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Multipotentials of new asymmetric cellulose triacetate membrane for on-line hemodiafiltration both in postdilution and predilution

Yusaku Tanaka[1*], Hiroyuki Michiwaki[1], Hirofumi Asa[1], Daisuke Hirose[1], Tomohiro Tao[1] and Jun Minakuchi[2]

Abstract

Background: On-line hemodiafiltration (OL-HDF) has been generally provided mainly by the postdilution method in Europe and the rest of the world; however, in Japan, it has been provided mostly by the predilution method in order to ameliorate dialysis-related symptoms of dialysis patients by removing larger low molecular weight proteins. This study aimed to elucidate the removal properties of a newly launched asymmetric triacetate (ATA) membrane in OL-HDF both in the postdilution and predilution comparison with other synthetic polymer membranes.

Methods: Six patients treated by OL-HDF at the Kawashima Hospital Group were randomly chosen for each membrane study. The removal properties of low molecular weight proteins were evaluated by β_2-microglobulin (β_2-MG), α_1-microglobulin (α_1-MG), albumin leakage, selective removal index of α_1-MG for albumin, and transmembrane pressure for each treatment group. Two types of ATA membrane were evaluated in the study: FIX-S with mild protein permeability and FIX-U with higher protein permeability in the comparisons with other three types of synthetic polymer membranes.

Results: The removal rate of β_2-MG showed almost no significant differences between the postdilution and predilution methods in most membrane groups at around 75–80% without relations to the membrane material and the substitution volume.
The removal rates of α_1-MG were markedly different depending on the dilution method of HDF, the membranes, and the substitution volume. Generally, the removal rates of α_1-MG were better in the postdilution than the predilution but the selective removals of α_1-MG were better in the predilution. The high volume OL-HDF had the risk of excessive albumin leakage in a certain membrane choice.
In the FIX series, the removal rates of α_1-MG were sufficient both in the postdilution and predilution with the increase of the substitution volume with suppressing the albumin leakage during the dialysis session. Especially, FIX-U showed higher removal of α_1-MG with suppressing the albumin leakage.

Conclusions: The newly launched ATA membrane could remove α_1-MG, selectively suppressing the excessive albumin leakage and increasing the substitution volume safely even in high-volume postdilution.

Trial registration: Trial registration: University hospital Medical Information Network (UMIN), UMIN 000035705. Registered 28 January 2019 - Retrospectively registered, https://www.umin.ac.jp/ctr/index-j.htm.

Keywords: On-line hemodiafiltration, Asymmetric cellulose triacetate, β_2-microglobulin, α_1-microglobulin, Albumin leakage

* Correspondence: yu-tanaka0724@khg.or.jp
[1]Clinical Engineering Department, Social Medicine Corporation Kawashima Association, Kawashima Hospital, 1-1-39, Kitasako, Tokushima City, Tokushima Prefecture 770-0011, Japan
Full list of author information is available at the end of the article

Introduction

On-line hemodiafiltration (OL-HDF) has been generally provided in the postdilution method in Europe and the rest of the world; however, it is quite different in Japan, where most of OL-HDF have been performed in the predilution method. The CONTRAST Study and ESHOL Study reported a better survival of patients in a high-volume substitution group using the postdilution method compared with that in a low-volume substitution group and low-flux HD group [1–3]. However, the membranes used in these reports had smaller pore size and lower permeability than the membranes widely used in Japan. Furthermore, the relationship between substitution volume and solute removal property has not been considered in the studies, which could explain the mechanism of survival advantages of high-volume postdilution OL-HDF.

On the other hand, for OL-HDF in Japan, the predilution method accounted for 95.6% of all OL-HDF therapies at the end of 2016 [4]. In Japan, the average blood flow rate by predilution and postdilution is 228.7 mL/min and 224.9 mL/min, respectively, which was lower than that in Europe and the world [4]. The predilution method can freely increase the substitution volume even with a low blood flow rate and is able to improve the solute removal efficiency of low molecular weight proteins (LMWPs). Furthermore, if we use a large pore size filter in the predilution method, we can remove larger LMWPs without explosive albumin leakage [5]. The Japanese pioneer doctors found that dialysis prescriptions with larger LMWP removal incurring a certain level of albumin loss have improved various uremic symptoms. Based on these experiences, "protein permeable dialysis" has developed in Japan [5, 6].

To increase the removal of LMWPs both in the postdilution and predilution HDF, we have to increase the substitution volume as safely as we can. The newly developed FIX series (NIPRO) is the first membrane for HDF composed of cellulose triacetate (CTA). The current CTA membrane has a symmetric structure, and it has not generally indicated for HDF because of its vulnerability against the high transmembrane pressure (TMP). The new CTA membrane has an asymmetric structure (asymmetric triacetate (ATA)) with similar stiffness to other synthetic polymer membranes such as polysulfone, with a smooth inner surface by nanotechnology. Owing to its ability to suppress excessive albumin leakage by reducing fouling through protein adhesion inhibition and avoiding the rise in the TMP, these membranes are expected to have different removal properties from other synthetic polymer membranes. This study aimed to elucidate the removal properties of the ATA membrane in OL-HDF compared to those of synthetic polymer membranes as well as examine the influence of the dilution method and substitution volume on the solute removal.

Subjects and methods

Six maintenance dialysis patients treated by OL-HDF at Kawashima Hospital Group were randomly selected for each study protocol with each membrane (Table 2). The patient selection criteria required patients to be 20 years or older, but did not concern gender, inpatient/outpatient classification, medical history, or the presence of complications for the patient. We excluded patients with significant inflammatory symptoms and severe impairment of the liver, heart, lungs, etc. This study was reviewed by the Kawashima Hospital Ethics Committee (Approval No.: 0199) and was implemented based on the spirit of the Declaration of Helsinki and in compliance with the ethical guidelines. We obtained written consent from all patients.

We used five types of membranes for OL-HDF, namely TDF20-PV (TDF: Toray Medical Co., Ltd.), GDF-21 (GDF: Nikkiso Co., Ltd.), MFX-25U eco (MFX: NIPRO), FIX-250S eco (FIX-S: NIPRO), and FIX-250U eco (FIX-U: NIPRO). The characteristics of each membrane are shown in Table 1. The treatment conditions were set: 4 h, 3 times a week, blood flow rate (QB) = 280 mL/min, and total dialysis fluid flow rate (QD) = 500 mL/min, with substitution flow rate (QS) kept constant at 250 and 350 mL/min (60 and 84 L/4 h) for predilution and 50

Table 1 Filters' performance

	TDF-20PV	GDF-21	MFX-25 U eco	FIX-250S eco	FIX-250 U eco
Membrane material	PS	PEPA	PES	CTA	CTA
Membrane bore (μm)	210	210	200	200	200
Membrane thickness (μm)	40	30	40	25	25
Effective membrane area (m^2)	2.0	2.1	2.5	2.5	2.5
UFR (mL/mmHg/hr)	72.2	64	91	90	99
SC					
Alb	0.029 ≧	0.03	0.01	0.01	0.02
β_2-MG	0.90	0.87	0.91	0.93	1.05

PS Polysulfone, *PES* Polyethersulfone, *UFR* Ultrafiltration coefficient, *Alb* Albumin, *PEPA* Polyester polymer alloy, *CTA* Cellulose triacetate, *SC* Sieving coefficient, *β_2-MG* β_2-microglobulin and 66 mL/min (12 and 16 L/4 h) for postdilution. However, in each dialysis session with GDF, QS was decreased at 250 and 300 mL/min (60 and 72 L/4 h) for predilution and 42 and 50 mL/min (10 and 12 L/4 h) for postdilution for avoiding the excessive albumin leakage during the session with GDF. The contents of the dialysis fluid were Na, 140 mEq/L; K, 2.0 mEq/L; Ca, 2.75–3.0 mEq/L; Mg, 1.0 mEq/L; Cl, 112–113 mEq/L; acetate, 8.0 and 10.2 mEq/L; bicarbonate, 25–27.5 mEq/L; and glucose, 100 and 125 mg/dL.

The evaluation items were the removal rate (RR) of β_2-microglobulin (β_2-MG) and the RR of α_1-microglobulin (α_1-MG), the removed β_2-MG quantity and α_1-MG, the albumin leakage quantity, the selective removal index of α_1-MG (SRIA), and TMP for each treatment group. The SRIA was calculated as the removed α_1-MG quantity divided by the albumin leakage quantity in a single session shown in the formula below (Formula 1).

$$\text{Selective removal index of } \alpha_1 - \text{MG (SRIA)} = \alpha_1 - \text{MG removal quantity} \tag{1}$$

We also evaluated the relationship between the removed α_1-MG quantity and the albumin leakage quantity. The RR was measured by taking blood samples at the start of dialysis and 4 h after, and then corrected by the hematocrit value as shown in the formula below (Formula 2).

$$\text{Removal Rate (RR)} = [1-\{\text{Ht}_{\text{Pre}}/\text{Ht}_{\text{Post}}\} \times \{(1-\text{Ht}_{\text{Post}}/100)/(1-\text{Ht}_{\text{Pre}}/100)\} \times \{\text{CBI}_{\text{Post}}/\text{CBI}_{\text{Pre}}\}] \times 100 \tag{2}$$

CBI $_{\text{pre}}$, CBI $_{\text{post}}$ Solute concentration before and after dialysis

Ht $_{\text{pre}}$, Ht $_{\text{post}}$ Hematocrit before and after dialysis (%)

The removed quantity of each solute and albumin leakage was evaluated using the partial storage method of the spent dialysate. In the partial storage method, the drained dialysate was extracted at a rate of 0.9 L/h using a multi-roller pump (MF-01: manufactured by JMS) and was then stored for 4 h. At our hospital, we recognize that there is no significant difference between the measurement errors of total storage method and partial storage method.

We calculated the mean and standard deviation of the RR of β_2-MG, β_2-MG removal quantity, the RR of α_1-MG, the α_1-MG removal quantity, the albumin leakage quantity, the SRIA, and the TMP for each treatment group. Comparisons of the substitution volume for each dilution method were made with the corresponding *t* test and the Wilcoxon signed rank sum test. Spearman's rank correlation coefficient was used to examine the correlation. All statistical analyses were performed using SPSS statistics ver.23 (IBM), with a significance level of 5%.

Results

Patients' demographics

There were no differences among the patients' background characteristics (Table 2).

β_2-MG removal

The RR of β_2-MG showed almost no significant differences between the postdilution and predilution methods at around 75–80% without relations to the membrane material and the substitution volume. However, the TDF group showed a slight increase in postdilution by the increase of substitution volume as 78.8 ± 5.1% for 12 L and 79.8 ± 5.1% for 16 L ($p = 0.028$). There were no significant differences in the removed β_2-MG quantity per session between the postdilution and predilution methods, while

Table 2 Demographic characters of subjects

	TDF-20PV	GDF-21	MFX-25 U eco	FIX-250S eco	FIX-250 U eco	*P*
Patients, N	6	6	6	6	6	
Age (−years-old)	69.2 ± 5.4	64.3 ± 5.5	59.4 ± 8.6	67.3 ± 9.3	67 ± 11.8	0.331
HD dur (years)	7.9 ± 6.3	13.3 ± 9.2	9.5. ± 9.4	9 ± 11.1	12.5 ± 6.5	0.693
DW (Kg)	58 ± 11.2	65.3 ± 12	61.1 ± 5.3	59.2 ± 6	63.7 ± 5.1	0.500
WBC (10^3/μL)	5.6 ± 1.1	5.5 ± 1.4	5.9 ± 1.8	5.9 ± 1.7	6.8 ± 2.5	0.758
RBC (10^6 μL)	3.5 ± 0.4	3.5 ± 0.5	3.3 ± 0.2	3.6 ± 0.2	3.6 ± 0.4	0.666
Hct (%)	34 ± 4	32 ± 3	32 ± 2	35 ± 1	33 ± 4	0.315
HGB (g/dL)	11.2 ± 0.9	11 ± 1.2	10.4 ± 0.8	11.6 ± 0.2	10.5 ± 1.8	0.392
PLT (10^3/μL)	179 ± 59	197 ± 14	171 ± 42	185 ± 63	218 ± 59	0.597
TP (g/dL)	6.1 ± 0.4	6.1 ± 0.3	6.2 ± 0.2	6.6 ± 0.3	6.2 ± 0.4	0.165
Alb (g/dL)	3.4 ± 0.3	3.3 ± 0.2	3.2 ± 0.3	3.6 ± 0.2	3.3 ± 0.4	0.278

HD dur Hemodialysis duration, *WBC* White blood cell count, *HGB* Hemoglobin, *TP* Total protein, *DW* Dry weight, *RBC* Red blood cell count, *PLT* Platelet, *Alb* Albumin the GDF group showed a significant decrease in the predilution method, with 181.3 ± 17.2 mg for 60 L and 137.3 ± 40.8 mg for 72 L (p = 0.035) (Table 3).

α_1-MG removal and albumin leakage

TDF group

In the postdilution method, the RR of α_1-MG was 39.9 ± 9.1% and 43.8 ± 7.1% for 12 L and 16 L, which indicated a significant increase (p = 0.027). The removed α_1-MG quantity was 145.5 ± 34.4 mg and 154.8 ± 24.8 mg for 12 L and 16 L. The albumin leakage was 3.5 ± 0.3 g and 4.7 ± 0.7 g for 12 L and 16 L, which indicated a significant increase (p = 0.007). The SRIA was 41.1 ± 7.6 and 34.1 ± 7.9 for 12 L and 16 L, which indicated a significant decrease (p = 0.01).

In the predilution method, the RR of α_1-MG was 38.6 ± 8.9% and 43.4 ± 11% for 60 L and 84 L. The removed α_1-MG quantity was 132.4 ± 22 mg and 165 ± 50.3 mg for 60 L and 84 L. The albumin leakage was 3.2 ± 0.4 g and 5.3 ± 0.8 g for 60 L and 84 L, which indicated a significant increase (p = 0.002). The SRIA was 42.7 ± 10.9 and 31.1 ± 7.4 for 60 L and 84 L, which indicated a significant decrease (p = 0.005) (Tables 4 and 5).

GDF group

In the postdilution method, the RR of α_1-MG was 44.9 ± 6.5% and 50.6 ± 5.4% for 10 L and 12 L, which indicated a significant increase (p = 0.001). The removed α_1-MG quantity was 213.1 ± 62.6 mg and 255.9 ± 58.2 mg for 10 L and 12 L. The albumin leakage was 7.9 ± 4.5 g and 16.5 ± 8.8 g for 10 L and 12 L, which indicated a significant increase (p = 0.028). The SRIA was 33.7 ± 16.3 and 18.2 ± 6.9 for 10 L and 12 L, which tended to decrease.

In the predilution method, the RR of α_1-MG was 46.1 ± 8.9% and 44.7 ± 9% for 60 L and 72 L. The removed α_1-MG quantity was 226.1 ± 49.4 mg and 201.2 ± 40.1 mg for 60 L and 72 L, which indicated a significant decrease (p = 0.022). The albumin leakage was 11.5 ± 4.3 g and 11.5 ± 5.9 g for 60 L and 72 L. The SRIA was 22 ± 8.2 and 21.7 ± 10.7 for 60 L and 72 L (Tables 4 and 5).

MFX group

In the postdilution method, the RR of α_1-MG was 46.1 ± 10% and 54 ± 9.8% for 12 L and 16 L, which indicated a significant increase (p = 0.001). The removed α_1-MG quantity was 215.4 ± 40.7 mg and 244 ± 40.1 mg for 12 L and 16 L, which indicated a significant increase (p = 0.02). The albumin leakage was 8.1 ± 1.9 g and 13.2 ± 3.9 g for 12 L and 16 L, which indicated a significant increase (p = 0.008). The SRIA was 28.3 ± 10.7 and 20.1 ± 8 for 12 L and 16 L, which indicated a significant decrease (p = 0.005).

In the predilution method, the RR of α_1-MG was 37.2 ± 11% and 40.7 ± 11.9% for 60 L and 84 L. The removed α_1-MG quantity was 164.6 ± 37.2 mg and 185 ± 34.7 mg for 60 L and 84 L. The albumin leakage was 4.3 ± 0.6 g and 5.6 ± 1.3 g for 60 L and 84 L. The SRIA was 38 ± 7.3 and 34.3 ± 9.3 for 60 L and 84 L (Tables 4 and 5).

FIX-S group

In the postdilution method, the RR of α_1-MG was 33.6 ± 9.3% and 34.6 ± 6.5% for 12 L and 16 L. The removed α_1-MG quantity was 155.3 ± 30 mg and 153.6 ± 30.6 mg for 12 L and 16 L. The albumin leakage was 6.4 ± 1.5 g and 6.6 ± 1.8 g for 12 L and 16 L. The SRIA was 25.3 ± 6.6 and 24 ± 5.7 for 12 L and 16 L.

Table 3 Removal rate and removed β_2-MG quantity

Substitution volume (L/session)	Predilution			Postdilution			p (4 groups)
	60	84 (72)	p	12 (10)	16 (12)	p	
RR (%)							
TDF-20PV	78.5 ± 5.4	78.5 ± 6.8	0.937	78.8 ± 5.1	79.8 ± 5.1*	0.028	0.974
GDF-21	77 ± 9.9	74.3 ± 11.6	0.117	78.3 ± 2.9	78.4 ± 5.4	0.897	0.886
MFX-25U eco	81.7 ± 2.4	82.8 ± 2	0.219	81.5 ± 2.7	83 ± 2.4	0.145	0.625
FIX-250S eco	80.5 ± 2.2	80.9 ± 3.3	0.587	81 ± 2.4	81.6 ± 3.5	0.538	0.927
FIX-250U eco	80.2 ± 3.7	80.5 ± 3.9	0.672	80.8 ± 4.1	81.7 ± 3.6	0.233	0.902
RA (mg)							
TDF-20PV	156.6 ± 29.8	168.1 ± 46.5	0.206	165.8 ± 37.7	161.6 ± 33.8	0.661	0.954
GDF-21	181.3 ± 17.2	137.3 ± 40.8*	0.035	154.8 ± 53.4	178.2 ± 25.7	0.236	0.163
MFX-25U eco	212.3 ± 29	251.2 ± 99.1	0.321	220.4 ± 42.6	± 36.4	0.081	0.564
FIX-250S eco	167.2 ± 18.7	168.8 ± 26.3	0.731	169 ± 24.2	180.6 ± 28.7	0.303	0.772
FIX-250U eco	226.2 ± 53.1	274.1 ± 89.4	0.053	219.1 ± 21.9	226.5 ± 24.2	0.319	0.304

Comparisons between 60 L and 84 L (72 L) in the predilution and between 12 L (10 L) and 16 L (12 L) in the postdilution were analyzed by the corresponding t test. *P<0.05. And comparison among four treatment conditions for each membrane was analyzed by one-way ANOVA

RR removal rate, *RA* removal amount

Table 4 Removal rate and removed α_1-MG quantity

Substitution volume (L/session)	Predilution			Postdilution			p (4 groups)
	60	84(72)	p	12(10)	16(12)	p	
RR (%)							
TDF-20PV	38.6 ± 8.9	43.4 ± 11	0.083	39.9 ± 9.1	43.8 ± 7.1*	0.027	0.703
GDF-21	46.1 ± 8.9	44.7 ± 9	0.226	44.9 ± 6.5	50.6 ± 5.4*	0.001	0.518
MFX-25U eco	37.2 ± 11	40.7 ± 11.9	0.155	46.1 ± 10	54 ± 9.8*	0.001	0.065
FIX-250S eco	29.2 ± 6.9	27.1 ± 7.4	0.111	33.6 ± 9.3	34.6 ± 6.5	0.673	0.299
FIX-250U eco	45.3 ± 6.1	46.7 ± 5.2	0.303	52.4 ± 4.4	54.5 ± 4.9*	0.012	60–16 L
RA (mg)							
TDF-20PV	132.4 ± 22	165 ± 50.3	0.061	145.5 ± 34.4	154.8 ± 24.8	0.184	0.432
GDF-21	226.1 ± 49.4	201.2 ± 40.1*	0.022	213.1 ± 62.6	255.9 ± 58.2	0.095	0.347
MFX-25U eco	164.6 ± 37.2	185 ± 34.7	0.056	215.4 ± 40.7	244 ± 40.1*	0.02	60–16 L
FIX-250S eco	131.1 ± 31.8	126.3 ± 37	0.415	155.3 ± 30	153.6 ± 30.6	0.805	0.309
FIX-250U eco	224 ± 77.1	231.5 ± 62.4	0.415	238.1 ± 43.8	254.9 ± 52.6*	0.036	0.835

Comparisons between 60 L and 84 L (72 L) in the predilution and between 12 L (10 L) and 16 L (12 L) in the postdilution were analyzed by the corresponding *t* test. *P<0.05. And comparison among four treatment conditions for each membrane was analyzed by one-way ANOVA and Tukey-Kramer test
RR Removal rate, *RA* Removal amount

In the predilution method, the RR of α_1-MG was 29.2 ± 6.9% and 27.1 ± 7.4% for 60 L and 84 L. The removed α_1-MG quantity was 131.1 ± 31.8 mg and 126.3 ± 37 mg for 60 L and 84 L. The albumin leakage was 4.1 ± 0.4 g and 3.7 ± 0.5 g for 60 L and 84 L. The SRIA was 31.8 ± 7.1 and 34 ± 9.1 for 60 L and 84 L (Tables 4 and 5).

FIX-U group

In the postdilution method, the RR of α_1-MG was 52.4 ± 4.4% and 54.5 ± 4.9% for 12 L and 16 L, which indicated a significant increase (p = 0.012). The removed α_1-MG quantity was 238.1 ± 43.8 mg and 254.9 ± 52.6 mg for 12 L and 16 L, which indicated a significant increase (p = 0.036). The albumin leakage was 8.2 ± 1.4 g and 9.7 ± 2.2 g for 12 L and 16 L, which indicated a significant increase (p = 0.048). The SRIA was 29.1 ± 3.1 and 26.5 ± 2.6 for 12 L and 16 L.

In the predilution method, the RR of α_1-MG was 45.3 ± 6.1% and 46.7 ± 5.2% for 60 L and 84 L. The removed α_1-MG quantity was 224 ± 77.1 mg and 231.5 ± 62.4 mg

Table 5 Albumin leakage and filtration capacity

Substitution volume (L/session)	Predilution			Postdilution			p (4 groups)
	60	84(72)	p	12(10)	16(12)	p	
Albumin leakage(g/ session)							
TDF-20PV	3.2 ± 0.4	5.3 ± 0.8*	0.002	3.5 ± 0.3	4.7 ± 0.7*	0.007	60–84 L, 60–16 L, 84–12 L, 12–16 L
GDF-21	11.5 ± 4.3	11.5 ± 5.9	0.996	7.9 ± 4.5	16.5 ± 8.8*	0.028	0.149
MFX-25U eco	4.3 ± 0.6	5.6 ± 1.3	0.074	8.1 ± 1.9	13.2 ± 3.9*	0.008	60–12 L, 60–16 L, 84–16 L, 12–16 L
FIX-250S eco	4.1 ± 0.4	3.7 ± 0.5	0.163	6.4 ± 1.5	6.6 ± 1.8	0.736	60–12 L, 60–16 L, 84–12 L, 84–16 L
FIX-250U eco	6.2 ± 2.1	6.7 ± 1.7	0.129	8.2 ± 1.4	9.7 ± 2.2*	0.048	60–16 L
SRIA							
TDF-20PV	42.7 ± 10.9	31.1 ± 7.4*	0.005	41.1 ± 7.6	34.1 ± 7.9*	0.01	0.089
GDF-21	22 ± 8.2	21.7 ± 10.7	0.936	33.7 ± 16.3	18.2 ± 6.9	0.072	0.118
MFX-25U eco	38 ± 7.3	34.3 ± 9.3	0.286	28.3 ± 10.7	20.1 ± 8*	0.005	60–16 L
FIX-250S eco	31.8 ± 7.1	34 ± 9.1	0.087	25.3 ± 6.6	24 ± 5.7	0.557	0.069
FIX-250U eco	36.4 ± 3.9	34.4 ± 3	0.053	29.1 ± 3.1	26.5 ± 2.6	0.051	60–12 L, 60–16 L, 84–12 L, 84–16 L

Comparisons between 60 L and 84 L (72 L) in the predilution and between 12 L (10 L) and 16 L (12 L) in the postdilution were analyzed by the corresponding *t* test. *P<0.05. And comparison among four treatment conditions for each membrane was analyzed by one-way ANOVA and Tukey-Kramer test
SRIA selective removal index of α_1-MG

for 60 L and 84 L. The albumin leakage was 6.2 ± 2.1 g and 6.7 ± 1.7 g for 60 L and 84 L. The SRIA was 36.4 ± 3.9 and 34.4 ± 3 for 60 L and 84 L (Tables 4 and 5).

Relationship between the removed α_1-MG quantity and the albumin leakage quantity

In the TDF group and GDF group, we saw no correlation between the removed α_1-MG quantity and albumin leakage quantity (Fig. 1a, b).

We observed a positive correlation of the removed α_1-MG quantity to the albumin leakage quantity in the MFX group (Spearman's $r = 0.576$, $p = 0.006$), FIX-S group (Spearman's $r = 0.552$, $p = 0.008$), and FIX-U group (Spearman's $r = 0.829$, $p = 0.0001$) (Fig. 1c–e).

The correlation coefficient tended to differ according to the membrane, and in particular, the FIX-U group showed a strongly positive correlation between the removed α_1-MG quantity and the albumin leakage quantity (Fig. 1e).

Change over time in TMP

In the TDF group, the TMP lowered the postdilution method and predilution method for 60 L. Although the TMP showed a high value of 268 ± 72 mmHg in the predilution method for 84 L at 240 min, the albumin leakage quantity was 5.3 ± 0.8 g, so we observed no excessive albumin leakage quantity (Fig. 2a).

In the GDF group, the TMP was high in both the postdilution and predilution HDF. In the postdilution method, the TMP was showed 122 ± 140 mmHg for 12 L at 240 min, but the albumin leakage quantity increased excessively to 16.5 ± 8.8 g. On the other hand predilution method, the TMP was showed 166 ± 148 mmHg and 237 ± 181 mmHg for 60 L and 72 L at 240 min, and the albumin leakage quantity was approximately 11.5 g, which was nearly the same between them (Fig. 2b).

The TMP in the MFX group, FIX-S group, and FIX-U group was lowered for both postdilution and predilution approaches. However, the albumin leakage quantity varied depending on the membrane, and postdilution by 12 L showed 13.2 ± 3.9 g in the MFX group, 6.6 ± 1.8 g in

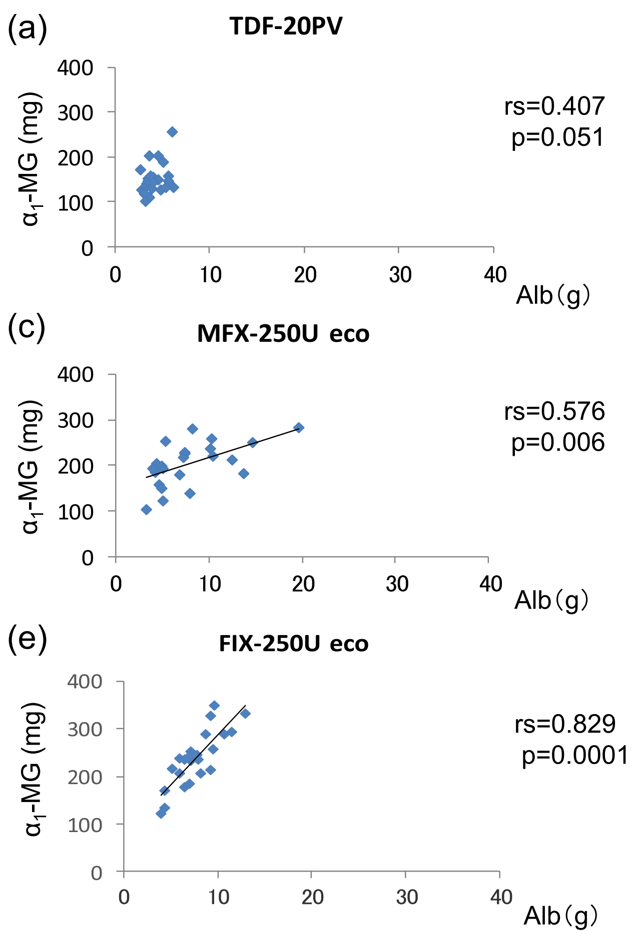

Fig. 1 Correlation between the removal amount of α_1-MG and albumin leakage by filter. The correlation was analyzed by Spearman's rank correlation coefficient in the treatment group. **a** TDF. **b** GDF. **c** MFX-250U. **d** FIX-250S. **e** FIX-250U

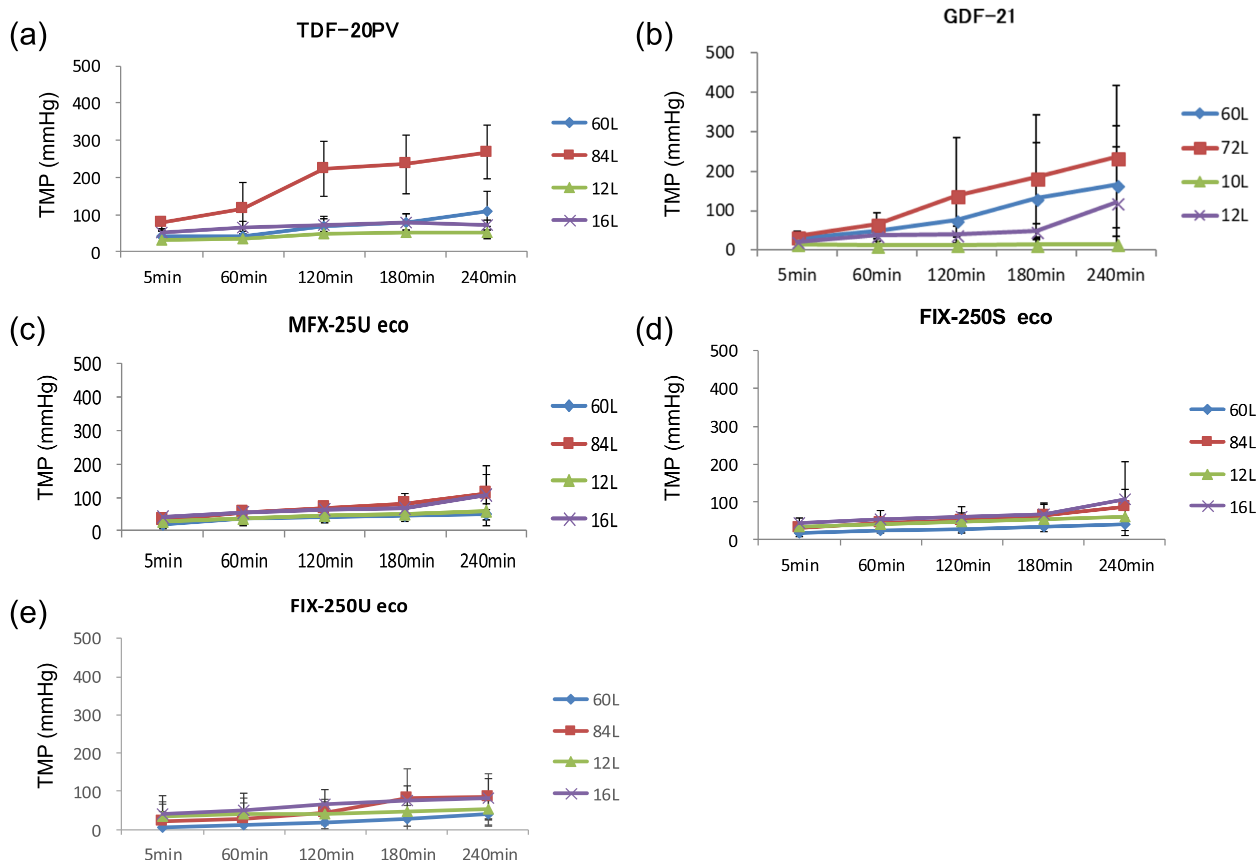

Fig. 2 Transmembrane pressure (TMP) by filter. TMP was measured at 5 min, 60 min, 120 min, 180 min, and 240 min after the treatment. In each treatment group, all values are expressed as mean ± SD. **a** TDF. **b** GDF. **c** MFX-250U. **d** FIX-250S. **e** FIX-250U

the FIX-S group, and 9.7 ± 2.2 g in the FIX-U group (Fig. 2c–e).

Discussion

High-volume postdilution OL-HDF has become one of the mainstreams in chronic dialysis based on the evidence of randomized control trials conducted mainly in Europe [1–3]; however, the membrane performances or solute removal properties have never discussed in these trials. In other words, it has not been clear on how they should increase the substitution volume or how they modified the dialysis prescriptions. The mechanism of the better survival in the high-volume HDF group has also still been unclear. On the other hand, in Japan, the dialysis prescriptions are determined according to solute removal, which includes albumin leakage quantity and the RRs and removed amounts of α_1-MG and β_2-MG. To achieve the target of the removal of them, we increase the substitution volume. OL-HDF was originally developed to effectively remove the middle molecules, and so we need the removal targets for them. The molecular weights of the middle molecules range from 1000 to 50,000 Da, and there are also many other functional proteins like inflammatory cytokines [7, 8]. Although it has been reported that low serum β_2-MG concentration decreased the risk of dialysis-related amyloidosis and mortality risk [9–11], in Japan, there is also a focus on the removal of larger LMWPs as α_1-MG and albumin, in addition to β_2-MG [12, 13]. The molecular weight of α_1-MG is 33,000 Da, and while this compound has not been recognized as a uremic toxin but a uremic retention solute. However, there have been reports on the link between α_1-MG removal and improvement of clinical symptoms like joint pain, pruritus, and restless leg syndrome (RLS), with an α_1-MG removal rate of at least 38% required to improve the symptoms of intractable RLS, which is a problem observed in long-term dialysis patients [14, 15]. Interleukin-6 (IL-6) and prolactin are uremic toxins with a similar molecular weight of α_1-MG. IL-6 is one of the inflammatory cytokines that regulate humoral immunity, with a molecular weight of 21,000 to 28,000 Da. For this reason, the removal rate of α_1-MG has been usually used for evaluating the removal of LMWPs and it indicates the recent trend of OL-HDF in Japan for the proactive removal of LMWPs larger than β_2-MG.

However, if we try to increase the removal of α_1-MG, some albumin leakage during a dialysis session is unpreventable because the Stokes radius of α_1-MG is similar to that of albumin at 28.4 Å and 35.5 Å, respectively, regardless of the difference of the molecular weight as 33,000 Da and 66,000 Da [16, 17]. Thus, SRIA was established for assessing the selectivity of the α_1-MG removal to avoid excessive albumin leakage. However, if the amount of albumin leakage is small, even with a lower amount of α_1-MG removed, it would provide a high calculated SRIA; while on the other hand, excessive albumin leakage would decrease SRIA. For this reason, it is important to evaluate the correlation between the removed amount of α_1-MG and the albumin leakage quantity, as well as the α_1-MG removal rate altogether.

The results in the current study also suggest that it is better to choose postdilution for the proactive removal of LMWPs that excels in solute removal and also to increase the substitution volume. The removal properties of β_2-MG were not different depending on the membrane used, the dilution method, or the substitution volume, so we could consider that β_2-MG was removed not only by the diffusion, but also by the convection. However, the RR of α_1-MG in the MFX and FIX-U groups was better in high-volume postdilution methods than predilution methods. On the other hand, like GDF, we also identified a membrane where the albumin leaks excessively when following a postdilution approach and increasing the substitution volume. The high-volume postdilution could have a risk of excessive albumin leakage depending on the membrane, so we should consider the safety of the treatment. With synthetic polymer membranes except ATA showing the albumin leakage quantity increased and the SRIA decreased particularly in postdilution, the correlation coefficient between the α_1-MG removal quantity and the albumin leakage was between 0.3 and around 0.6. It suggests that the removal of α_1-MG would become a plateau as the albumin leakage increases in the current synthetic polymer membranes. From this viewpoint, the high-volume postdilution HDF is not a good modality to selectively and safely remove α_1-MG and the similar LMWPs because it particularly increases the albumin leakage.

The driving force of solute removal in convection therapies is TMP, and the influence of TMP on albumin leakage differed depending on the membrane being used. When we increase the substitution volume, we should evaluate the TMP, the removal property of LMWPs, and the albumin leakage for the safety of the therapy. Increase of TMP during a dialysis session means the formation of protein fouling on the membrane surface, and it is different depending on the membrane being used. The protein fouling is one of the important triggers of explosive albumin leakage and may deteriorate the solute removal itself. However, there was an explosive albumin leakage of 16.5 ± 8.8 g in the postdilution HDF with the substitution volume of 12 L in the GDF group even without an increase in TMP. It suggests that a wrong dialysis choice in the high-volume postdilution HDF occasionally might not be safe for the patients. We would like to propose measuring the removed amount of LMWPs and the albumin leakage in the spent dialysate for the evaluation of the efficacies and safety of the therapy.

ATA is a newly developed membrane to provide high convective therapy, and it has a smooth inner surface to avoid the formation of protein fouling and the increase of TMP during a dialysis session. In the current study, ATA membrane (FIX series) can be used safely for both the postdilution OL-HDF as well as the predilution OL-HDF. The albumin leakage remains unchanged in both postdilution and predilution methods when the substitution volume was increased. In the predilution HDF with the FIX series, we can increase the substitution volume while keeping the albumin leakage at around 4 g/session. It might maintain the oncotic and plasma osmotic pressures, so we believe this method can be beneficial for patients with intradialytic hypotension [18]. In the postdilution HDF with FIX-S, the albumin leakage stayed constant at 6.6 ± 1.8 g/session, even when the substitution volume was raised up to 16 L. However, the removal rate of α_1-MG was not enough even when increasing the substitution volume while suppressing excessive albumin leakage. The RR of α_1-MG by FIX-S is 27.1 ± 7.4% for 84 L by predilution and 34.6 ± 6.5% for 16 L by postdilution. There were no significant differences in the α_1-MG removal for both predilution and postdilution, so the superiority of high-volume postdilution is not recognized. The FIX-U series has a larger pore size of the membrane than the FIX-S series. The removal rate of α_1-MG by FIX-U was 46.7 ± 5.2% for 84 L by predilution and 54.5 ± 4.9% for 16 L by postdilution. Furthermore, the correlation coefficient between α_1-MG removal quantity and albumin leakage quantity shows a strong positive correlation of 0.829, which allowed us to confirm that α_1-MG removal is increasing relative to albumin leakage. Therefore, FIX-U can safely increase the substitution volume while suppressing the excessive albumin leakage, which would therefore be an excellent choice for the selective removal of α_1-MG even with the high-volume postdilution. As previously addressed, the high-volume postdilution OL-HDF with the current synthetic polymer membranes could have a risk of excessive albumin leakage. The FIX series should be a good choice to avoid this phenomenon. In Japan, the average blood flow rate has been lower than that in Europe, so we could not increase the substitution volume in postdilution HDF for the fear of the excessive albumin leakage. However, FIX-U can be considered a great option for selective and sufficient removal of α_1-MG in the postdilution HDF as well as the predilution HDF.

In the current study, we did not evaluate the relationship between the removal of LMWPs or SRIA and the patient survival. Recently, the survival advantages of Japanese-style predilution OL-HDF with the substitution volume greater than 40 L predilution were reported but the removal of LMWPs was not determined in the study [19]. In the future, there is an urgent need to elucidate the relationship between the LMWPs' removal and the patient's survival.

Conclusions

The removal of LMWPs varies dramatically depending on the dialysis prescription, such as the choice of the membrane, the dilution method, and the substitution volume as presented in the current study. Although high-volume postdilution OL-HDF has been widely provided in the world, it has a risk of excessive albumin leakage during dialysis session in certain prescriptions. To improve the safety and dialysis-related symptoms, it is necessary to choose a proper dialysis prescription for each patient by evaluating the removal properties of larger LMWPs such as α_1-MG and albumin leakage quantity. The newly launched ATA membrane could remove α1-MG, selectively suppressing the excessive albumin leakage and increasing the substitution volume safely both in the high-volume postdilution and the predilution OL-HDF.

Abbreviations

Alb: Albumin; ATA: Asymmetric triacetate; CTA: Cellulose triacetate; DW: Dry weight; HD dur: Hemodialysis duration; HD: Hemodialysis; HDF: Hemodiafiltration; HGB: Hemoglobin; Ht: Hematocrit; IL: Interleukin; LMWPs: Low molecular weight proteins; MW: Molecular weight; PEPA: Polyester polymer alloy; PES: Polyethersulfone; PLT: Platelet; PS: Polysulfone; QB: Quantity of blood flow; QD: Quantity of dialysate flow; QS: Quantity replacement fluid; RA: Removal amount; RBC: Red blood cell count; RLS: Restless leg syndrome; RR: Removal rate; SC: Sieving coefficient; SRIA: Selective removal index of α_1-microglobulin; TMP: Transmembrane pressure; TP: Total protein; UFR: Ultrafiltration coefficient; WBC: White blood cell count; α_1-MG: α_1-microglobulin

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Availability of data and materials

1. When anyone wants to use the data and materials from the current manuscript without modifications, all data and materials are freely available.
2. All data generated or analyzed during this study are included in this published article.

Authors' contributions

YT designed the study, performed the data analysis, and wrote the manuscript. YT, HA, DH, and HM collected the clinical data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

1. This research was approved by the ethical committee of Kawashima Hospital. The approval no. is 0199.
2. The original data had been totally anonymized, so there are no risks for deteriorating the privacy of patients.
3. The data presented in the current manuscript does not contain any images, videos, and voice recording which might have a risk for identifying an individual.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Clinical Engineering Department, Social Medicine Corporation Kawashima Association, Kawashima Hospital, 1-1-39, Kitasako, Tokushima City, Tokushima Prefecture 770-0011, Japan. [2]Kidney Internal Medicine (Dialysis, Renal Transplantation), Tokushima, Japan.

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