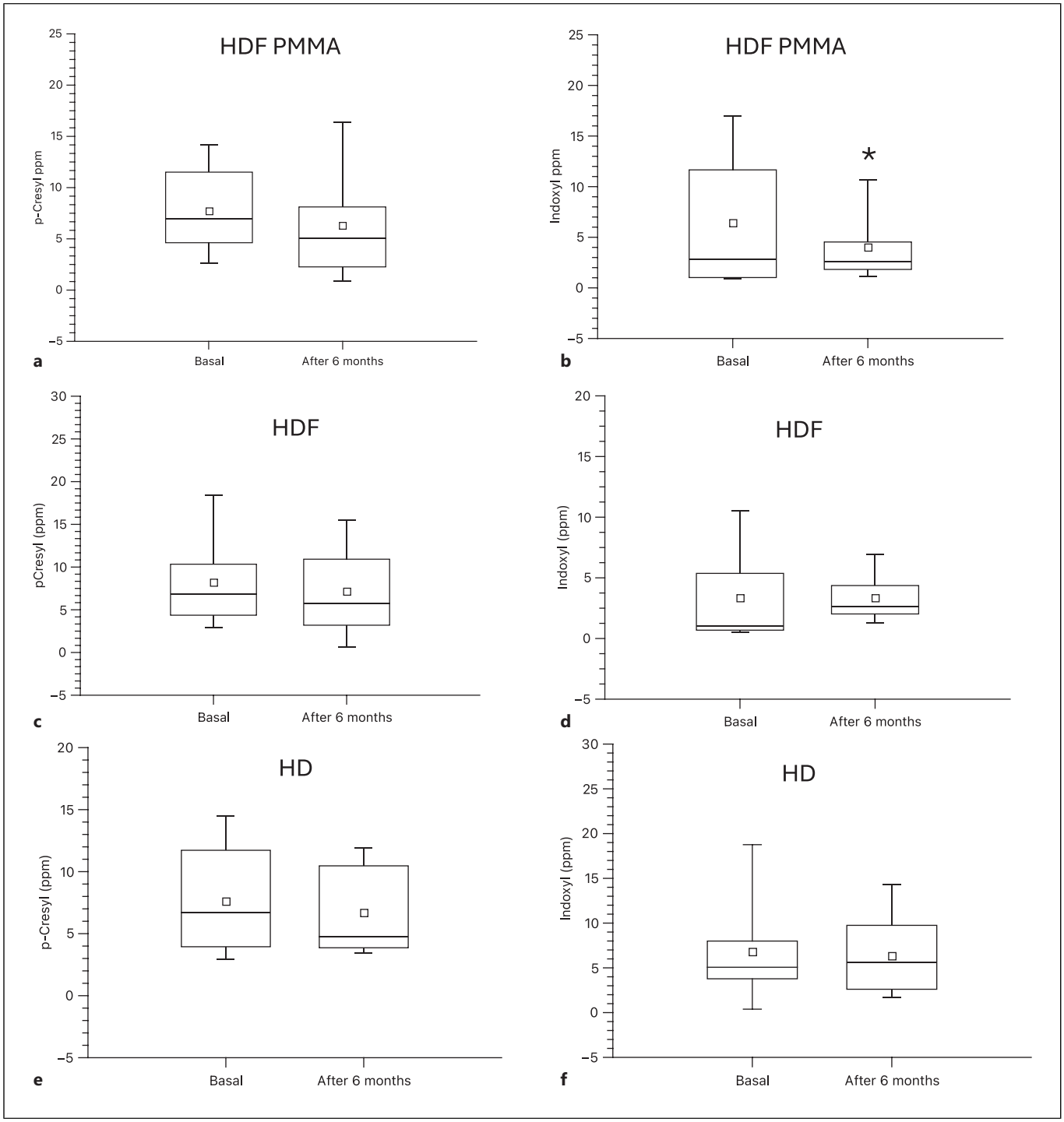

Fig. 4. Change of pre-dialysis levels of protein-binding uremic toxins (PBUTs) according to different study treatments. Boxplots represent pre-dialysis levels of p-cresyl sulfate (for HDF-PMMA (**a**), for HDF (**c**), for HD (**e**)) and indoxyl (for HDF-PMMA (**b**), for HDF (**d**), for HD (**f**)) at the beginning and after 6 months of different type of treatments. Indoxyl was significantly reduced only in HDF-PMMA modality (**b**), while did not change significantly in all other treatments (**d**, **f**). p-cresyl sulfate was not significantly modified in any of the studied groups (**a**, **c**, **e**). *$p < 0.05$ versus basal levels.

different manners, for example, in the first 80 patients participating in the CONvective TRAnsport STudy (CONTRAST), a randomized controlled trial that compared the effects of online HDF versus low-flux HD, the authors tested the hypothesis that HDF could lower PBUT plasma concentrations. They measured, between others, both indoxyl and p-cresyl, at baseline and after 6 months of follow-up. Only indoxyl decreased by 8.0% in patients treated with HDF (4). These different removal rates can be in general explained by the complex influence that several factors may have on PBUT plasma concentrations, like differences in the composition and function of the gut microbiome, but more probably also by the different concomitant medications, which can interfere on albumin-uremic toxin bound. Nevertheless, in our study, patients were used as their own controls, hence reducing the interindividual differences regarding all the aforementioned conditions. For the numerosity of our population and for the characteristics of the study design, we cannot exclude that indoxyl was better removed because of concomitant medications or other independent modifying factors.

This study presents some limitations, first of all the numerosity of patients which should be increased to try to confirm trends that did not reach statistical significance. Second, we should have added a fourth period of observation with PMMA HD in order to exactly test the contribution of convection on the already described PMMA adsorption capacities. In conclusion, HDF-PMMA is a possible type of treatment which can introduce adsorption into high-volume HDF; moreover, the new PMMA membranes recently released on the market [17] have an improved permeability to water and may be of even more interest to perform a "tridimensional" (adsorption, convection, and diffusion) dialysis.

Statement of Ethics

All patients provided informed written consent, the study was conducted in accordance with the World Medical Association Declaration of Helsinki, and the study was approved by the Local Ethical Committee (Monza and Brianza), Reference No. 459/4th May 2016.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The study did not receive any public or private funding, and it was conducted using local resources.

Author Contributions

Paolo Fabbrini and Vincenzo Cantaluppi designed the study as principal investigators. Denise Vergani, Anna Malinverno, Marita Marengo, Guido Merlotti, and Alessandro Quercia contributed with the recruitment of patients, data collection, data analysis, and editing the manuscript. Claudio Medana mainly involved in sample processing. Federico Pieruzzi contributed to result interpretation and data analysis.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author (P.F.) upon reasonable request.

References

1 Blankestijn PJ, Grooteman MP, Nube MJ, Bots ML. Clinical evidence on haemodiafiltration. Nephrol Dial Transplant. 2018;33(Suppl l_3):iii53–8. https://doi.org/10.1093/ndt/gfy218

2 Blankestijn PJ, Vernooij RWM, Hockham C, Strippoli GFM, Canaud B, Hegbrant J, et al. Effect of hemodiafiltration or hemodialysis on mortality in kidney failure. N Engl J Med. 2023;389(8):700–9. https://doi.org/10.1056/NEJMoa2304820

3 Meena1 P, Locatelli F. Unmasking the CONVINCE trial: is hemodiafiltration ready to steal the spotlight in real-world practice? Clin Kidney J. 2023;0(0):1–5.

4 van Gelder MK, Middel IR, Vernooij RWM, Bots ML, Verhaar MC, Masereeuw R, et al. Protein-bound uremic toxins in hemodialysis patients relate to residual kidney function, are not influenced by convective transport, and do not relate to outcome. Toxins. 2020;12(4):234. https://doi.org/10.3390/toxins12040234

5 Rocchetti MT, Cosola C, Ranieri E, Gesualdo L. Protein-bound uremic toxins and immunity. Methods Mol Biol. 2021;2325:215–27. https://doi.org/10.1007/978-1-0716-1507-2_15

6 Ronco C, Clark WR. Haemodialysis membranes. Nat Rev Nephrol. 2018;14(6):394–410. https://doi.org/10.1038/s41581-018-0002-x

7 Torii Y, Yamada S, Yajima M, Sugata T. Polymethylmethacrylate membrane dialyzer: historic but modern. Blood Purif. 2022;52(Suppl 1):1–7. https://doi.org/10.1159/000526996

8 Gomez M, Bañon-Maneus E, Arias-Guillén M, Fontseré N, Broseta JJ, Ojeda R, et al. Distinct solute removal patterns by similar surface high-flux membranes in haemodiafiltration: the adsorption point of view. Blood Purif. 2022;51(1):38–46. https://doi.org/10.1159/000514936

9 Aucella F, Vigilante M, Gesuete A, Maruccio G, Specchio A, Gesualdo L. Uraemic itching: do polymethylmethacrylate dialysis membranes play a role? Nephrology, dialysis. Nephrol Dial Transplant. 2007;22(Suppl 5):v8–12. https://doi.org/10.1093/ndt/gfm293

10 Goeksel T, Xie W, Ritzerfeld M, Heidenreich S, Mann H. Prurigo nodularis and dialyzer membrane. Blood Purif. 2013;35(Suppl 2):26–7. https://doi.org/10.1159/000350845
11 Kreusser W, Reiermann S, Vogelbusch G, Bartual J, Schulze-Lohoff E. Effect of different synthetic membranes on laboratory parameters and survival in chronic haemodialysis patients. NDT Plus. 2010;3(Suppl 1):i12–9. https://doi.org/10.1093/ndtplus/sfq032
12 Galli F, Benedetti S, Floridi A, Canestrari F, Piroddi M, Buoncristiani E, et al. Glycoxidation and inflammatory markers in patients on treatment with PMMA-based protein-leaking dialyzers. Kidney Int. 2005;67(2):750–9. https://doi.org/10.1111/j.1523-1755.2005.67138.x
13 Fabbrini P, Sirtori S, Casiraghi E, Pieruzzi F, Genovesi S, Corti D, et al. Polymethylmethacrylate membrane and serum free light chain removal: enhancing adsorption properties. Blood Purif. 2013;35(Suppl 2):52–8. https://doi.org/10.1159/000350849
14 Matsumura Y, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Watanabe E, et al. Treatment of septic shock with continuous HDF using 2 PMMA hemofilters for enhanced intensity. Int J Artif Organs. 2012;35(1):3–14. https://doi.org/10.5301/ijao.5000044
15 Ueda N, Takasawa K. Impact of inflammation on ferritin. Hepcidin and the management of iron deficiency anemia in chronic kidney disease. Nutrients. 2018;10(9):117.
16 Tomisawa N, Yamashita AC. Amount of adsorbed albumin loss by dialysis membranes with protein adsorption. J Artif Organs. 2009;12(3):194–9. https://doi.org/10.1007/s10047-009-0469-0
17 Maduell F, Broseta JJ, Rodríguez-Espinosa D, Hermida-Lama E, Rodas LM, Gómez M, et al. Evaluation and comparison of polysulfone TS-UL and PMMA NF-U dialyzers versus expanded hemodialysis and postdilution hemodiafiltration. Artif Organs. 2021;45(9):E317–23. https://doi.org/10.1111/aor.13968