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MAIN TEXT

Efficacy of HA130 Hemoadsorption in Removing Advanced Glycation End Products in Maintenance Hemodialysis Patients

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ABSTRACT

Background: Patients on maintenance hemodialysis (HD) face complications due to the accumulation of protein-bound uremic toxins, such as advanced glycation end products (AGEs), which contribute to inflammation, oxidative stress, and cardiovascular disease. Conventional HD techniques inadequately remove AGEs. This study evaluates the efficacy of the HA130 hemoadsorption cartridge combined with high-flux HD (HF-HD) in enhancing AGE removal.

Methods: This prospective, single-center study included 20 maintenance HD patients randomized into two groups: HF-HD alone ($n = 10$) and HF-HD plus hemoadsorption ($n = 10$). Blood samples were collected before and after a single session to measure carboxymethyllysine (CML), soluble RAGE (sRAGE), prolactin, and parathyroid hormone (PTH) levels. Reduction ratios (RR) were calculated, including corrected for hemoconcentration (RRc), to ensure accuracy. Statistical analyses included Mann–Whitney *U* and Chi-square tests.

Results: The HF-HD plus hemoadsorption group showed significantly enhanced removal of CML compared to HF-HD alone, with RRc of 64.7% [52.6–74.9] versus 39.3% [33.8–49.4], respectively ($p = 0.045$). Similarly, uncorrected reduction ratios demonstrated a trend favoring hemoadsorption, with values of 57.5% [45.1–70.7] versus 30.3% [19.1–44.5] ($p = 0.053$). Importantly, sRAGE levels were preserved in both groups (RRc: 23.4% (15.1–30.4) vs. 21.8% (16.6–31.7), $p = 0.791$), highlighting the safety of hemoadsorption. Other biochemical parameters, including prolactin, PTH, albumin, and electrolytes, showed no significant differences between groups. All sessions were completed without adverse events.

Conclusion: Combining hemoadsorption with HF-HD significantly enhances CML removal, as evidenced by corrected RR, without compromising protective sRAGE levels. This innovative approach offers a promising adjunctive therapy for reducing AGEs-related complications in end-stage renal disease patients. Further longitudinal studies are needed to confirm these findings and evaluate long-term outcomes.

1 | Introduction

Despite significant technological advancements, maintenance hemodialysis patients continue to face a high rate of medium- to long-term complications and frequent hospitalizations. This has resulted from the retention and accumulation of uremic toxins with specific effects on inflammation, anemia, osteoarticular and cardiovascular alteration [1, 2]. These observations have spurred new interest in increasing the removal of solutes in the medium-large molecular weight spectrum, including protein-bound uremic toxins, well beyond what classic dialysis techniques can achieve [3–5]. In this scenario, advanced glycation end products (AGEs) constitute a heterogeneous group of compounds derived from the nonenzymatic glycation of proteins, lipids, and nuclear acids through a complex sequence of Millard reactions [6]. At least 20 types of AGEs have been described: N-carboxymethyllysine (CML), pentosidine, and hydroimidazolone are among the best characterized and are markers of AGEs accumulation in several tissues [6].

The accumulation of AGEs in patients with chronic kidney diseases (CKD) is primarily driven by reduced renal clearance, oxidative stress, and chronic inflammation [6, 7]. These pro-inflammatory and pro-oxidative compounds contribute to endothelial dysfunction and cardiovascular disease by binding to the receptor for advanced glycation end products (RAGE). This interaction activates pathways that increase reactive oxygen species (ROS) levels through NADPH oxidase and mitochondrial dysfunction, as well as induce pro-inflammatory gene transcription, including cytokines like IL-6, IL-1α, and TNF-α [6, 8–10].

Additionally, soluble forms of RAGE (sRAGE) have been described as generated by either alternative splicing or proteolytic cleavage, acting as decoy receptors and thus exerting a protective function by mitigating the deleterious effects of the activation of the full-length receptor [11].

AGEs also cause vascular damage independent of receptors by altering proteins and lipoproteins. Glycation of LDL promotes macrophage uptake, leading to foam cell formation and atherosclerosis. Additionally, AGE-modified LDL and matrix proteins like collagen VI disrupt endothelial adhesion and amplify inflammation, exacerbating vascular complications in diabetes and CKD [6].

AGEs represent protein-bound uremic retention solutes, which are poorly eliminated because of their protein-binding characteristics and large molecular weight, particularly in patients who have lost their residual renal function. Dialyzer membranes have been developed to remove the PBUT and reduce mortality in HD patients [12]. However, the removal rate of AGEs obtained by using hemodialysis or hemodiafiltration is only $<20\%$–32%, and only low-molecular-mass AGEs (<10 kDa AGEs peptide), which may not be able to effectively remove the toxins that are producing rapidly in maintenance hemodialysis patients [12].

New sorbent materials with enhanced porosity and biocompatibility characteristics have recently become available [13]. The sorbent is composed of a mixture of styrene and divinylbenzene, with a specific porosity generated during the formation of the beads. Van der Waals forces, ionic bonds, and hydrophobic bonds specifically adsorb molecules in the range of 10–50 kDa [14]. These characteristics allow for overcoming the limitations of classic and innovative dialysis membranes. Independent of the hemodialyzer utilized, the sorbent cartridge HA130 (Jafron Medical, Zhuhai, China) placed in series before the dialysis filter, has demonstrated remarkable efficacy in reducing the levels of β_2M, PTH, cytokines, and significant improvement in several different symptoms and clinical outcomes. This has led to considering hemodialysis plus hemoadsorption as a new option for kidney failure patients [15].

In the AGEs accumulation and sorbents scenario, no data are reported on the utilization of HA130 cartridges concerning AGEs removal. Therefore, this study aims to evaluate the efficacy of HA130 hemoadsorption in reducing AGEs and middle molecules in patients undergoing maintenance hemodialysis, compared to high-flux hemodialysis.

2 | Materials and Methods

2.1 | Study Design and Setting

This prospective, single-center study was conducted at the Dialysis Center of Carlos Van Buren Hospital, Valparaíso, Chile, between July and August 2024. The aim was to evaluate the efficacy of the HA130 hemoadsorption cartridge in reducing AGEs and other middle molecules during high-flux hemodialysis (HF-HD).

Patient selection

- Inclusion criteria:
  - Patient aged ≥ 18 years
  - Stable on conventional HF-HD thrice weekly for >3 months
  - No residual renal function
- Exclusion criteria:
  - Active neoplasia
  - Hypersensitivity to hemodialysis membranes
  - Life expectancy <6 months
  - Pregnancy
  - Inability to achieve a blood flow ≥ 350 mL/min
  - Refusal to participate

The patients were assigned to two groups, ensuring a balanced distribution regarding age, gender, and years on dialysis. Baseline clinical data were obtained from hospital registries, including demographic characteristics, causes of renal failure, comorbidities, years on dialysis, blood flow, and session time. None of the patients had residual renal function.

2.2 | Interventions

2.2.1 | Patient Groups and Treatments

A total of 20 patients undergoing maintenance HD for more than 3 months were included in the study. These patients were divided into two groups: 10 patients received one session of HF-HD, while

the other 10 underwent one session of HF-HD combined with hemoadsorption using the HA130 cartridge. During all sessions, the blood flow rate was maintained between 350 and 400 mL/min, with a dialysis flow rate of 500 mL/min and a session duration of 210–240 min. Net fluid removal was individually tailored according to the clinical needs of each patient.

All patients were treated with a polyethersulfone/polyvinylpyrrolidone dialysis membrane (Clearum HS series, Medtronic), characterized by a K_{UF} of 64 mL/h/mmHg, polypropylene housing free of bisphenol-A, no adsorption properties, and an albumin sieving coefficient of 0.004. The hemoadsorption cartridge used in the combined treatment group was the HA130 (Jafron, China), a neutral mesoporous resin device containing 130 mL of polystyrene resin beads with a 54% packing density, a biocompatible styrene-divinylbenzene coating, and enhanced mesopore distribution. This design allows the adsorption of solutes with molecular weights between 500 and 40 000 Da [16]. The cartridge was primed following the manufacturer's instructions and installed in a prefilter position, as shown in Figure 1. The first dialysis of the week was used to perform the sessions and measure PBUT reduction. Heparin was used as the anticoagulant during all treatments.

2.2.2 | Blood Sampling and Analysis

Blood samples were collected at the start and end of each session to assess serum levels of carboxymethyllysine, soluble RAGE (sRAGE), prolactin, ferritin, parathyroid hormone, calcium, phosphorus, bicarbonate, and blood urea nitrogen (BUN). For each time point, 5 mL of blood was drawn using EDTA as an anticoagulant, centrifuged at 1000×*g* for 15 min at 2°C–8°C within 30 min of collection, and stored at −20°C until analysis. AGEs concentrations were measured using an ELISA kit at the Biomedical Research Labs, Catholic University of Maule, Talca, Chile.

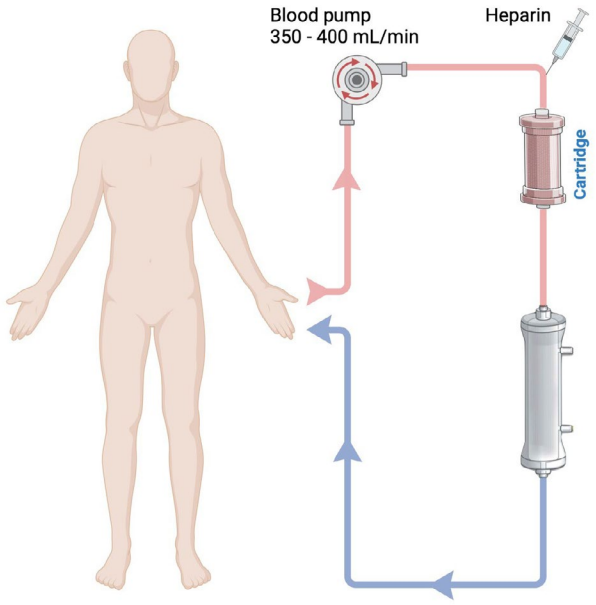

FIGURE 1 | Circuit diagram of HF-HD plus hemoadsorption. HF-HD, high-flux hemodialysis. [Color figure can be viewed at wileyonlinelibrary.com] [Color figure can be viewed at wileyonlinelibrary.com]

2.2.3 | Calculation of Removal Ratios

The removal ratio (RR) of uremic toxins was calculated using the formula:

$$RR\,(\%) = 100\left(C_0 - C_{end}\right)/C_0$$

where C_0 is the baseline concentration, and C_{end} is the posttreatment concentration.

To account for hemoconcentration, the corrected RR was calculated as follows:

$$RR_c\,(\%) = 100\left(C_0 - cC_{end}\right)/C_0$$

where: $cC_{end} = C_{end}/(1 + [\Delta BW/0.2 \quad (BW_{post})])$. ΔBW = body weight refers to the change in body weight during the treatment, used to account for variations due to ultrafiltration.

2.3 | Statistical Analysis

The data obtained were presented as medians and interquartile ranges for quantitative variables after assessing the normality of the data using the Shapiro–Wilk test. Values of the reduction ratio of HF-HD plus hemoadsorption were compared with the results obtained with the HF-HD group using nonparametric statistical tests. The Chi-squared test was used to compare categorical variables, and the Mann–Whitney *U* test was applied for continuous variables. $p \leq 0.05$ was defined as statistically significant. All analyses were conducted using the SPSS 25 statistical software (SPSS Inc. Chicago, IL, USA).

2.4 | Ethical Considerations

The San Antonio Valparaíso Health Service Ethics Committee approved this study under resolution 002120, Act No. 61. Informed consent was required for all patients.

3 | Results

The median age was 61.0 [48.0–65.0] years, and 12 patients were male (60%). Eight patients had ESRD due to diabetic kidney disease (40%), 45% had an undetermined etiology, and 10% had a chronic glomerulopathy. The median time on dialysis was 8.0 [4.8–11.0] years. Seven patients with catheters (35%) and 13 patients with arteriovenous fistula (65%) received HF-HD or HF-HD plus hemoadsorption treatment. No adverse events were noted during the procedure.

The patient's demographic characteristics and laboratory values at the beginning are presented in Table 1. Biochemical parameters did not significantly differ between the treatment groups. The session time of the HF-HD plus hemoadsorption group and in the HF-HD group was 240 min. The median blood flow in the HF-HD plus hemoadsorption group was 360.0 [350.0–400.0] mL/min versus 400.0 [380.0–400.0] mL/min in the HF-HD group. No significant differences were observed between groups. The blood flow rate remained constant

TABLE 1 | Demographic data and clinical characteristics of patients.

	Total	HA + HF-HD	HF-HD	*p*
Age, years	61.0 [48.0–65.0]	62.5 [57.3–72.5]	53.5 [43.8–63.3]	0.139
High blood pressure	85.0% (17)	47.1% (8)	52.9% (9)	0.531
Diabetes	45.0% (9)	55.6% (5)	44.4% (4)	0.653
Chronic heart failure	50.0% (10)	50.0% (5)	50.0% (5)	1.000
Cardiovascular diseases	25.0% (5)	60.0% (3)	40.0% (2)	0.606
Blood flow, mL/min	390.0 [350.0–400.0]	360.0 [350.0–400.0]	400.0 [380.0–400.0]	0.142
Time in dialysis, years	8.0 [4.8–11.0]	9.0 [6.5–12.5]	6.0 [4.25–8.75]	0.287
BUN (pre), mg/dL	64.4 [54.1–70.5]	61.9 [52.9–69.5]	66.0 [60.0–70.1]	0.384
BUN (post), mg/dL	13.5 [11.8–17.6]	13.4 [12.9–17.2]	13.6 [11.2–17.7]	0.929
Ferritin, ng/mL	601.1 [224.4–862.5]	538.2 [198.3–891.3]	601.1 [366.8–807.7]	0.850
Albumin, g/dL	3.8 [3.7–3.92]	3.85 [3.7–3.9]	3.8 [3.5–3.9]	0.969
Bicarbonate, mmol/L	22.0 [19.8–23.6]	21.7 [20.1–22.5]	22.2 [19.6–25.2]	0.437
Calcium, mg/dL	8.8 [8.5–9.4]	8.8 [8.4–9.4]	8.8 [8.6–9.3]	0.819
Phosphorus, mg/dL	4.8 [3.7–6.2]	5.2 [4.1–6.1]	4.2 [3.2–6.1]	0.427

Abbreviations: HA, hemoadsorption; HF-HD, high-flux hemodialysis.

throughout the session. No coagulation events were observed in the extracorporeal circuit during the treatment sessions. All therapies were completed successfully without interruptions, maintaining consistent blood flow throughout the procedures. All groups utilized 500 mL/min of dialysis flow rate. Albumin, phosphorus, calcium, ferritin, bicarbonate, and BUN levels were similar at baseline and are shown in Table 1.

Serum prolactin, PTH, CML, and sRAGE levels are presented in Table 2. Baseline levels of the medium-middle molecules prolactin and PTH were 22.9 [15.9–40.7] ng/mL and 522.8 [246.4–902.2] pg/mL, respectively. Large-middle molecules baseline level (sRAGE) were 3691.6 [2464.5–5373.4] pg/mL. In relation to PBUT, the median level of CML was 926.9 [709.3–1042.5] pg/mL.

The reduction ratio was calculated for both the procedures, and results are displayed in Table 2. Comparing HF-HD plus hemoadsorption with HF-HD, albumin, phosphorus, calcium, ferritin, bicarbonate, and BUN levels did not shown significant differences between the RR% levels of the two groups.

A significant reduction of solute levels was only observed for corrected CML (64.7% [52.6–74.9] versus 39.3% [33.8–49.4], $p = 0.045$) (Figure 2). In contrast, no significant differences were observed for this comparison concerning RR and corrected RR of sRAGE, PTH, and prolactin.

4 | Discussion

Our results demonstrate that the HA130 adsorption cartridge used in the maintenance hemodialysis protocol evaluated in this cross-sectional study (Figure 1) significantly enhances the removal of CML, a PBUT of the AGEs family of epitopes. A median difference in the RR% value of this PBUT of 25.4% was observed comparing the two treatment groups (64.7% [52.6 − 74.9] in the HF-HD plus hemoadsorption group compared to 39.3% [33.8 − 49.4] in HF-HD group).

These findings are consistent with prior research demonstrating great potential of adsorption techniques in addressing conventional dialysis's limitations in removing PBUT. However, the magnitude of CML reduction observed in our study surpasses results reported in a similar survey, highlighting the potential of the cartridge used in our research. In the context of AGEs accumulation and sorbent materials, only one study reported the utilization of hemoadsorption as a method to reduce AGEs, utilizing a neutral macroporous resin device (MG350) with a diameter of porous about 10 nm. They showed a significant reduction of AGEs (45%−50%) with the combination of hemodialysis with hemoadsorption. In addition, serum levels of AGEs were slowly increased again after switching to the hemodialysis treatment only [17]. In addition to the presented data, a study evaluating direct hemoadsorption with hexadecyl-immobilized cellulose beads (Lixelle) during hemodialysis showed limited efficacy in adsorbing free PBUTs, such as indoxyl sulfate, indole acetic acid, and p-cresyl sulfate, without a significant reduction in total PBUTs [18]. By contrast, studies with PMMA membranes reported RRs of 32.9% for p-cresyl sulfate and 34.5% for total pentosidine, reflecting the limitations of current technologies in PBUT and AGE removal [5, 19]. As Saar-Kovrov et al. emphasized, studies specifically targeting AGEs are notably scarce, underscoring the difficulty of effectively removing PBUTs, even with advanced adsorption-based methods [19].

Unlike other studies that primarily focused on uremic toxins, our work targets explicit AGEs, which are increasingly recognized for their role in chronic inflammation and cardiovascular complications in ESRD.

TABLE 2 | PBUT, medium-middle, and large-middle molecules reduction rate.

	HA + HF-HD	HF-HD	*p*
CML (pre), pg/mL	847.3 [722.8–1074.4]	956.7 [648.6–1009.2]	0.969
CML (post), pg/mL	427.1 [281.2–650.6]	612.9 [398.9–780.9]	0.472
CML ($post_c$), pg/mL	357.2 [241.6–538.3]	539.9 [343.2–649.6]	0.473
CML RR	57.5% [45.1–70.7]	30.3% [19.1–44.5]	0.053
CML RR_c	64.7% [52.6–74.9]	39.3% [33.8–49.4]	0.045*
sRAGE (pre), pg/mL	3915.8 [2454.2–4740.5]	3390.0 [3184.1–5915.8]	0.967
sRAGE (post), pg/mL	3249.5 [2331.8–3882.4]	3300.2 [2662.2–3710.9]	0.965
sRAGE ($post_c$), pg/mL	2839.4 [2035.9–3222.9]	2824.9 [2378.8–3153.7]	0.896
sRAGE RR	9.8% [0.7–18.5]	15.9% [5.9–21.2]	0.572
sRAGE RR_c	23.4% [15.1–30.4]	21.8 [16.6–31.7]	0.791
PTH (pre), pg/mL	782.1 [418.0–914.9]	313.5 [121.2–761.0]	0.133
PTH (post), pg/mL	507.4 [344.1–726.9]	228.3 [33.7–574.1]	0.185
PTH ($post_c$), pg/mL	429.6 [293.4–660.5]	204.2 [29.9–556.4]	0.185
PTH RR	17.7 [15.0–37.4]	34.8 [27.2–45.6]	0.216
PTH RR_c	29.8 [24.7–44.9]	44.1 [34.9–55.4]	0.289
Prolactin (pre), pg/mL	20.4 [13.9–23.6]	32.5 [17.3–45.7]	0.570
Prolactin (post), ng/mL	11.09 [8.4–14.1]	20.1 [11.0–26.4]	0.480
Prolactin ($post_c$), ng/mL	9.39 [7.7]	21.7 [13.5–32.0]	0.236
Prolactin RR	38.5 [37.6–52.0]	36.3 [31.4–41.0]	0.167
Prolactin RR_c	47.3 [45.4–59.3]	47.7 [36.7–51.2]	0.321

*$p \leq 0.05$.
Abbreviations: CML, N-carboxymethyllysine; HA, hemoadsorption; HF-HD, high-flux hemodialysis; postc, corrected post; RR, reduction ratio; RRc, corrected reduction ratio.

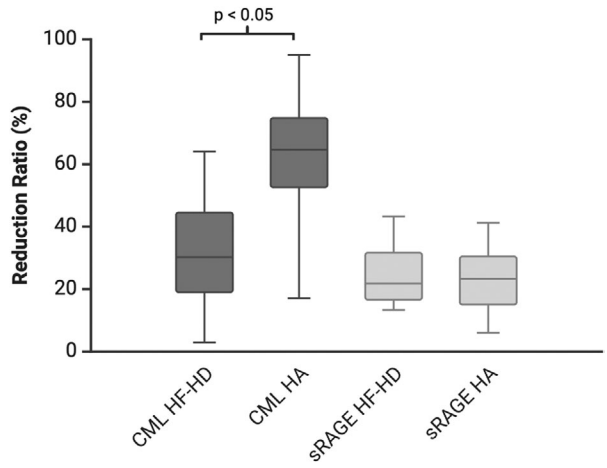

FIGURE 2 | Corrected reduction ratios of CML and sRAGE across different treatment modalities. CML, N-carboxymethyllysine; HA, hemoadsorption; HF-HD, high-flux hemodialysis; sRAGE, soluble advanced glycation end product-specific receptor.

The interaction of AGEs with RAGE triggers signaling cascades that amplify oxidative stress and inflammation, leading to endothelial dysfunction, arterial stiffening, and calcification [20–23]. This AGE-RAGE axis creates a feedback loop of chronic inflammation and oxidative damage, accelerating atherosclerosis and cardiac remodeling. Furthermore, AGEs disrupt cellular proteostasis and induce apoptosis in immune and endothelial cells, weakening vascular and immune function [12, 21, 23, 24].

AGEs also contribute to tissue remodeling by cross-linking proteins like collagen, causing structural abnormalities in the vascular wall. Beyond cardiovascular effects, AGEs are implicated in neurological damage, including neuroinflammation, blood–brain barrier disruption, and amyloid-beta aggregation, contributing to cognitive impairments in CKD patients [6, 20, 22, 25, 26].

Conventional dialysis techniques are insufficient to remove protein-bound AGEs due to their high molecular weight and strong binding to plasma proteins, exposing patients to their toxic effects [17, 24]. Studies show that standard hemodialysis with low-flux membranes fails to adequately clear AGEs and advanced oxidation protein products (AOPPs), as protein-bound pentosidine levels in these patients can reach 20 times those of healthy controls. While high-flux membranes offer some improvement, their ability to remove protein-bound AGEs and oxidative stress markers like AOPPs remains limited, with temporary reductions and levels rebounding post-dialysis. These findings highlight the inadequacy of current membranes and the need for advanced approaches, such as daily dialysis or

specialized membranes, to achieve sustained toxin removal and reduce long-term complications [27, 28].

Advanced dialysis strategies, such as medium-cut-off (MCO) membranes, have demonstrated the potential to enhance AGEs removal by targeting medium molecular weight toxins like pentosidine and CML. In a recent study [22], the RR for pentosidine with MCO membranes was 4.1% during the first 12 sessions and 8.7% after the crossover phase, compared to 8.4% and 19.4% with high-flux membranes during the same periods. Similarly, the RR for CML with MCO membranes was 15.8% during the first 4 weeks but diminished to 0.5% in the subsequent crossover phase. These results not only suggest improved clearance of protein-bound AGEs compared to conventional approaches but also highlight the limitations of MCO membranes in achieving consistent reductions. Factors such as individual oxidative stress levels, toxin dynamics, and treatment duration may influence these outcomes. Although MCO membranes represent a step forward, their benefits must be contextualized within a broader strategy to target AGEs, emphasizing the critical need for innovative therapeutic approaches to reduce CVD risk and improve survival in this vulnerable population [22, 23].

In addition, soluble RAGE (constituted by cleaved soluble RAGE form and secreted soluble esRAGE), acts as a scavenger that neutralizes RAGE ligands, promoting protective action by limiting inflammation associated with different diseases [29]. Interestingly, sRAGE levels were not significantly reduced in either groups, with corrected RRs of 23.4% in the HF-HD plus hemoadsorption group and 21.8% in the HF-HD group ($p = 0.791$). sRAGE has a molecular weight of approximately 40 kDa and lacks a transmembrane domain. The size of the pores defined by the cartridges limits the adsorption of this molecule. Preserving sRAGE during hemoadsorption is advantageous, as its reduction could potentially diminish its protective anti-inflammatory role. Maintaining sRAGE levels while enhancing the clearance of pathogenic AGEs like CML highlights the potential to balance efficacy with safety.

Regarding medium-molecular-weight molecules, prolactin was moderately reduced in both groups, but no statistically significant difference was observed (47.3% vs. 47.7%, $p = 0.321$). This indicates that hemoadsorption may not confer additional benefits for molecules of this size compared to HF-HD alone.

A limitation of the study, which may explain the RR values observed, is that while the RR is a standard metric to evaluate toxin removal efficiency during hemodialysis, it has limitations when assessing long-term impact. The RR measures only the relative reduction between the start and end of the session, failing to account for interdialytic fluctuation, where toxins can reaccumulate due to ongoing endogenous production and tissue redistribution. For instance, while the intra-dialysis RR for total homocysteine is similar between conventional and polymethylmethacrylate (PMMA) dialyzers (~30%), only PMMA dialyzers achieve a sustained reduction in pre-dialysis total homocysteine levels over months [30]. This suggests that, although RR provides immediate insights, it does not fully capture the progressive improvements or sustained clinical benefits, which require long-term monitoring; therefore, future studies should include longitudinal analyses.

5 | Conclusion

The combination of HF-HD with hemoadsorption significantly enhances the removal of CML, a deleterious AGEs, without adversely affecting sRAGE levels. This balance between efficacy and safety positions hemoadsorption as a promising adjunctive therapy for ESRD patients, particularly those at high risk of AGEs-related complications. Further studies are warranted to confirm these findings and explore the long-term benefits of this approach.

Author Contributions

G.R.-G., T.R., and B.S.-H., designed the work. G.R.-G., B.S.-H., C.V., F.A., C.P.-R., F.G., and A.R. collected and analyzed the data. G.R.-G., B.S.-H., A.R., F.A., C.V., M.M., J.L., C.P.-R., A.R., and C.R. drafted the work or substantively revised it, and all authors read and approved the final manuscript.

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Conflicts of Interest

C.R. has received funding for lectures, been a consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioM'erieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. T.R. has received funding for lectures and has been a consultant or advisory board member for Alexion, AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Contatti (CytoSorbents), Eurofarma, George Clinical, Jafron, Lifepharma, Medcorp, Nipro, and Nova Biomedical. G.R.-G. has received funding for lectures for AstraZeneca, B. Braun, Baxter, Fresenius Medical Care, and Novo Nordisk. None of the other authors declare any competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The authors alone are responsible for the content and writing of this article.

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