Original Research Article

The Egyptian Journal of Immunology

The Egyptian Journal of Immunology
Volume 29 (4), 2022: 106–114.
www.Ejimmunology.org

High-Flux dialyzer 2.6 m^2 is promising for free light chains removal in high-flux hemodialysis and in hemodiafiltration

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Abstract

Immunoglobulin light chains are classified as middle molecule uremic toxins and its removal through effective dialyzer is needed with less albumin loss. This study assessed the free light chains (FLC) removal using dialyzer surface area (SA) 2.6m2 in high-flux dialysis (HF-HD) versus hemodiafiltration (HDF) and its relation to cumulative dialysate albumin loss. This pilot cross-over study included 25 patients who underwent hemodialysis (HD) using dialyzer surface area 2.6m2 on HF-HD followed by online post-dilution HDF with washout period of 2 weeks using high-flux dialyzers (max 2.0 m2 SA). All patients were subjected to single session measurement of dialysate albumin every hour and pre/post dialysis levels of FLC Kappa (K) and Lambda (λ) by ELISA. Dialyzer (SA) 2.6m2 showed a significant reduction in post-dialysis kappa and lambda level in comparison to pre-dialysis level on HF-HD and hemodiafiltration (P<0.001). HDF showed higher kappa and lambda FLC reduction ratio (45.16 ± 6.53 %, 28.68 ± 4.36 %, respectively compared to HF-HD (29.52 ± 6.38 %, 19.48 ± 1.96, respectively, P<0.001 for both). Patients on HDF dialysis had significant total albumin loss in dialysate [median (IQR) 2.97; 1.98 – 3.37 gm] compared to HF-HD [median (IQR) 0.67; 0.49 – 1.13 gm] (P <0.001). In conclusion, high-flux dialyzer 2.6 m2 (SA) may be effective in free light chains removal especially with online post-dilution hemodiafiltration with acceptable albumin loss.

Keywords: Serum free light chains, High-flux, albumin, hemodiafiltration.

Date received: 15 April 2022; **accepted:** 22 July 2022

Introduction

Uremic toxins are defined as molecules that accumulate in kidney impairment and have an adverse biologic effect. They can be broadly classified into three groups: small water-soluble molecule, middle molecule, and protein-bound solutes.[1] The primary goal of dialysis is toxins' removal. Removal capacity should be extended to include substances up to a molecular weight of 50 kDa because this is the cut-off the natural kidney.[2] Immunoglobulin light chains are classified as middle molecule uremic toxins, they have a mean molecular weight of 25KDa for monomers (kappa "K" free light chains) and approximately 50 kDa for dimers (lambda "λ" free light chains).[3] In pre-dialysis patients, polyclonal free light chains (FLC) increase

dramatically as the glomerular filtration rate (GFR) declines and in dialysis patients it gets higher levels up to 20–30 times the normal values.[4] Elevated levels are associated with chronic inflammatory state, vascular calcification, and higher risk of bacterial infections through impairment of neutrophils function.[5, 6, 3]

Serum levels of free FLCs are elevated in a variety of diseases such as in multiple myeloma, active stage of juvenile idiopathic arthritis, in Systemic Lupus Erythematosus (SLE) patients and in CKD patients at which their level progressively increases. In CKD, the accumulating immunoglobulin light chains are polyclonal [6]. Excess, FLC inhibit neutrophils functions by inhibiting chemotactic movement, reducing activation of glucose uptake, and inhibiting apoptosis. This impairment of neutrophil function can contribute to the chronic inflammatory state of uremic patients and to the increased risk of bacterial infections.[3,10] Furthermore, FLC levels were previously positively correlated with aortic calcification.[15]

Most hemodialysis techniques remove small water-soluble molecules, and the classical dialyzers have difficulties in efficiently removing FLC.[4] Convective therapies and highly permeable membranes are known to remove medium - large molecular weight solutes giving higher dialysis adequacy but associated with higher transmembrane albumin loss than the previously routinely used low flux-HD.[7] The hemodiafiltration (HDF) technique improves the clearance of molecules up to 25 kDa and newer'medium cut-off' (MCO) membranes are known to have the potential to remove larger molecules up more effectively to 50 kDa, with acceptable albumin loss,[8] but in comparison with HF dialyzers, MCO and convective techniques are somehow costly and are not always available worldwide especially in middle-low-income countries.

Since the middle molecules are known to be cleared more efficiently by increasing the membrane's pore size, require applying higher convection and prolongation of HD session duration.[9] Therefore, it is speculated that the usage of big SA high-flux dialyzer, with or without HDF, may achieve better removal of FLCs and middle-sized molecules reaching reduction levels comparable to MCO dialyzers while using feasible, cheaper and more available dialyzers.

In this study we aimed to assess removal of free light chains using high-flux dialyzer SA 2.6 m^2 on high-flux dialysis in comparison to hemodiafiltration and its relation to albumin loss.

Subjects and Methods

Study population

This pilot crossover study was carried out at the dialysis units of Ain Shams University hospitals. It included 25 end-stage renal disease (ESRD) patients undergoing regular hemodialysis (three sessions/week, each for at least 4 hours, for > 6 months). The hemodialysis sessions were based on using bicarbonate dialysate and unfractionated heparin as anticoagulation, blood flow (QB) ≥300ml/min. Patients with temporary dialysis catheters, active inflammation and/or infections, decompensated heart failure, liver cell failure Child B or C were excluded. All patients were subjected to full history taking and clinical examination. Routine laboratory tests were obtained from the patients' hospital records and recorded at the beginning of the study. These included complete blood count, and blood chemistry. The chemistry tests included blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, and phosphorous. Data of parathyroid hormone (PTH), serum ferritin, serum iron, total iron binding capacity (TIBC), high sensitivity C-reactive protein (hsCRP), and serum albumin were also obtained.

Dialyzer and Dialysis conditions

All patients were dialyzed using a dialyzer machine (BIOPURE (Biorema) 260 HF, Allmed Medical Industries, Gmbh, Germany). The dialyzer membrane has a surface area of 2.6 m^2, High-flux hollow fiber with steam sterilization, myoglobin SC 0.7, membrane cutoff value of 40,000 Daltons. Patients were dialyzed on a single session on two hemodialysis modalities (conventional HD and online post-dilution HDF)

with washout period of 2 weeks using high-flux dialyzers with maximum surface area 2.0 m^2. Hemodialysis sessions' conditions remained unchanged regarding dialysate flow (Qd:500ml/min), blood flow ≥300 ml/min, ultrafiltration rate remained variable according to patient's weight gain. The substitution volume of online post-dilution HDF sessions was ≥20 L.

Free light chain measurement

Pre and post dialysis levels of kappa and lambda free light chains were measured upon a single session of HF-HD and HDF. All blood samples were collected from the arterial line at the beginning and end of the dialysis session. The collected sample was allowed to clot for 10 – 20 minutes at room temperature, then centrifuged for 20-min at a speed of 2000-3000 rpm. Following centrifugation, the supernatant was removed, and if precipitated material appeared, centrifugation was done again. Kappa and lambda serum levels was measured by an enzyme linked immunosorbent assay (ELISA) kit (Catalogue No. 201-12-00198, 201-12-0193 respectively, Shanghai Sunred Biological Technology Co., Ltd, China), according to the manufacturer's instructions.

Measurement of dialysate albumin level

Dialysate albumin samples were collected from spent dialysate after half, 1st,2nd ,3rd hour and at the end of the dialysis session to estimate the cumulative albumin loss upon single session of HF-HD and HDF. Albumin dialysate was assessed using Microalbuminuria Immunoturbidimetry assay (BioSystems, S.A. Costa Brava 30, 08030 Barcelona, Spain) according to the manufacturer's instructions.

Calculations used in the study

-FLCs reduction ratio were calculated using the equation,[10],[11],[12]

$$RR = \frac{Fpre - Fpost}{Fpre}$$

RR: reduction ratio, F_{pre} and F_{post} are serum FLC concentrations (kappa/lambda) pre- and post-treatment respectively.

-Reduction percentages were calculated by multiplying the reduction ratio by 100 %.

-κ/λ ratio was calculated.

-Calculation of FLC post-dialysis concentration corrected for net ultrafiltration with the following equation:[4,13]

$$Fpost.c = \frac{Fpost}{1 + \frac{\Delta BW}{0.2X\ BWpost}}$$

Fpost. c: serum FLC level post session after correction of net UF, F_{post} is serum FLC level post session, BW_{post} is the body weight after ultrafiltration.

-Cumulative albumin loss was measured by the following equations:[12,14]

Cumulative dialysate Albumin (gm)
= Albumin ½ hr + Albumin 1st hr +Albumin 3rd hr + Albumin 4th hr

-Albumin lost over first half or 1st hour was measured by equation "A".[12, 14]

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

-Albumin lost over 2nd or 3rd, or 4th hours was measured by equation "B". [1214]

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

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

Statistical analysis

Data were collected, revised, coded, and entered into a computer using the statistical IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Shapiro-Wilk test was used to verify the normality of distribution. The qualitative data were presented as number and percentage, whereas quantitative data were presented as mean with standard deviation (±SD) or median with interquartile ranges (IQR) for nonparametric data (Ferritin, PTH and dialysate albumin). Comparison between two groups with qualitative data was done by using the $\chi 2$ test. Comparison between two groups with quantitative data was done by two-tailed independent t-test when the distribution of the data was found parametric. Mann–Whitney test was used with the nonparametric data. Pearson coefficient was used to assess the correlations. A *P*-value of <0.05 was considered significant.

Results

Table 1 shows descriptive data of the 25 patients and dialysis parameters of HDF session. The mean age (±SD) in years was 48.4 ± 11.4, and 23 patients were males (92%). There was no difference between pre-dialysis k/λ ratio between both HD modalities (*P*=0.418). Dialyzer (SA) 2.6m^2 showed significant reduction in post-dialysis levels of kappa and lambda in comparison to pre-dialysis levels on high-flux hemodialysis and hemodiafiltration (p<0.001 for both). HDF showed higher kappa and lambda FLC reduction ratio (45.16 ± 6.53% and 28.68 ± 4.36 %, respectively) compared to high-flux HD (29.52 ± 6.38 % and 19.48 ± 1.96 %, respectively) (*P*<0.001). HDF/HD fold change of kappa and lambda were (1.56 ± 0.23 and 1.48 ± 0.26, respectively) (Table 2). There was no correlation between FLCs reduction ratio and convection volumes (K: *P*=0.112, λ *P*=0.761)

Table 1. Descriptive data of patients' characteristics, laboratory findings and dialysis parameters of hemodiafiltration (HDF) session.

Variables	Mean ± SD/ Median (IQR)
Age (years)	48.4 ± 11.4
Gender (M/F)	23/2
Dry weight (Kg)	85(75-95)
BMI	31.06 ± 5.47
PTH (pg/ml)	458.0 (175.0 – 679.0)
Calcium (mg/dl)	8.47 ± 0.69
Phosphorus (mg/dl)	5.34 ± 1.06
Sodium (mEq/L)	134.0 ± 4.47
Potassium (mEq/L)	5.39 ± 0.70
Ferritin (ng/ml)	848.7 (362.2 – 951.0)
TIBC (µg/dl)	216.4 ± 42.69
Iron (µg/dl)	60.52 ± 18.91
Total Leucocytic Count (*10^3/ mm^3)	7.02 ± 1.65
Lymphocytes (%)	23.49 ± 7.57
Neutrophils (%)	65.14 ± 8.62
Hemoglobin (gm/dl)	10.65 ± 1.26
Hematocrit (%)	34.30 ± 3.41
Platelets (*10^3/mm^3)	208.7 ± 66.28
HsCRP (ng/ml)	7532.0 ± 2114.38
Parameters of HDF session	
Ultrafiltration (L)	2.96 ± 0.96
Substitution volume (L)	21.12 ± 0.87
Convection volume (L)	24.06 ± 0.86
Blood flow (ml/min)	341.6 ± 19.08
Total processed Blood (L)	81.98 ± 4.58
Filtration Fraction (%)	29.42 ± 1.59

SD; Standard deviation, IQR; Interquartile range, (M/F): male/female, BMI; body mass index, HDF; hemodiafiltration, PTH: parathormone hormone, TIBC: total iron binding capacity, HsCRP: highly sensitive CRP.

Table 2. Comparison between high-flux dialysis (HD) and hemodiafiltration (HDF) according to different parameters.

	HD	HDF	*P value
FLC (K)			
K pre (ng/ml)	250.60 ± 73.03	249.0 ± 65.32	NS
K post (ng/ml)	177.24 ± 54.83	136.8 ± 40.07	<0.001
P value	<0.001	<0.001	
RR (%)	29.52 ± 6.38	45.16 ± 6.53	<0.001
Fold Change	1.56 ± 0.23		
FLC (λ)			
λ pre (ng/ml)	267.80 ± 33.61	275.8 ± 34.39	NS
λ post (ng/ml)	215.49 ± 26.60	195.9 ± 19.24	<0.001
p value	<0.001	<0.001	
RR%	19.48 ± 1.96	28.68 ± 4.36	<0.001
Fold Change	1.48 ± 0.26		
k/λ			
Pre	0.93 ± 0.23	0.90 ± 0.21	NS
Post	0.81 ± 0.23	0.70 ± 0.19	<0.001
P value	<0.001*	<0.001*	
Urea			
Pre	68.28 ± 16.99	68.04 ± 14.05	NS
Post	23.52 ± 5.90	21.40 ± 6.16	0.043
P value	<0.001*	<0.001*	
RR	65.17 ± 6.11	65.17 ± 6.11	
Fold Change	1.05 ± 0.06		
Serum Albumin (gm/dl)	3.76 ± 0.37	3.72 ± 0.40	NS

HD; Hemodialysis, HDF; Hemodiafiltration, FLC (K); free light chains Kappa, K pre: pre dialysis kappa level, K post: post dialysis Kappa level, RR: reduction ratio, FLC (λ); Free light chains lambda, λ pre; pre dialysis lambda level, λ post; post dialysis lambda level, k/λ; kappa/ lambda ratio. **P*> 0.05 is not significant (NS).

Patients on HDF had higher high transmembrane pressure (TMP) at 1st, 2nd, 3rd, and 4th hour with mean TMP of 170.80±19.56, in comparison with patients on HF-HD with mean TMP of 93.0 ± 18.14 (*P* <0.001 for all). The cumulative dialysate albumin loss over the 4 hours indicated that there was statistically significant loss on HDF dialysis with median of 2.97 gm (1.98 – 3.37) compared to HF-HD with median of 0.67 gm (0.49 – 1.13) (*P* <0.001). The maximum albumin loss for patients on HDF was observed over the first hour with median of 1.43 gm (0.92 – 1.52) and lower albumin loss over the following hours reaching median of 0.22 gm (0.11 – 0.29) in the fourth hour. In comparison, there was a significant reduction in albumin loss on HF-HD dialysis (*P*<0.001, Figure 1).

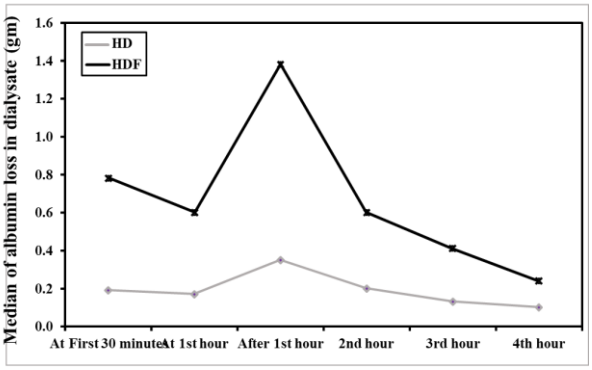

Figure 1. Median of albumin loss in dialysate (gm) in high flux dialysis (HF-HD) and hemodiafiltration (HDF) in relation to dialysis. duration. The figure shows maximum albumin loss for patients on hemodiafiltration (HDF) was over the first hour with median 1.43 gm (0.92 – 1.52) with lower albumin loss in the next hours reaching median 0.22 gm (0.11 – 0.29) in the fourth hour, in comparison to albumin loss on high flux dialysis (HF-HD). The albumin loss on the HF-HD was significantly lower than that in the HDF (*P*<0.001).

For the HF-HD dialysis, the 3rd and 4th hours, and mean TMP were positively correlated with albumin loss in 3rd, 4th hour and total loss (*P*= 0.007, 0.006, 0.025, respectively). In HDF 1st, 2nd, 3rd, 4th hour TMP and the mean TMP was positively correlated with albumin loss in dialysate (*P* <0.001 for all, Figure 2). There was no correlation between albumin loss and convection volume on HDF sessions.

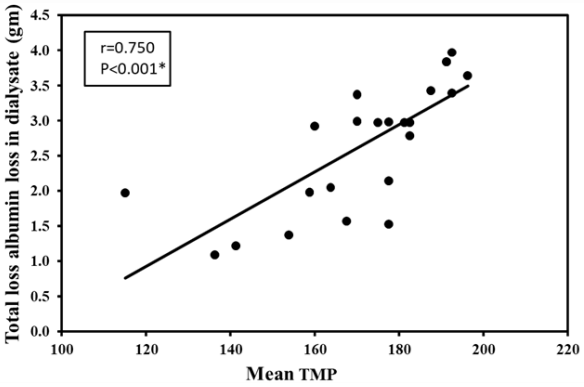

Figure 2. Correlation between total albumin loss (gm) in dialysate of the 25 studied patients and mean transmembrane pressure (TMP) in hemodiafiltration (HDF).

Discussion

This study aimed at assessing free light chains removal using BIOPURE (Biorema) 260 H SA 2.6 m^2 dialyzer with steam sterilization on HF-HD and HDF sessions. The results showed statistically significant reduction on both modalities with better removal on online HDF with average percent "K: 45.16 % λ: 28.68%". Our study findings came in agreement with those of previous studies (see below) indicating significant reduction of FLC on HDF better than HF-HD.

A study by Morena et al., 2019, compared 4 dialyzers (Leoceed-21 HX (2.1m^2 SA), Polypure-22S+ (2.2 m^2 SA), Rexsys-27 H (2.7m^2 SA) and VIE-21A (2.1m^2 SA)), showed superiority of HDF over HD in middle/large-sized molecule removal and significant reduction with different dialyzers whatever the HD mode used was, reaching levels greater than 70% on HDF. The Rexsys 27H dialyzer, which was used in their study showed higher reduction ratio, reaching 76% on HDF, higher than those previously observed with Elisio™-210H,[4] and higher than we observed in our study. This might be attributed to different assay method of serum FLC and their mean dialysate flow 650 ml/min vs 500 ml/min on our sessions.

As regard the study by Bourguignon et al., 2016, it showed kappa RR of 73.5% on HDF vs 65.5% on HD and lambda RR of 51% on HDF vs 36.5% on HD using *Elisio TM 210* dialyzer (with SA 2.1 m^2). The reduction ratio of both FLCs were higher when compared to our study results, this might be attributed to the nature of "*Elisio TM 210"* dialyzer. This dialyzer has a Polynephron™ membrane with effective longer length that allow huge internal convection allowing better removal of middle-large sized molecules.[4, 12]

A study by Donati et al., 2016 showed significant reduction of kappa FLCs using HFR 17. The HFR 17 consists of a double chamber filter used for online HFR: polyphenylene high-flux surface area of 0.7 m2 and a membrane cut-off value of 35,000 Daltons, polyphenylene low flux (KUF 13 ml/h/mmHg, surface area 1.7 m2) and poly methyl methacrylate (PMMA) dialyzer (surface area of 2.1 m2, a membrane cut-off value of 20,000 Daltons) with reduction ratio higher on PMMA. The λ light chain removal peaked after two hours of dialysis treatment but with no differences among the three filters: PMMA, HFR 17 and F7 (Polysulfone membrane, cut-off value of 11,500 Daltons). PMMA, showed significantly higher reduction ratios for K (average 55%) and λ (average 37%) free light chains than the HFR17 and F7 dialyzers and higher than the Biorema 260H used in our study. The difference was mostly attributed to its adsorptive characters [3].

The study by Lamy et al., 2014, also showed significant reduction ratio of K-FLC over HDF when compared to HD sessions (66±14 % vs 52±13%, respectively). However, there was no significant increase in lambda RR between dialysis modalities (37% reduction ratios for both techniques). Such findings do not agree with our results. This discrepancy could be explained by the difference in molecular weight of the chains, as K-FLC molecular weight is 25 kDa whereas λ-FLC has molecular weight of 45–50 kDa.[10]

A study by Kleeberg et al., 2009, used Polymide HCO 1100 hemofilter (surface area 1.1 m^2, cutoff value: 60-80 kDa) and achieved FLC reduction with median of 40.8 % (range: 13.9-66.4) on HDF vs 23.7% (-32.9-55.8) on HD and that was lower than our results despite the difference between dialyzers membranes and cutoff values.[16]

As regard the cumulative dialysate albumin loss, our results came close to these of a study by Morena et al., 2019, who reported albumin loss on HDF sessions with median of 2.8 gm (2.1–4.5) using Rexsys 27H dialyzer.[12]

Furthermore, we reported higher albumin loss in HDF sessions compared to HF-HD (*P* <0.001) and this loss was considered within reasonable range when compared to other dialyzers and dialysis modalities. As demonstrated by a study of van Gelder et al., 2017, who reported that on HF-HD membranes (with molecular weight cut-off (MWCO) ~ 20kDa) albumin loss was usually absent or low (<2.4gm/4hrs) while on HCO membranes (MWCO ~ 60KDa) albumin loss was reported to reach (6 to 9 g/4–5 h treatment). Furthermore, convective therapies increase albumin loss especially in the post-dilution HDF mode reaching (range: 0.08–7 g/4 h treatment).[7]

In our study, using the BIOPURE 260H dialyzer had an advantage that dialysate albumin loss was within acceptable range on convective techniques. Such loss could be replaced by adequate nutrition, as HD patients are advised to consume 1.2 g/kg/day of protein.[20] The current study has certain limitations. The relatively small number of studied patients, and all measurements were based on a single session of HD for both modalities (HF-HD, HDF).

In summary, our study demonstrated that the maximum albumin loss took place over the first hour of HDF, because of the high TMP applied to the intact membrane. Albumin loss was positively correlated with TMP on HDF over the 4 hours. Furthermore, albumin loss was limited 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'.[21,7] There was no statistically significant correlation between convection volume and albumin loss, but convection was proportional to TMP. Cumulative albumin loss for a given treatment had a strong dependence on substitution fluid rate, this relationship tended to be nonlinear for dialyzers with greater albumin permeability.[21] Most of dialysis sessions' characteristics such as blood flow, dialysate flow, ultrafiltration rate were almost similar on HF-HD and HDF, but at the same time there was no statistically significant correlation between RRs and convection volume.

In conclusion, the High-flux BIOPURE 260H 2.6 m^2 dialyzer with steam sterilization may be effective for free light chains removal especially with online post-dilution hemodiafiltration with acceptable albumin loss.

Acknowledgment

The authors gratefully acknowledge the contributions of individuals in the Nephrology Department of Ain Shams University hospitals who participated in data preparation and collection for this study.

Author Contributions

HE; research idea. RS; data collection and sampling. HE, ME, WA, SA, AE and RS; data interpretation, writing and revision of the manuscript.

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.

Funding

The author(s) denies receipt of any financial support for the research, authorship, and/or publication of this article.

Ethical approval

The protocol of the study was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (MD 15/2020).

Informed consent

A signed consent form was obtained from each study participant.

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