Renal Replacement Therapy

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New polymethylmethacrylate membrane, NF-U, improves nutritional status and reduces patient-reported symptoms in older dialysis patients

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Abstract

Introduction: We previously reported the nutritional advantage of polymethylmethacrylate (PMMA) membranes to prevent the progression of malnutrition in dialysis patients. In this study, we examined whether a new PMMA dialyzer, NF-U, has advantages to improve the nutritional condition, patient-reported symptoms, and other clinical parameters in older dialysis patients.

Methods: We selected ten older chronic dialysis patients who were treated with NF-U for improving their worsening nutritional parameters and retrospectively evaluated nutrition and patient-reported symptoms. Patient-reported symptoms were surveyed by our original questionnaire including 20 items of symptom.

Results: Serum albumin concentration, geriatric nutritional risk index, and percent creatinine generation rate increased from 3.01 ± 0.16 to 3.25 ± 0.17 g/dL, 87.7 ± 5.8 to 91.4 ± 6.2, 100.2 ± 21.6 to 111.9 ± 20.9% at 1 and 4 months after switching to NF-U, respectively. For patient-reported outcomes, fatigue and the total score of patient-reported outcomes were improved after switching to NF-U.

Conclusion: Our results suggest that NF-U is a good choice for older dialysis patients to ameliorate their nutritional status and patient-reported outcomes.

Keywords: Polymethylmethacrylate, Malnutrition, Patient-reported outcomes, Dialysis-related fatigue, Older dialysis patient

Introduction

Malnutrition frequently develops in hemodialysis patients and is considered to be the most important risk factor for mortality [1]. Older hemodialysis patients can easily develop malnutrition due to a decrease in food intake, nutrient loss by dialysis, and physical and social factors [2]. Malnutrition in older patients is thought to induce sarcopenia, reduce physical activity, and worsen their survival [3].

Currently, there has been a paradigm shift from important outcomes in evidence-based medicine (EBM) such as mortality, hospitalization, and complications, to beneficial outcomes for patients (patient-reported outcomes; PROs) in chronic kidney disease (CKD) treatment and in all medical fields [4]. Standardized Outcomes in Nephrology-hemodialysis (SONG-HD) was formed to improve health and quality of life outcomes for people on hemodialysis. Outcomes are classified into three, core outcomes, middle tire and outer tire based on importance on all

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Table 1 List of patients

Sex	Age (years)	Dialysis vintage (years)	Dialysis time (h)	Blood flow rate (mL/min)	DM (Y or N)	BMI	Before			After		
							Dialyzer	Membrane material	Modality	Dialyzer	Membrane material	Modality
F	79	7	4.5	250	N	22.7	FDW-18	PEPA	HD	NF-1.6U	PMMA	HD
F	88	9	4	300	Y	30.6	FDW-18	PEPA	HD	NF-2.1U	PMMA	HD
M	76	5	4	300	N	21.3	VPS-21VA	PS	HD	NF-2.1U	PMMA	HD
F	75	12	4	300	N	20.1	MFX-21Seco	PES	Pre-HDF	NF-2.1U	PMMA	HD
F	79	8	4	300	N	26.8	MFX-21Seco	PES	Pre-HDF	NF-2.1U	PMMA	HD
M	85	7	4	250	Y	22.7	FDW-21	PEPA	HD	NF-1.6U	PMMA	HD
M	78	14	4	250	Y	24.2	TDF-20MV	PS	Pre-HDF	NF-2.1U	PMMA	HD
M	91	11	4	250	N	18.2	FDW-15	PEPA	HD	NF-1.6U	PMMA	HD
M	91	26	4	300	N	18.7	FDW-15	PEPA	HD	NF-1.6U	PMMA	HD
F	86	13	4	250	N	19.4	FDW-18	PEPA	HD	NF-1.6U	PMMA	HD

M, male; F, female; DM, diabetes mellitus; BMI, body mass index; PS, polysulfone; PES, polyethersulfone; PEPA, polyester polymer alloy; PMMA, polymethylmethacrylate; HD, hemodialysis; pre-HDF, pre-dilution online hemodiafiltration stakeholder [5]. Fatigue is one of outcomes included in core outcomes [5].

Polymethylmethacrylate (PMMA) membrane is a dialysis membrane that has an adsorption property for protein, and PMMA can remove large molecular weight proteins (LMWPs) that are not effectively removed by hemodialysis and hemofiltration [6, 7]. There are several clinical reports on hemodialysis using PMMA, and these include improvement of symptoms such as dialysis itchiness and immune function [8–12]. There are other reports that showed a better prognosis in patients who were dialyzed with PMMA [13, 14]. We previously reported that patients' body weight tended to increase when the dialysis membrane was changed to PMMA from polysulfone (PS), but body weight tended to decrease when changing to PS from PMMA [11]. NF-U was developed as a hemodialyzer that has superior biocompatibility compared with the previous PMMA membrane [15], and that has low albumin leakage.

In this study, we examined the influence of NF-U on the nutritional status and PROs in older hemodialysis patients.

Materials and methods

Patients and study design

In this retrospective study, we collected data on the evaluated items from the patients' medical records. We selected ten older maintenance hemodialysis patients (five men, five women) who were over 75 years of age and who were started on dialysis using NF-U (Toray Industries, Inc., Tokyo, Japan) in August 2018 owing to decrease of serum albumin concentration compared with that of last month. Their average age was 82.8 ± 5.8 years, and the average dialysis duration was 11.2 ± 5.7 years. The patients' underlying diseases were as follows: nephrosclerosis (four patients), diabetic nephropathy (three patients), chronic glomerulonephritis (two patients), and unknown (one patient). The patients' average blood flow rate was 275 ± 25 mL/min, dialysate flow rate was 500 mL/min, and average dialysis time was 4.1 ± 0.2 h. Dialyzers that were used in hemodialysis therapy before changing to NF-U were as follows: six patients were dialyzed with a polyester polymer alloy dialyzer (PEPA, Nikkiso Co., Tokyo, Japan), and one patient was dialyzed with a vitamin E-coated polysulfone dialyzer (VPS-VA, Asahi Kasei Medical Co., Ltd., Tokyo, Japan). For pre-dilution online hemofiltration (HDF) therapy, two patients were dialyzed using polyethersulfone (MFX-S, Nipro Corp., Osaka, Japan), and one patient was dialyzed using polysulfone (TDF-M, Toray Industries Inc., Tokyo, Japan). The flow rate for the substitution fluid in HDF therapy was 12 L/h in patients (Table 1). There was no change in the other dialysis conditions except for the dialyzers.

Evaluation of nutrition status

For blood biochemistry tests for nutrition, we measured the serum albumin, serum β_2 microglobulin (β_2MG), and serum C-reactive protein (CRP) concentrations, and we calculated normalized protein catabolic rate (nPCR) [16], geriatric nutritional risk index (GNRI) [17], and creatinine generation rate (%CGR) [18].

The patients' physical condition was evaluated using dry weight (DW), which is the patients' body weight after dialysis, body mass index (BMI), and cardiothoracic ratio (CTR). Appropriate DW for each patient was determined every 2 months by using CTR. Seasonal variations were taken into account by examining the change in DW and CTR for 1 year before switching to NF. As body composition, muscle mass and fat amount were measured using an Inbody770® (Inbody Japan, Tokyo, Japan).

Regarding evaluation items that were measured within 1 month after switching to NF-U, the data just after switching to NF-U were defined as "Control Data". Regarding evaluation items that were measured after 1 month or more switching of dialyzer, we defined the data just before switching to NF-U as "Control Data". "Control Data" were compared with the data after 3 months switching to NF-U shown as "Data after switching to NF-U" in Table 2.

Evaluation of patient-reported outcomes

Twenty patient-reported outcomes were semi quantitatively evaluated using a five-point grading scale in accordance with a previous report [19]. Results were compared 3 months before and after switching to NF-U.

Ethical considerations

This study conforms to the provisions of the Declaration of Helsinki and was approved by the Institutional Review Board of Yabuki Hospital (approval number: 115, approval date: August 27, 2019).

Data and statistical analysis

Regarding evaluation items of nutritional status, statistical analysis was conducted using Student's *t*-test. Patient-reported outcomes were compared using the Mann–Whitney *U* test. Results were presented as the mean ± standard deviation. A p value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using the JMP Pro software ver. 14 (SAS Institute Inc., NC, USA).

Table 2 Comparison of parameters before and after the switching to NF-U

Item	Control data	Data after 3 months switching to NF-U	*p* value
Albumin (g/dL)	3.01 ± 0.16	3.25 ± 0.17	< 0.05
GNRI	87.7 ± 5.8	91.4 ± 6.2	< 0.05
%CGR (%)	100.2 ± 21.6	111.9 ± 20.9	< 0.05
DW (kg)	52.0 ± 6.5	52.7 ± 6.5	< 0.05
BMI	22.6 ± 3.7	22.8 ± 3.8	< 0.05
nPCR	0.81 ± 0.09	0.87 ± 0.17	n.s
CTR (%)	50.5 ± 3.0	50.6 ± 2.8	n.s
β2-MG (mg/L)	29.0 ± 5.0	29.8 ± 3.1	n.s
CRP (g/dL)	0.23 ± 0.23	0.22 ± 0.31	n.s
Muscle mass (kg)	18.3 ± 3.6	18.7 ± 3.7	n.s
Fat amount (kg)	17.9 ± 6.7	18.4 ± 6.7	n.s

Results are presented as the mean ± standard deviation ($n = 10$)

β2-MG; β2-microglobulin; CRP, C-reactive protein; nPCR, normalized protein catabolism rate; GNRI, geriatric nutritional risk index; %CGR, percent creatinine generation rate; CTR, cardiothoracic ratio; DW, dry weight; BMI, body mass index; n.s., not significant

Results

We evaluated the patients' parameters, which were collected 1 and 4 months after switching to NF-U, as shown in Table 2. Albumin, GNRI, %CGR, and BMI significantly increased from 3.01 ± 0.16 g/dL to 3.25 ± 0.17 g/dL, 87.7 ± 5.8 to 91.4 ± 6.2, 100.2 ± 21.6% to 111.9 ± 20.9%, and 22.6 ± 3.7 to 22.8 ± 3.8 kg/m^2, respectively (Table 2). There was no change in β_2MG, CRP, and nPCR (Table 2).

As comparison of body composition, muscle mass and fat amount were compared between before and after switching to NF-U. Both muscle mass and fat amount did not change (Table 2).

Before switching to NF-U, DW had been maximum decreasing to 51.7 ± 8.2 kg from 52.7 ± 8.6 kg. However, DW significantly increased to 52.7 ± 8.4 kg after 3 months switching to NF-U compared with that just after switching to NF-U (Fig. 1, filled circle). Although fluctuation of DW in each patient before switching to NF-U was diverseness, after switching to NF-U, DW increased in 7 of 10 patients, did not change in 2 patients, and decreased in 1 patient. There was no significantly change in CTR during observation period (Fig. 1 open circle).

For patient-reported outcomes, the total score significantly decreased to 20.8 ± 13.5 from 27.0 ± 17.9 ($p < 0.05$, Table 3) and the score for fatigue significantly decreased to 0.9 ± 0.6 from 2.1 ± 1.3 before compared with after switching to NF-U ($p < 0.05$, Table 3). There was no significant difference for the other symptoms.

Discussion

There have been several reports that suggested the effectiveness of PMMA for maintaining the nutritional status and ameliorating patient-reported outcomes [11, 15]. NF-U series is a new type of PMMA membrane of which the hemocompatibility was refined compared with previous models [15], and we examined in this study that NF-U is a useful dialyzer for older patients.

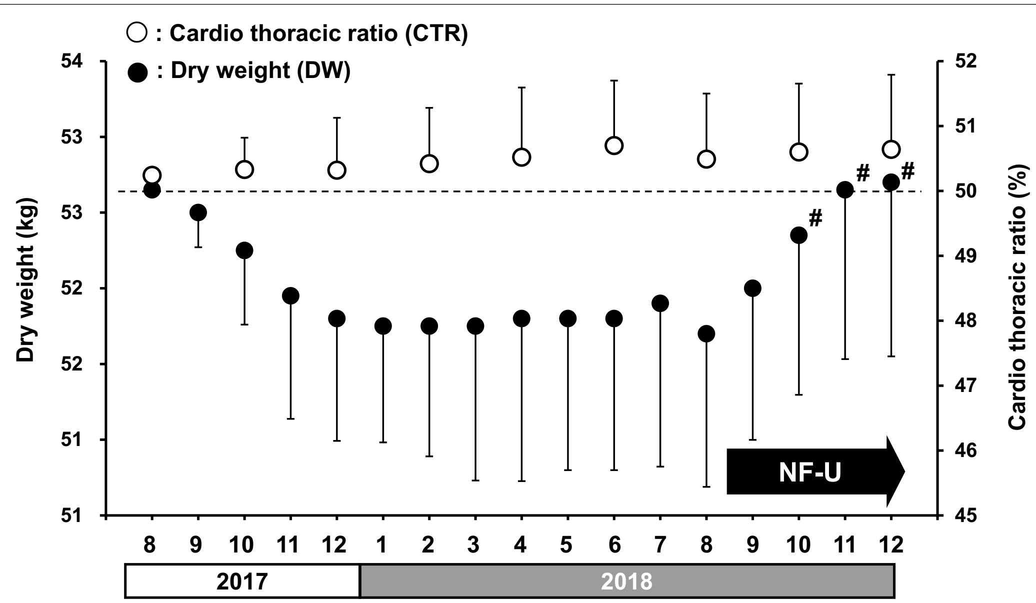

Fig. 1 Change of dry weight (DW) and cardiothoracic ratio (CTR) before and switching to NF-U. Results are presented as the mean ± standard deviation

Table 3 Comparison of patient-reported outcomes for 3 months before and after replacement with NF-U

Item	Before	After	*p* value
Joint pain	2.0	2.0	n.s
Itching	1.4	1.1	n.s
Distraction	1.3	0.9	n.s
Fatigue	2.1	0.9	< 0.05
Palpitation	1.5	1.0	n.s
Constipation	1.6	0.8	n.s
Falling sleep	1.6	1.9	n.s
Sleep well	1.6	1.5	n.s
Terebrant pain	1.4	1.4	n.s
Headache	1.1	0.8	n.s
Hypotension	1.9	1.1	n.s
Reg cramp	1.1	0.9	n.s
Movement	0.9	1.0	n.s
Appetite	1.3	1.0	n.s
Deliciousness	1.3	0.9	n.s
Dry mouth	1.6	1.3	n.s
Meal restrictions	1.0	1.1	n.s
Melancholy	1.5	1.0	n.s
Interest	1.0	0.5	n.s
Satisfaction	1.9	1.8	n.s
Total score	27.0	20.8	< 0.05

Results are presented as the mean

n.s., not significant

Beside serum albumin concentration used in this study, there are several markers to assess nutritional status such as GNRI, %CGR, DW and BMI. It is desirable to combine several markers to assess nutritional status because it remains controversial which marker is appropriate. We use serum albumin concentration as a marker to screen regularly nutritional status because that is measured simply and affordably and the results are highly reproducible.

In this study, the average serum albumin concentration increased significantly from 3.01 ± 0.16 g/dL to 3.25 ± 0.17 g/dL. Hypoalbuminemia has been shown to be an independent risk factor for prognosis in hemodialysis patients [20, 21]. A registry data study from the Japanese Society for Dialysis showed that the serum albumin concentration was less than 3.5 g/dL in about 50% of hemodialysis patients who were over 75 years of age [22], and the serum albumin concentration of older dialysis patients tended to be low. The GNRI also increased significantly from 87.7 ± 5.8 to 91.4 ± 6.2. Along with the serum albumin concentration, GNRI is widely used to screen for malnutrition on older people, and it is strongly associated with mortality [23]. Yamada et al. reported that the risk of malnutrition was higher in Japanese hemodialysis patients whose GNRI was 91.2 or less [24].

After switching to NF-U, a significant increase in DW was observed. DW before switching to NF-U decreased from August through December of the2017 and, after that, was stable at low levels until September 2018. We consider that this reduction phase occurred because of a decrease in appetite due to high temperatures in the summer, and frequently observe this in everyday clinical practice. DW after switching to NF-U subsequently increased from September to December of the 2018, in spite of the period where body weight easily decreases by seasonal issues. We think that this clinical phenomenon occurred due to improvement effects of the NF-U dialyzer on nutrition. Because CTR, which we were using to decide DW, did not change significantly during this study period, we consider that the patients' DW increased without water retention. Some cohort studies reported that body weight loss in older patients increases their mortality [25, 26].

Other nutritional indexes such as %CGR and BMI, also increased significantly after 3 months switching to NF-U. These results as mentioned above suggest that HD therapy using NF-U would be useful to improvement of nutrition in older dialysis patients concerned about nutrition status.

Malnutrition in hemodialysis patients is affected by various factors such as inflammation, nutrient removal by dialysis therapy, reduction of protein intake [27]. It is reported that PMMA, which has the adsorbed property, can remove inflammatory cytokines including Interleukine-6 (IL-6) [28, 29]. Blood cells including white blood cells (WBCs) and platelets are activated by contact with dialysis membrane, and it is one of cause for induction of inflammatory responses [30, 31]. Since platelet activation is low levels in HD therapy using NF-U having the improved antithrombogenicity, inflammatory status might have been reduced [32]. In addition, PMMA membrane does not include polyvinylpyrrolidone (PVP) and bisphenol species such as BPA and BPS which often take up as an inducer of inflammation [11], and its membrane material has superior biocompatibility [33]. These biocompatible aspects of NF-series might have contributed to the reduction of inflammation. Although we did not measure inflammatory cytokines such as IL-6 in this study, reduction of them might have contributed to improvement of nutritional status.

Hemodialysis removes some amount of albumin, which is one of nutrient, together with uremic toxins. According to the report of Maduell et al., albumin loss was about 600 mg in a dialysis session when high convection volume post-online HDF was conducted with NF-U, and it was lower compared with post-online HDF with polysulfone [34]. We consider that albumin loss in HD with NF-U was lower than HD with PS, and low albumin loss might have contributed to improvement of nutrition status.

Since before, our dialysis facility regularly has investigated patient-reported outcomes (PROs) and has used that results to set dialysis prescription. In this study, we observed that both the score for the total score for PROs and fatigue significantly decreased by switching to NF-U.

SONG-HD showed that fatigue is the most important PRO in hemodialysis patients [5]. Fatigue is strongly associated with prognosis, and that is a powerful independent predictor of cardiovascular disturbance [35]. Compared with healthy people, hemodialysis patients feel fatigue, and older hemodialysis patients feel more fatigue [36]. Fatigue is reported to affect on preparation of meals in HD patients and to become barrier toward dietary intake [37]. We think that improvement of fatigue by NF-U might have contributed to improvement of nutritional status, although we had not investigated dietary intake.

Only a few articles reported that the dialysis modality improves fatigue after dialysis. Furthermore, there is no established evidence that HDF, which has been performed worldwide in recent years, improves QOL. Many studies reported that online HDF did not improve the recovery time after dialysis which is an index relating to fatigue. Suda et al. reported that hemodialysis patients felt less fatigue and the water removal was easily conducted until body weight reached DW when they underwent hemodialysis using PMMA [38]. Our results are consistent with this report. Although it is reported that fatigue is correlated with ultrafiltration rate and anemia, those did not significantly change during period of study. The mechanism by which NF-U improves fatigue could be its solute removal property and/or biocompatibility, which were discussed above with the mechanism for improving the nutritional status.

This study has several limitations because it is a single-center retrospective study. First, the number of evaluated patients was small. Second, the evaluated patients were treated with various dialysis membrane materials and dialysis modalities before switching to NF-U. Third, the control group including patients who received dialysis prescription other than dialysis using NF-U could not be prepared. Furthermore, there was not clear standard for the determination of dialyzer switching such as serum albumin concentration and drop width of serum albumin because dialyzers were switched under routine medical care. In the future, it is necessary to conduct a randomized controlled trial to examine the change in each patient's physical status and their nutritional status with long-term NF-U use, which will reduce bias.

Conclusion

This retrospective study showed that NF-U, which is a new PMMA membrane, was associated with an improved nutritional status in older dialysis patients who were at a high risk of malnutrition. NF-U also improved patient-reported outcomes including fatigue, which is strongly associated with patient prognosis. A gold standard that is the most appropriate dialysis method for older patients has not been established. However, it is beneficial to improve the nutritional status and fatigue in older dialysis patients. Thus, we suggest that a dialysis method using NF-U is an optimal therapy for older dialysis patients.

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Authors' contributions
TC planned the study, analyzed the data, and drafted the manuscript. HI analyzed the data and drafted the manuscript. IM revised the manuscript and supervised the entire research project. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate
This clinical study was approved by the Institutional Review Board at Yabuki Hospital.

Consent for publication
Not applicable.

Competing interests
The author declare that they have no competing interests.

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