

# The effect of hemodiafiltration vs. high-flux hemodialysis on alpha 1-microglobulin level and dialysate albumin loss using a dialyzer surface area of 2.6 m<sup>2</sup>

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## Abstract

Dialysis therapy has remarkably evolved through the innovation in dialyzers and hemodialysis modalities, enhancing patients' quality of life. The efficacy of dialysis can be determined by measuring the reduction ratio (RR) of middle molecules, such as alpha 1-microglobulin (A1M). In this study, we tested a high-flux dialyzer, BIOPURE (Biorema) 260 HF, with a surface area (SA) of 2.6 m<sup>2</sup>, in terms of A1M removal and concurrent albumin loss in dialysate while receiving high-flux hemodialysis (HF-HD) and post-dilution online hemodiafiltration (OL-HDF). This crossover study comprised 25 patients who received a session of HF-HD using the BIOPURE (Biorema) 260 H, followed by a session of post-dilution OL-HDF. A washout period of 2 weeks was instilled between the two sessions, during which the patients received HF-HD using high-flux dialyzers (maximum SA 2.0 m<sup>2</sup>). All patients' hourly dialysate albumin and pre/post dialysis concentrations of A1M were measured. The dialyzer used in this study resulted in significantly higher A1M RR of 41.9±7.93% with HDF than with HF-HD 27.12±7.65% ( $p<0.001$ ), and a median cumulative dialysate albumin loss of 2.97g (IQR 1.98 – 3.37), and 0.67g (IQR 0.49 – 1.13) with HDF and HF-HD, respectively. In conclusion, the dialyzer BIOPURE (Biorema) 260 HF (SA 2.6 m<sup>2</sup>) is efficient in eliminating A1M, especially with OL-HDF compared to HF-HD, with acceptable albumin loss in the dialysate.

**Keywords:** Serum alpha 1-microglobulin, albumin, High-flux, hemodialysis, hemodiafiltration.

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## Introduction

Uremic toxins are defined as substances, organic or inorganic, that accumulate in the body fluids of subjects with impaired kidney function<sup>1</sup>. Uremic retentive toxins are divided into three groups, per the European Union

Toxin Working Group (EUTox), based on inherent factors that impact their elimination pattern via dialysis.<sup>1</sup> These toxins comprise small solutes with a molecular weight (MW) >500 Daltons (Da), protein-bound uremic toxins (PBUTs), and middle molecules with an MW >500 Da.<sup>1</sup>

Renal replacement therapy, in the form of dialysis, has been advancing for the past few years to enhance patients' quality of life and reduce the incidence of complications encountered in patients with renal failure. Nonetheless, patients undergoing standard hemodialysis experience various complications that ultimately lead to a diminished survival rate and deteriorating quality of life.<sup>2</sup> Some of these symptoms can be attributed to the incomplete removal of middle-high molecular weight uremic toxins during hemodialysis, such as alpha 1-microglobulin (A1M).<sup>3</sup>

In contrast to hemodialysis, hemodiafiltration (HDF) employs diffusion and convection to effectively remove uremic toxins of both low and high molecular weight.<sup>5</sup> However, HDF has various limitations, including the need for additional equipment, a significant amount of ultrapure replacement fluid, and highly trained medical personnel. These requirements hinder the liberal use of HDF in current hemodialysis practice.<sup>6</sup>

Regarding dialyzers, a class of dialyzers composed of a medium cut-off (MCO) membrane has recently garnered interest. The MCO membrane's customized pore sizes potentiate the removal of middle-high uremic toxins by providing a higher retention onset and molecular weight cut-off (MWCO).<sup>7</sup> Furthermore, unlike high cut-off membranes, the MWCO of the MCO membrane is slightly lower than that of albumin, preventing albumin loss during dialysis.<sup>8,9</sup> In addition, it allows for exceptional internal filtration without the need for replacement fluid, enabling additional convection during hemodialysis.<sup>9</sup>

A1M is a peptide composed of 183 amino acids with a molecular weight of 33000 Da.<sup>10</sup> It is produced by the liver, and under normal physiological conditions, 50% of it is present in the blood in free form, while 50% is bound with dimeric immunoglobulin A10. It is filtered by the glomeruli and then reabsorbed in the proximal parts of the renal tubules, where it then catabolized. A1M has strong antioxidant activity exhibited by its ability to scavenge free radicals and transform to a reduced form upon exposure to oxidative stress.<sup>11</sup>

A1M is neither labeled as a uremic toxin nor included in the middle molecule category in the EUTox classification.<sup>12</sup> However, it is a convenient biomarker that reflects the efficiency of dialysis in middle molecule removal, as it has a stable synthesis rate and serum concentration under normal physiological conditions. Most importantly, it is primarily removed via convection and accumulates in renal failure. Furthermore, A1M measurement is available in commercial labs with a low risk of measurement errors.<sup>13</sup> Incidentally, it has been used in Japan for over 30 years to assess the efficacy of HDF in middle molecule removal.<sup>14</sup>

Hypoalbuminemia in patients with renal failure is an imperative cause of increased morbidity and mortality in clinically stable, hospitalized, and acutely ill patients.<sup>15</sup> It has several etiologies, including malnutrition, chronic inflammation, protein catabolism, and albumin loss in dialysate.<sup>15</sup> Hence, besides promoting an adequate nutritional supply, limiting albumin loss by enhancing dialyzer technology would positively impact the prevalence of hypoalbuminemia amongst renal failure patients.

High-flux membrane dialyzers, which are defined by an ultrafiltration rate of  $\geq 15$  mL/mmHg/h and a  $\beta$ 2-microglobulin clearance rate of  $\geq 15$  mL/min. High-flux membranes have high hydraulic permeability and higher solute permeability for middle-sized solutes than low-flux membrane dialyzers.

This study aimed to compare the efficacy of high-flux hemodialysis (HF-HD) against HDF. Therefore, we assessed A1M removal, as well as cumulative dialysate albumin loss, using a dialyzer surface area (SA) of 2.6m<sup>2</sup> in high-flux hemodialysis (HF-HD) versus HDF.

## Patients and Methods

### Study population

This crossover study was conducted at the Ain Shams University Specialized Hospital's dialysis center. Our study comprised 25 patients diagnosed with End-Stage Renal Disease (ESRD) for over six months. Our patients received four hourly hemodialysis sessions, thrice per week,

with a blood flow (QB)  $\geq 300$  ml/min. Sodium bicarbonate dialysate was used, and unfractionated heparin was administered as anticoagulation. Patients with temporary dialysis catheters, active inflammation or infections, decompensated heart failure, and Child B or C liver cirrhosis were excluded.

#### *Ethical considerations*

The protocol of the present study was reviewed and approved by the Research Ethics Committee (approval number: FMASU MD 196/2020). For all patients, an informed written consent was obtained before included in the study.

#### *Dialyzer and Dialysis conditions*

Each patient received two hemodialysis sessions; one was HF-HD, while the other post-dilution online hemodiafiltration (OL-HDF), using the dialyzer *BIOPURE (Biorema) 260 HF* (SA  $2.6 \text{ m}^2$ , high-flux hollow fiber with steam sterilization, myoglobin SC 0.7, membrane cut-off value 40,000 Da; Allmed Medical GmbH, Germany). We instilled a washout period of two weeks between the two sessions, during which the patients received HF-HD using a dialyzer with a maximum SA  $2.0 \text{ m}^2$ .

Hemodialysis sessions' conditions remained unchanged regarding dialysate flow (Qd: 500ml/min) and blood flow  $\geq 300$  ml/min, yet the ultrafiltration rate varied according to each patient's weight before each session. Regarding the post-dilution OL-HDF session, the substitution volume was  $\geq 20$  L for all patients.

#### *Laboratory Tests*

The following laboratory tests were analyzed at baseline, using standard laboratory methods available for routine check-up at Ain Shams University hospitals: Complete Blood Count, blood urea nitrogen (BUN), serum creatinine, sodium, potassium, calcium, and phosphorus, parathyroid hormone level (PTH), ferritin, iron, total iron binding capacity (TIBC), and serum albumin. Data of these laboratory investigations were obtained from hospital records. In addition, serum A1M and dialysate albumin were measured, and appropriate calculations were made as follows:

#### *Serum alpha 1-microglobulin*

Serum A1M levels were measured before and after each patient's two modalities of hemodialysis (HF-HD and post-dilution OL-HDF). All blood samples were collected from the arterial line at the beginning and end of the dialysis session. The collected samples were allowed to rest for 10 – 20 minutes, at room temperature, to clot, then centrifuged at  $704 \text{ xg}$  for 20 minutes after which the supernatant was removed. If precipitation appeared, centrifugation was repeated. A1M levels were measured using a double antibody sandwich enzyme-linked immunosorbent (ELISA) assay (Catalogue No. 201-12-1093, Sunred Biological Technology Co., Ltd., Shanghai, China), according to the manufacturer's instructions.

The optical density (OD), of tested samples and standards, was measured at 450 nm wavelength using a microtiter reader (The Awareness Technology Stat Fax 2100 microplate reader, Awareness Technology inc, USA). According to the standard's concentration and the corresponding OD value, a standard curve linear regression equation was calculated then the OD values of the samples were applied to the regression equation to calculate the corresponding sample's concentration.

The sensitivity of this assay or lower limit of detection was defined as the lowest protein concentration that could be differentiated from zero. The minimum detectable dose of human A1M was determined to be 0.586 mg/L (Assay range: 0.6 mg/L-180 mg/L). This was established by adding two standard deviations to the mean OD value of twenty zero standard replicates and calculating the corresponding concentration.

#### *Dialysate albumin*

Samples from spent dialysate after 30 minutes, 1<sup>st</sup>, 2<sup>nd</sup>, and 3<sup>rd</sup> hour, and at the end of the dialysis session were collected to estimate the cumulative albumin loss in both HF-HD and HDF. Dialysate albumin was measured using commercially available microalbuminuria Immunoturbidimetry assay. Kits (BioSystems, S.A. Costa Brava 30, 08030 Barcelona, Spain), according to the manufacturer's instructions.

### Calculations

A1M reduction ratio (RR) was calculated using the following equation.<sup>15</sup>

$$RR = \frac{C_{pre} - C_{post}}{C_{pre}} \times 100\%$$

RR: reduction ratio,  $C_{pre}$ , and  $C_{post}$  are serum A1M concentrations, pre-, and post-treatment, respectively.

Calculating A1M post-dialysis concentration corrected for net ultrafiltration, with the following equation<sup>15</sup>

$$C_{post.c} = \frac{C_{post}}{\left(1 + \frac{\Delta BW}{0.2 \times BW_{post}}\right)}$$

$C_{post.c}$ : serum A1M level post session after correction of net UF,  $C_{post}$  is serum A1M level post-session,  $BW_{post}$  is the body weight after ultrafiltration.

Cumulative albumin loss was measured by the following equations.<sup>15,16</sup>

$$\begin{aligned} \text{Cumulative dialysate Albumin (gm)} \\ = \text{Albumin } \frac{1}{2} \text{ hr} + \text{Albumin 1st hr} + \text{Albumin 2nd hr} \\ + \text{Albumin 3rd hr} + \text{Albumin 4th hr}. \end{aligned}$$

Albumin lost over the first half or 1<sup>st</sup> hour was measured by equation "A".<sup>15,16</sup>

$$\text{Albumin (gm)} = \frac{\text{Dialysate Alb.} \left(\frac{\text{mg}}{\text{dl}}\right)}{100} \times \frac{[\text{Quf} + \text{SUB VOLUME} + \text{Qd} \left(\frac{\text{ml}}{\text{min}}\right)] \times 30 \text{ (mins)}}{1000}$$

Albumin lost over 2<sup>nd</sup> or 3<sup>rd</sup>, or 4<sup>th</sup> hours was measured by equation "B"<sup>15,16</sup>

$$\text{Albumin (gm)} = \frac{\text{Dialysate Alb.} \left(\frac{\text{mg}}{\text{dl}}\right)}{100} \times \frac{[\text{Quf} + \text{SUB VOLUME} + \text{Qd} \left(\frac{\text{ml}}{\text{min}}\right)] \times 60 \text{ (mins)}}{1000}$$

Qd: dialysate flow, QUF: ultrafiltration rate, Sub. Volume: substitution volume (in case of HDF only).

### Statistical analysis

Collected data were revised, coded, tabulated, and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). The Shapiro-Wilk test was used to verify the normality of distribution. Qualitative data were presented as numbers and percentages; quantitative data presented as mean  $\pm$ SD (standard deviation) for normally distributed data or median with interquartile ranges (IQR) for nonparametric data. In qualitative data, independent variables were analyzed using the Chi-Square ( $\chi^2$ ) test. In quantitative data, a two-tailed independent t-

test was used to compare two independent groups with normally distributed data, while the Mann-Whitney test was used for nonparametric data. Correlations were done using the Pearson correlation coefficient test (r). Significance was defined by the p-value where  $p < 0.05$  was considered significant.

### Results

Baseline characteristics of the study cohort regarding age and gender, as well as baseline laboratory work-up, are summarized in Table 1.

**Table 1.** Description, characteristics, and laboratory findings of the 25 study patients.

Variables	Mean $\pm$ SD/ Median (IQR)
Age (years)	48.4 $\pm$ 11.4
Gender (M/F)	23/2
Dry weight (Kg)	85(75-95)
BMI	31.06 $\pm$ 5.47
PTH (pg/ml)	458.0 (175.0 – 679.0)
Calcium (mg/dl)	8.47 $\pm$ 0.69
Phosphorus (mg/dl)	5.34 $\pm$ 1.06
Sodium (mEq/L)	134.0 $\pm$ 4.47
Potassium (mEq/L)	5.39 $\pm$ 0.70
Ferritin (ng/ml)	848.7 (362.2 – 951.0)
TIBC ( $\mu$ g/dl)	216.4 $\pm$ 42.69
Iron ( $\mu$ g/dl)	60.52 $\pm$ 18.91
Total Leucocytic Count ( $\times 10^3/\text{mm}^3$ )	7.02 $\pm$ 1.65
Lymphocytes (%)	23.49 $\pm$ 7.57
Neutrophils (%)	65.14 $\pm$ 8.62
Hemoglobin (gm/dl)	10.65 $\pm$ 1.26
Hematocrit (%)	34.30 $\pm$ 3.41
Platelets ( $\times 10^3/\text{mm}^3$ )	208.7 $\pm$ 66.28

BMI; body mass index, IQR; Interquartile range, TIBC; total iron binding capacity, (M/F); male/female, SD; Standard deviation.

Parameters of the total studied patients collected during the HDF machine sessions included a mean ultrafiltration volume of  $2.96 \pm 0.96$  L, a mean substitution volume of  $21.12 \pm 0.87$  L, a mean convection volume of  $24.06 \pm 0.86$  L, and a mean blood flow (Qb) of  $341.6 \pm 19.08$  ml/min. Furthermore, the average total processed blood calculated was  $81.98 \pm 4.58$  L, and the average calculated filtration fraction was  $29.42 \pm 1.59\%$ .

Regarding the measured A1M levels, no statistically significant difference was found pre-

dialysis in HF-HD and HDF ( $p = 0.418$ ), as highlighted in Table 2. The *BIOPURE (Biorema) 260 HF* dialyzer resulted in a statistically significant reduction in the mean A1M level post-dialysis, as compared to pre-dialysis levels, in both HF-HD and HDF ( $p < 0.001$ ). Notably, HDF brought about a significantly higher A1M RR ( $41.9 \pm 7.93\%$ ) in contrast to the A1M RR observed for the HF-HD ( $27.12 \pm 7.65\%$ ) ( $p < 0.001$ ).

**Table 2.** Comparison between high-flux hemodialysis (HF-HD) and hemodiafiltration (HDF) regarding A1M levels and reduction ratio.

	HF-HD	HDF	<i>p</i> value
A1M (C)			
C pre (ng/ml)	47.90 ± 13.74	55.67 ± 14.23	NS
C post (ng/ml)	34.83 ± 10.76	32.16 ± 48.94	<0.001
<i>p</i> value	<0.001	<0.001	
RR (%)	27.12 ± 7.65	41.9 ± 7.93	<0.001

A1M (C); alpha 1-microglobulin concentration, C pre; pre-dialysis A1M concentration, C post; post-dialysis A1M concentration, HDF; Hemodiafiltration, HF-HD; High-flux Hemodialysis, RR; reduction ratio. *P* > 0.05 is not significant (NS).

Hourly trans-membrane pressure (TMP) was recorded by the dialysis machine, for all patients during both HF-HD and HDF dialysis sessions, as shown in Table 3. TMP recorded during HDF

throughout the four hours, as well as the mean TMP, was significantly higher compared to hourly and the mean TMP recorded during HF-HD (*p* < 0.001, for all).

**Table 3.** Comparison between trans-membrane pressure (TMP) in high-flux hemodialysis (HF-HD and hemodiafiltration (HDF).

TMP	HF-HD (n = 25)	HDF (n = 25)	<i>p</i> value
1 <sup>st</sup> hour			
Min. – Max.	60.0 – 140.0	105.0 – 185.0	<0.001
Mean ± SD.	89.0 ± 16.14	155.8 ± 20.50	
2 <sup>nd</sup> hour			
Min. – Max.	60.0 – 160.0	110.0 – 195.0	<0.001
Mean ± SD.	96.0 ± 20.97	166.4 ± 20.74	
3 <sup>rd</sup> hour			
Min. – Max.	60.0 – 135.0	120.0 – 200.0	<0.001
Mean ± SD.	94.0 ± 20.21	177.2 ± 20.47	
4 <sup>th</sup> hour			
Min. – Max.	40.0 – 130.0	125.0 – 210.0	<0.001
Mean ± SD.	93.0 ± 26.22	183.8 ± 20.32	
Mean			
Min. – Max.	60.0 – 127.5	115.0 – 196.25	<0.001
Mean ± SD.	93.0 ± 18.14	170.80 ± 19.56	

HDF; hemodiafiltration, HF-HD; high-flux hemodialysis, IQR: Inter quartile range, SD; standard deviation; t, paired t-test.

\**P* ≤ 0.05 is significant.

Dialysate albumin loss was measured and recorded hourly, as demonstrated in Table 4. Of note, the albumin loss was significantly higher with HDF than HF-HD dialysis sessions (*p* < 0.001). Maximum albumin loss for patients

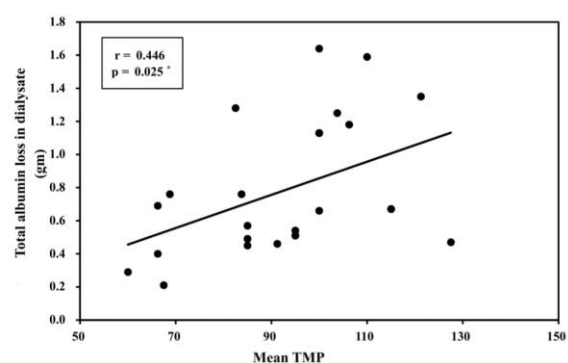
on both HDF and HF-HD was recorded in the first hour, after which albumin loss becomes less profound over the next three hours, reaching its lowest by the fourth hour.

**Table 4.** Comparison between hemodialysis (HD) and hemodiafiltration (HDF) regarding albumin loss in dialysate.

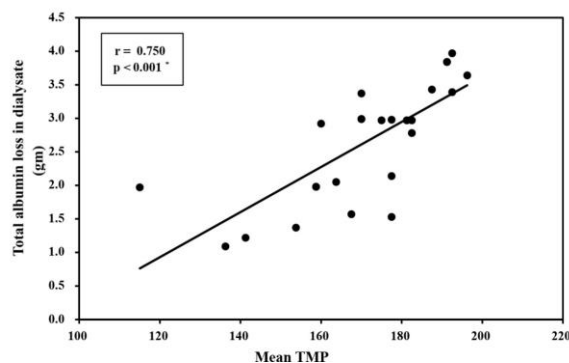
Albumin loss in dialysate (g)	HF-HD (n = 25)	HDF (n = 25)	p value
At First 30 minutes			
Min. – Max.	0.02 – 0.54	0.18 – 1.53	
Median (IQR)	0.14 (0.14 – 0.23)	0.73 (0.54 – 0.97)	
At 1 <sup>st</sup> hour			
Min. – Max.	0.0 – 0.47	0.14 – 0.98	
Median (IQR)	0.12 (0.06 – 0.23)	0.56 (0.48 – 0.73)	
After 1 <sup>st</sup> hour			
Min. – Max.	0.05 – 0.77	0.61 – 2.51	
Median (IQR)	0.26 (0.20 – 0.51)	1.43 (0.92 – 1.52)	
2 <sup>nd</sup> hour			
Min. – Max.	0.03 – 0.47	0.11 – 1.08	
Median (IQR)	0.12 (0.09 – 0.31)	0.61 (0.36 – 0.75)	
3 <sup>rd</sup> hour			
Min. – Max.	0.0 – 0.31	0.04 – 0.87	<0.001
Median (IQR)	0.09 (0.09 – 0.18)	0.43 (0.32 – 0.58)	
4 <sup>th</sup> hour			
Min. – Max.	0.03 – 0.25	0.04 – 0.73	<0.001
Median (IQR)	0.06 (0.03 – 0.12)	0.22 (0.11 – 0.29)	
Total loss			
Min. – Max.	0.21 – 1.64	1.09 – 3.97	<0.001
Median (IQR)	0.67 (0.49 – 1.13)	2.97 (1.98 – 3.37)	

g; grams, HDF; hemodiafiltration, HF-HD; high-flux hemodialysis, IQR; Inter quartile range, SD; standard deviation, n; number. \* $P \leq 0.05$  is significant.

Lastly, TMP in the third and fourth hours in the HF-HD dialysis sessions showed a statistically significant positive correlation with albumin loss ( $p=0.007$  and  $p=0.006$ , respectively). In addition, the mean TMP showed a statistically significant positive correlation with total albumin loss ( $p=0.025$ ) (Figure 1). On the other hand, TMP recorded in the first, second, third and fourth hours in HDF dialysis sessions and mean TMP showed statistically significant positive correlations with hourly dialysate albumin loss and total albumin loss ( $p < 0.001$ , for all) (Figure 2).

**Figure 1.** Correlation between total albumin loss in dialysate (g) and mean trans-membrane pressure (TMP) in high-flux hemodialysis (HF-HD) of the 25 patients.





**Figure 2.** Correlation between total albumin loss in dialysate (g) and mean trans-membrane pressure (TMP) in hemodiafiltration (HDF) of the 25 patients.

## Discussion

Renal replacement therapy has witnessed remarkable progression, since its conception, through the advancement in dialyzers and hemodialysis modalities, reducing the complications of renal replacement therapy and improving patients' quality of life. The efficacy of dialysis can be assessed by measuring the RR of middle molecules, such as A1M.<sup>17</sup> In our study, we tested a high-flux dialyzer, BIOPURE (Biorema) 260 HF (SA 2.6 m<sup>2</sup>), in terms of A1M elimination and concurrent albumin loss in dialysate while receiving HF-HD versus HDF.

The BIOPURE (Biorema) 260 HF dialyzer used in this study resulted in an A1M RR of 27.12 ± 7.65% ( $p < 0.001$ ) with HF-HD and 41.9 ± 7.93% ( $p < 0.001$ ) with HDF. Countless studies tested dialyzers of different yet smaller surface areas using either HDF, HF-HD, or both.

For instance, Kamya et al., 2022 studied the removal of A1M in ten ESRD patients undergoing HF-HD using Solacea-190H (SA 1.9 m<sup>2</sup>) and FX-80 (SA 1.8 m<sup>2</sup>) dialyzers. Solacea-190H resulted in a mean A1M RR of 0.17% (-42.4-33.3), while FX-80's A1M RR was -2.41% (-94.5-55.4). The smaller SA of the tested dialyzers can explain the inferior results observed in Kamya et al.'s study.<sup>18</sup>

Another study was conducted by Sakurai et al., 2021, included 435 patients and received post dilution OL-HDF with ten types of dialyzers (SA 2.1 ± 0.1 m<sup>2</sup>). The mean A1M RR of all 435 test subjects was 33.8 ± 9.4%, highlighting the

positive impact of a larger dialyzer SA and using OL-HDF in contrast to HF-HDF.<sup>19</sup>

In addition, Kirsch et al., 2017, performed crossover pilot studies incorporating 20 patients and used FX CorDiax 80 (SA 1.8 m<sup>2</sup>) on HF-HD and FX CorDiax 800 (SA 2 m<sup>2</sup>) on HDF. Mean A1M RR was 10 ± 8.97% and -8.9 ± 8.97%, respectively.<sup>20</sup>

Furthermore, Maduell with colleagues, performed several studies using different dialyzers, number of subjects, and dialysis modalities. One study, Maduell et al., 2017, included 15 patients who underwent dialysis using Clearum HS17 (SA 1.7 m<sup>2</sup>) in HD and post-dilution OL-HDF. The A1M RR in HDF sessions was 23.7 ± 10.5%, while the RR after the HD sessions was 12.2 ± 9.5%.<sup>21</sup>

In another study, Maduell et al., 2022, used an Elisio HX (SA 1.9 m<sup>2</sup>) dialyzer and carried out a prospective study, included 18 patients, received both HF-HD and HDF sessions. The mean A1M RR was 24.8 ± 10.4% with HDF sessions and 8.6 ± 7.7% using HF-HD.<sup>22</sup> A similar study, also by Maduell et al., 2019, included 21 patients underwent both HF-HD and HDF using a Helixone FX80 Cordiax dialyzer (SA 1.8 m<sup>2</sup>). Results revealed a mean A1M RR of 26.3 ± 13% with HDF and 10.1 ± 11% with HF-HD.<sup>23</sup> Finally, a study by Maduell et al., 2021, incorporated 12 patients on HF-HD and HDF sessions, used a Toraysulfone TS dialyzer (SA 1.8 m<sup>2</sup> and 2.1 m<sup>2</sup>) resulted in a mean A1M RR of 31.4 ± 6.5% with HDF and 13.1 ± 8.9% with HF-HD.<sup>24</sup>

Comparing the results of the present study, concerning A1M RR, with the mentioned above studies, it is apparent that the removal of middle molecules is superior with dialyzers of larger surface areas and with HDF in contrast to HF-HD.

In our study, the dialyzer BIOPURE 260 HF resulted in a median cumulative dialysate albumin loss of 2.97g (IQR 1.98 – 3.37) by the end of the HDF session, which was about four times higher than in HF-HD, where the median cumulative albumin loss was 0.67g (IQR 0.49 – 1.13). Consequently, we can argue that this is an acceptable albumin loss as it can be compensated for by maintaining an adequate protein intake of 1.2 g/kg/day.



In Maduell and his coworkers' various studies in which they tested numerous dialyzers, they also measured the albumin lost in the dialysate. For instance, when used the Clearum HS-17, the mean total albumin loss was 0.437 g with HD and 1.363 g with HDF.<sup>21</sup> The Elisio H19 resulted in a mean total albumin loss of 0.715 g with HD and 1.582 g with HDF.<sup>22</sup> Furthermore, when tested the FX80 Cordiax, the mean total albumin loss was 0.558 g with HD and 2.697 g with HDF.<sup>23</sup> The Toraysulfone TS 1.8/2.1 UL brought about a mean total albumin loss of 0.747 g with HD and 3.488 g with HDF.<sup>24</sup> These studies highlighted a higher dialysate albumin loss with high cut-off dialyzers and dialysis modalities that employ convective therapies, particularly in post-dilution mode. These agreed with our observation that use of the Biorema dialyzer resulted in a clinically significant reduction in the ratio of A1M using both dialysis modalities with an acceptable albumin loss.

Furthermore, our study demonstrated that maximum albumin loss occurred in the first hour of dialysis, whether HDF or HF-HD were used. This is because further albumin loss is halted by the formation of a secondary protein layer caused by the deposition of proteins such as fibrinogen on the dialysis membrane, a phenomenon referred to as 'fouling'.<sup>25</sup>

Of note, another study was conducted on the same group of patients included in this study that aimed to test the BIOPURE (Biorema) 260 HF dialyzer in terms of free light chains removal during HF-HD and HDF.<sup>26</sup> HDF showed significantly higher kappa and lambda free light chains RR ( $45.16 \pm 6.53\%$  and  $28.68 \pm 4.36\%$ , respectively) compared to HF-HD ( $29.52 \pm 6.38\%$  and  $19.48 \pm 1.96\%$ , respectively) ( $p < 0.001$ ).<sup>26</sup>

Finally, one limitation of our study, the relatively small number of studied patients. In addition, data collected for each patient were derived from a single session of the HF-HD and HDF.

In conclusion, data of the present study indicated that the dialyzer BIOPURE (Biorema) 260 HF, with a SA 2.6 m<sup>2</sup>, was efficient in eliminating A1M, especially with OL-HDF compared to HF-HD, with acceptable albumin loss in the spent dialysate.

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## Author Contributions

The study's principal investigators were HE, AK, and HSH. HE and ME proposed the topic of this research and designed the study. MF and AE collected the data. All authors contributed to preparing the final draft of the manuscript, revised the manuscript, and critically reviewed the intellectual contents.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## Ethical approval

The protocol of the present study was reviewed and approved by the Research Ethics Committee (approval number: FMASU MD 196/2020).

## Informed consent

An informed written consent was obtained from each patient before included in the study.

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