

Current approaches to middle molecule removal: room for innovation

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ABSTRACT

Aggressive removal of middle molecules or larger low-molecular-weight proteins (LMWPs) has been a growing concern following studies on their harmful effects on the mortality and morbidity of chronic dialysis patients. To remove larger LMWPs and some protein-bound uremic toxins (PBUTs), high- and medium-cutoff (HCOs and MCOs, respectively) membranes, convective therapy and protein adsorptive membranes are available. When we use HCO or MCO membranes for convective therapy, we have to take care to avoid massive albumin leakage during a dialysis session. Convection volume is an important element to increase middle molecule removal; however, a larger convection volume has a risk of larger leakage of albumin. Predilution hemodiafiltration is a useful measurement to increase larger LMWPs without massive albumin leakage. β_2 -microglobulin (B2M), α_1 -microglobulin (A1M) and albumin leakage during a dialysis session are useful parameters for assessing middle-molecule removal. Reduction ratios of B2M >80% and of A1M >35% are favorable to improve severe dialysis-related symptoms. The efficacy of middle molecule removal should be evaluated in comparison with clinical outcomes, mortality, morbidity and the improvement of dialysis-related symptoms. Recently some dialysis-related symptoms such as sleep disturbance, skin itchiness and dialysis hypotension have been recognized as good surrogate makers for mortality. Further studies to evaluate the relationship between middle molecule or PBUTs removal and the improvement of patient symptoms should be performed in well-designed randomized controlled trials.

Keywords: biocompatibility, convective therapy, middle molecule, protein adsorption, protein-bound uremic toxin

INTRODUCTION

Uremic retentive toxins have been classified into three groups by the European Union Toxin Working Group (EUTox): small solutes with a molecular weight (MW) <500 Da, protein-bound

uremic toxins (PBUTs) and middle molecules with a MW ≥ 500 Da [1]. This classification was performed based on the characteristics that potentially influence their removal pattern by dialysis and related therapies. In the early stage of chronic dialysis, the concept of middle molecules was developed as a part of the square meter/hour hypothesis for evaluating the pathogenesis of uremia-related neuropathy [2]. The removal of middle molecules, with MWs of 500–2000 Da, was better in peritoneal dialysis than in hemodialysis (HD) using an early-stage thick cuprophane membrane, and uremic neuropathy was seldom observed in peritoneal dialysis. However, as new synthetic membranes and convective therapies have been developed to remove these middle molecules as well as small solutes, the drive to identify middle molecules as uremic toxins and the concern regarding uremic neuropathy gradually decreased and the target of dialysis therapy shifted to small solutes to evaluate dialysis doses following the National Cooperative Dialysis Study [3]. In 1985, β_2 -microglobulin (B2M) was identified as a precursor of dialysis-related amyloidosis [4]. The MW of B2M is 11 800 Da, which is much larger than the MWs of middle molecules identified in the early era of chronic dialysis. B2M was classified as a low-MW protein (LMWP), a class with an MW ranging between 1000–50 000 Da [5], and just after the discovery of B2M as a uremic toxin, studies evaluating the toxicity or pathogenicity of various LMWPs in the uremic milieu were begun [5, 6].

In the early stage of chronic dialysis in Japan, several pioneer doctors found that aggressive removal of larger LMWPs with massive albumin leakage using ethylene-vinyl alcohol copolymer (EVAL) occasionally ameliorated uremic symptoms such as severe renal anemia [7]. They supposed that some larger LMWPs had toxic effects in chronic dialysis patients and they proposed the concept of protein-permeable dialysis [8]. This therapeutic concept has been generally accepted and protein-leaking dialysis and predilution online hemodiafiltration (HDF) with high-cutoff (HCO) membranes has been widely performed in Japan [8]. Recently, similar concepts were introduced, such as expanded dialysis by Ronco [9] and a

medium-cutoff (MCO) dialyzer by Kirsh *et al.* [10]. Interest in removing larger LMWPs, including some albumin, which is recognized as a carrier protein of PBUTs, has increased worldwide. In this article we summarize the current concepts for removing larger LMWPs, partially including some PBUTs, and introduce the present status of chronic dialysis in Japan where protein-permeable dialysis is widely performed.

WHAT ARE THE TARGETS OR PARAMETERS FOR MIDDLE MOLECULE REMOVAL?

As previously mentioned, concerns regarding the removal of middle molecules by blood purification have shifted from the original middle molecules to larger LMWPs. Many middle molecules and PBUTs have been proposed as removal targets. An ideal target should possess a clear relationship with clinical symptoms, dialysis-related complications and patient survival. Furthermore, as these solutes should be measured easily in commercial laboratories, only a few parameters should be established that meet these characteristics. Thus we consider here the kind of parameters that are favorable for evaluating middle molecule removal in relation to clinical outcomes.

B2M

B2M is an element of the major histocompatibility antigen with a MW of 11 800 Da, and it is well known as a precursor of the amyloid fibril of dialysis-related amyloidosis [4]. It is also well known as a mortality risk factor, according to the subanalysis of the Hemodialysis (HEMO) study and a Japanese cohort study [11, 12]. A survival advantage was observed in patients with a pre-dialysis serum B2M concentration of 27.5 mg/L in the former study and 32.2 mg/L in the latter study. Based on this evidence, the Japanese Society for Dialysis Therapy (JSDT) recommends that predialysis serum B2M concentration should be 30 mg/L, and 25 mg/L if possible [13]. The European Best Practice Guidelines also propose that B2M should be used to evaluate middle molecule removal and that removal should be maximized [14]. In Japan, reimbursement by the government for each dialyzer category was set according to the clearance of B2M. However, the target value for B2M is set in the predialysis concentration [11–13] but not in the reduction ratio (RR). In recent HD with high-flux membranes, B2M is mainly removed by diffusion, so correction with hematocrit for calculating the RR of B2M is not usually performed. The RR of B2M has been reported as 50–60% in high-flux dialysis, ~70% with an MCO dialyzer and 80–85% in high-efficiency HDF [10, 15, 16].

A1M

A1M is a 183 amino acid peptide with a MW of 33 000 Da, and urine A1M has been measured to assess the severity of tubulointerstitial fibrosis of the kidney. A1M is not recognized as a uremic toxin and is not included in the middle molecule category in the EUTox classification [1]. However, A1M measurement is available in commercial laboratories, so it is a very good surrogate marker to assess middle molecule removal [15, 17, 18]. There are several important middle molecules around A1M, including fibroblast growth factor 23 (FGF23) (32 000

Da), interleukin 1 β (32 000 Da) and TNF- α (26 000 Da). There have been few studies about the relationship between the removal of A1M and clinical outcome because A1M is not a toxin. The removal rate of A1M in the previous reports was 10–40% in various dialysis prescriptions in HD or online HDF [15, 16, 18].

Immunoglobulin free light chains

Immunoglobulin free light chains (FLCs) have been classified as middle molecule uremic toxins because serum levels of FLCs are elevated in uremia and as polymorphonuclear leukocyte function deteriorates [1, 19]. The MWs of FLCs (kappa FLCs and lambda FLCs) are ~25 000 Da as monomers and 50 000 Da in dimers. The increase of FLCs in chronic renal failure has been reported to be mainly due to the increase of lambda-type FLCs [20]. Conventional HD and HDF cannot efficiently reduce the serum level of FLCs, but HD with polymethylmethacrylate (PMMA) decreases it [20, 21]. Recently MCO dialyzers have been shown to be more effective at removing larger LMWPs, particularly lambda FLCs, compared with conventional high-flux HD and high-efficiency HDF [10].

Parathyroid hormone (PTH) and FGF23

PTH and FGF23 are key players in the development of chronic kidney disease mineral and bone disorder (CKD-MBD). PTH (MW 9225 Da) is classified as a middle molecule in the EUTox classification, but FGF23 (MW 32 000 Da) has not been included because the toxic effects of FGF23 were not recognized in chronic dialysis in the early 2000s. Recently attention has focused on FGF23 as a uremic toxin and it could be a representative parameter for the removal of larger LMWPs. However, the serum concentrations of PTH and FGF23 are more influenced by the therapeutic conditions of CKD-MBD, such as phosphate binders, vitamin D and calcium-sensing receptor agonist, than elimination by blood purification, so as yet no removal targets have been set for them.

P-cresyl sulfate (PCS) and indoxyl sulfate (IS)

PCS and IS are the most well-studied PBUTs, which are mainly bound to albumin; their non-protein-bound MWs are 108 Da (PCS) and 251 Da (IS). Their main toxic effects were originally thought to relate to vascular injury and cardiovascular events [1, 22]; however, whether PCS and/or IS have a significant influence on patient survival or cardiovascular events remains controversial. Bammens *et al.* [23] reported that PCS is an independent mortality risk factor in chronic dialysis patients. In the subanalysis of the HEMO study, the predialysis solute concentrations of PCS, IS, phenylacetylglutamine and hippurate were not associated with cardiovascular mortality [24]. However, if serum albumin was low, their toxicity could be enhanced [24]. A recent well-designed systematic review demonstrated the toxicity of PCS and IS and supported the idea that they have roles in vascular and renal disease progression [25]. Three important elements to keep PBUTs low were identified: aggressive removal of PBUTs by blood purification, maintenance of residual kidney function to eliminate middle molecules and PBUTs and intestinal probiotic therapy to prohibit the generation of intestine-derived uremic toxins such as PCS

and IS [26]. Bammens *et al.* [27] reported that convective therapy was superior for the removal of PBUTs compared with high-flux HD; however, the total removal of PBUTs and B2M was significantly lower than that of small solutes. They thought that they could remove only the free fraction of PBUTs with HD or HDF with non-protein-leaking membranes. On the other hand, even though the dialyzer size and blood and dialysate flows were increased to maximize the clearance of protein-bound solutes, this could have had a minimal effect on the predialysis PCS and IS levels [28].

Albumin

Serum albumin (MW 66 000 Da) is an indispensable element for maintenance of the colloid osmotic pressure of the blood. Albumin is also an important transporter of non-water-soluble drugs and a circulating radical scavenger. Albumin is one of the parameters for nutritional assessment and an independent mortality risk factor in chronic dialysis patients. So it was thought that albumin leakage during a dialysis session could be avoided, even if the removal of middle molecules and/or PBUTs had to be maximized.

Based on an early glomerular puncture study, ~ 3.5 g/day of albumin was filtered in the glomeruli [29]. Russo *et al.* [30] reported that the sieving coefficient of albumin in the glomerulus was much higher than the 0.034 in previous reports and that >100 g/day of albumin would be filtered in the glomeruli and metabolized in the urinary tubule [30]. The kidney could be described as a major metabolic organ for albumin. It has been reported that the binding functions and three-dimensional structure of albumin are impaired by PBUTs, chemical or oxidative stress and carbamylation or glycation in the uremic milieu [31]. Large amounts of LMWPs and deteriorated albumin might be eliminated in the kidney. When we try to maximize the removal of larger LMWPs, we have to accept some albumin leakage during a dialysis session. The Stokes radius of A1M and albumin are not so different, even if the MW of albumin is almost twice that of A1M. Some albumin leakage during a dialysis session has been widely accepted in Japan, as explained in the latter part of this article. In a recent systematic review evaluating the advantages of convective therapy, the survival rates and nutritional conditions were better in convective therapy, but the serum albumin was rather lower in convective therapy than in conventional HD [32].

DIALYSIS MODALITIES TO REMOVE MIDDLE MOLECULES

High-flux/HCO membranes

High-flux membranes composed of various membrane materials have been developed to efficiently remove middle molecules as well as small solutes and they have been used for convective therapy since 1970s [33]. In the early stage of their development, high flux meant highly permeable to water and this was convenient for convective therapy. However, as interest in removing middle molecules was shifted to the removal of larger LMWPs, a new concept for differentiating high-efficiency dialysis from the viewpoint of solute removal became necessary.

The size-dependent removal properties for middle molecules are specified by the average pore size, pore size distribution and pore densities. In 2006 in Japan, hollow-fiber dialyzers were categorized into five types (types 1–5) based on their B2M clearance and reimbursement was made according by each category [34]. B2M clearance of each type is as follows: type 1, 10 mL/min; type 2, 10–30 mL/min; type 3, 30–50 mL/min; type 4, 50–70 mL/min and type 5, ≥ 70 mL/min (Table 1). The prevalence of each dialyzer category was surveyed by the JSDT in 2008 and the prevalences of types 1–5 were 1.2, 0.9, 4.2, 81.5 and 12.2%, respectively, of all hollow-fiber dialyzers used in HD modalities [35]. In 2016 the categorization was modified to include the sieving coefficient (SC) of albumin, and dialyzers were then divided into a further four types based on B2M and SC albumin in a 2×2 manner. Type 1 and type 2 are defined by B2M clearance <70 and ≥ 70 mL/min, respectively, and subclassified in accordance with SC albumin levels <0.04 as type 1a and ≥ 0.04 as type 1b. In the same manner, type 2 dialyzers are divided into type 2a and type 2b (Table 1). The prevalences of the new categories were surveyed at the end of 2017 and the data should be published by the end of 2018.

Ronco [9] differentiated high-efficiency dialysis by the SC curve of MW. There are two essential terms for specifying membrane properties: retention onset (RO), which is the point where the retention of a certain solute at an SC of 0.9 is broken out, and the cutoff (CO), which is the point where the passage of a certain solute at an SC of 0.1 is no longer permitted. The SC of B2M in a high-RO (HRO) membrane is >0.9 , so B2M could be removed by diffusion with HRO membranes. The SC of albumin in HCO membrane is >0.1 , so some albumin leakage occurs in HCO membrane dialysis. Recently MCO dialyzers have been able to remove larger LMWPs, particularly lambda FLC, compared with conventional high-flux HD and high-efficiency HDF [10].

HDF

In late 1970s, hemofiltration (HF) was developed to increase middle molecule removal by convection, even in low-flux HD, but small solute removal deteriorated in HF. HDF has been developed to efficiently remove middle molecules as well as small solutes [33]. The profiles and total amounts of middle molecules removed vary according to the membrane pore size, convection volume and dilution method. Larger pore sizes and larger convection volumes are generally favorable to efficiently remove middle molecules. There are two major dilution techniques in HDF: post- and predilution. Postdilution HDF has been performed in Europe and in many other countries around the world, while predilution HDF has mostly been performed in Japan. In postdilution, the blood is concentrated inside the filter, so the convective volume is mainly restricted by the blood flow rate. If the substitution flow rate is increased beyond the limit, explosive albumin leakage or blood coagulation problems occur. On the other hand, in predilution we can increase the convection volume as much as is desired with no effect on the blood flow rate. Major differences between pre- and postdilution HDF are summarized in Table 2 [36]. To prescribe safe and efficient removal of middle molecules by

Table 1. Dialyzer categories in Japan

2006–15	2016 onwards
1. Dialyzer, hollow-fiber type (HD) CL-B2MG Type 1: <10 Type 2: ≤10, <30 Type 3: ≤30, <49 Type 4: ≤50, <70 Type 5: ≥70	1. Dialyzer, hollow-fiber type (HD) Type 1: CL-B2MG <70 (ex. 1–4) • Type 1a: SC albumin <0.03 • Type 1b: SC albumin ≥0.03 Type 2: CL-B2MG ≥70 (ex. 5) • Type 2a: SC albumin <0.03 • Type 2b: SC albumin ≥0.03 Type-S
2. Dialyzer, plate type (HD)	2. Dialyzer, plate type (HD)
3. Hemodiafilter (only for HDF)	3. CAVH filter
	4. Hemodiafilter (only for HDF)

CAVH, continuous arteriovenous hemofiltration; CL-B2MG, clearance of B2M.

Table 2. Comparison between pre- and postdilution [36]

	Predilution	Postdilution
Q _b (mL/min)	250–400	250–400
Q _s (mL/min)	100–300	30–100
Large pore filter	Available	Risky
TMP	No change	Increase
Protein leak	Controllable	Risk of explosive leak
SM removal	Reduce	High
LMWP removal	High	High
Indication	Itchiness, RLS	DRA
	Hypotension	Enhanced solute removal
Location used	Japan	Europe, worldwide

DRA, dialysis-related amyloidosis; Q_b, blood flow rate; Q_s, substitution flow rate; RLS, restless legs syndrome; SM, small solute; TMP, transmembranous pressure.

HDF, HRO membranes could be a good choice for postdilution and MCO membranes could be a good choice for predilution. HCO membranes for HDF need special attention to prevent massive albumin leakage, especially postdilution HDF.

The efficacies of middle molecule removal assessed by clearance or RR can be quite different according to each prescription. In an excellent systematic review that compared convective therapies with low-flux HD, the clearance of B2M was 64.77 mL/min greater than that of low-flux HD and the RR of B2M was 60.08% greater than that of low-flux HD [32]. According to Cornelis *et al.* [37], total removal of B2M and FGF23 was higher in an 8-h HDF session; however, the total removal of B2M was only 188.6 mg and clearance of B2M was 40.9 mL/min. Meert *et al.* [38] compared the clearance and removal of small solutes, middle molecules and PBUTs between post- and predilution HDF and predilution HF. The clearance of B2M in each modality was 82.8, 67.2 and 87.5 mL/min and the RR of B2M was 77.8, 67.2 and 76.2%, respectively. The clearance of PCF and IS was not different between post- and predilution HDF, but was lower in predilution HF. Reviewing these reports, an RR of ~60–70% for B2M could be achieved by HRO-membrane HD and ≥80% could be achieved by HDF.

Recent evidence has shown that the survival advantage of online postdilution HDF can only be achieved with a substitution volume >23 L/session [39, 40]. On the other hand, a survival advantage of predilution online HDF has been reported by the JSDT [36]. The survival advantage, both for all-cause

mortality and cardiovascular mortality, was observed only in patients treated by online predilution HDF with ≥40 L/session of substitution volume. No survival advantage was observed in either high-efficiency HD or online predilution HDF with a substitution volume <40 L/session. However, even in these excellent papers it is still unclear what convection volume means. The convection volume is generally increased to remove middle molecules more effectively; however, the relationship between the convection volume and middle molecule removal has not been analyzed. Furthermore, the main outcomes of these studies were all-cause and cardiovascular mortality, and there was no consideration of the relationship between mortality and middle molecule removal. These issues should be considered in future studies.

Protein adsorptive membrane

The protein adsorptive properties of a dialysis membrane depend on the internal pore structure and hydrophobic properties of the membrane. Generally proteins adsorbed onto the membrane surface would be deteriorated and some of them could accelerate the consequent activation of biological pathways as adsorbed fibrinogen can enhance platelet activation and consequent blood coagulation. On the other hand, it was postulated that protein adsorption onto the membrane might be beneficial for improving biocompatibility and removing some kinds of LMWPs [41]. Polyacrylnitrile (PAN), PMMA, polysulfone (PS) and polyamide (PA) are hydrophobic and adsorb more proteins than cellulosic membranes [41]. The clinical advantages of biocompatible protein adsorptive membranes have mainly been studied in acute kidney failure, and PAN and PMMA have been reported to be linked to a good clinical outcome [41, 42]. They have also been reported to have additional advantages for dialysis-related amyloidosis due to the adsorption of B2M [43, 44]. In protein-leaking and adsorptive membranes, PMMA was reported to reduce predialysis plasma homocysteine concentrations [45], immunoglobulin FLCs [20, 21] and inflammatory markers [46]. Some PBUTs were also reported to efficiently remove albumin-bound furancarboxylic acid in protein-leaking dialysis [47]. Using JSDT data, Abe *et al.* [48] reported that PMMA has a positive relationship with patient survival.

Recently proteomic studies of adsorptive proteins have clarified that adsorbed protein profiles differ depending on the membrane materials used [49, 50]. For instance, the profiles of adsorbed proteins were different between cellulose triacetate (CTA) and PS, as albumin and apo-lipoprotein were mainly found in CTA, but fibrinogen and other proteins due to the coagulation cascade and platelet activation were mainly found in PS. Thrombocytopenia has been well known as an adverse effect of PS [51]. Based on these findings, the protein adsorptive properties of each membrane modify the removal profile of middle molecules and its biocompatibility and might be related to clinical outcome.

Intensive dialysis

As we all know, a conventional dialysis program of 4-h sessions thrice weekly is a short period of time for the elimination

of middle molecules as well as small solutes compared with normal kidney function. Nocturnal home hemodialysis (NHHD) programs of 8–10-h sessions six or seven times per week have been globally promoted and amazing results have been emphasized [52, 53]. However, only a few reports have studied the kinetics of middle molecules or PBUTs in intensive dialysis programs. Cornelis *et al.* [37] reported that the total removal of B2M was higher in 8-h HD than in 4-h HD but was similar to 4-h HDF. In a study of frequent HD network trials, the kinetics of B2M were evaluated by dialysis regimens and the removal of B2M was 67% greater in six sessions/week NHHD than with conventional home HD. Further studies evaluating the relationship between the kinetics of middle molecules and clinical outcomes are needed. NHHD was also expected to reduce the serum levels of PBUTs by eliminating the free fraction of PBUTs during a longer dialysis period; however, a recent prospective study did not show a significant reduction of PCS, IS or tri-methylamine N-oxide [54]. Based on these reports, there is not yet any hard evidence regarding advantages of PBUT removal by intensive dialysis.

BIOCOMPATIBLE ASPECTS OF MIDDLE MOLECULE REMOVAL

Various types of synthetic membranes have been developed to improve the solute removal performance and biocompatibility of dialysis membranes. Many membrane materials are now available, however, there are few materials that have perfect biocompatibility. PS is the most widely used synthetic membrane worldwide, both for HD and HDF, but recently PS was reported to have several adverse effects, including anaphylaxis [55], skin lesions [56] and thrombocytopenia [51]. PS has hydrophobic and protein-adsorptive properties, so polyvinylpyrrolidone (PVP) is mixed with it to make a dialysis membrane that is hydrophilic. PVP is an indispensable component in PS, polyether-sulfone (PES) and several other synthetic membranes, however, some of these adverse effects were thought to be related to PVP [51, 56]. Bisphenol-A is an essential component of plastics and polycarbonates, which are widely used for dialyzer housing material. However, bisphenol-A is also well known as an environmental hormone and endocrine disrupter and it has been reported that bisphenol-A might have some adverse effects on dialysis patients [57].

Sirilli *et al.* [58] evaluated platelet aggregation and radical stress during dialysis sessions with PS, EVAL and PAN dialyzers. Platelet aggregation and increased radical stress was observed only in PS dialysis, not in EVAL or PAN dialysis. It was speculated that some of the physicochemical properties of dialysis membranes might affect the biocompatibility of dialysis therapy. Sato *et al.* [59] also reported that increased aggregation of platelets caused by PS deteriorated the peripheral circulation during a dialysis session, but this was not observed during dialysis with EVAL and vitamin E-coated PS.

Gritters *et al.* [60] reported that the platelet activation during a dialysis session assessed by the expression of CD62p was greater in postdilution HDF than conventional HD, but that the serum concentrations of β -thromboglobulin (B-TG) and platelet factor 4 (PF4) were lower in HDF. Activated platelets release

bioactive proteins such as B-TG and PF4 and promote the consequent process of blood coagulation. Gritters *et al.* [60] concluded that HDF was more biocompatible than conventional HD because platelet-derived bioactive proteins could be eliminated by convection. The shear stress to the blood cells might be greater in postdilution HDF than in predilution HDF because marked hemoconcentration in the filter occurs only in postdilution HDF. Sakurai *et al.* [61] clarified that interleukin-6 and Intercellular Adhesion Molecule (ICAM)-1 were decreased only in predilution online HDF and not in postdilution HDF. They concluded that predilution online HDF is more biocompatible than postdilution HDF.

There are many bioactive and pro-inflammatory substances that are classed as middle molecules, so aggressive removal of middle molecules could modulate the biocompatibility of dialysis therapy accompanied with membrane materials.

PRESENT STATUS OF PROTEIN-PERMEABLE DIALYSIS IN JAPAN

Dialysis modality

The JSDT has a long history of renal data registry, >50 years, and the JSDT began collecting data about the details of HDF in 2009. Based on the annual data report of a JSDT survey in 2016, there were 329 609 dialysis patients in 4396 dialysis facilities in a facility-based survey [62]. The number of HDF patients rapidly increased to 76 836 patients (23.3%) from 55 333 patients in 2015 (17.0%). Based on the patient-based survey, HDF prescriptions were collected from 74 799 HDF patients. The number of patients using online HDF, offline HDF (bag-type HDF), intermittent infusion HDF [63] and other HDF modes was 59 116 (79.0%), 4637 (6.2%), 10 728 (14.3%) and 318 (0.4%), respectively. The number of patients treated by online HDF has been rapidly increasing but the number of patients using offline HDF has been decreasing. Of note, 95.6% of online HDF patients were treated by predilution online HDF whereas 86.6% of the offline HDF patients were treated by postdilution HDF (Figure 1). The average substitution volume was 39.9 L in predilution and 10.2 L in postdilution online HDF. The average substitution volume was 12.0 L in predilution and 8.0 L in postdilution offline HDF (Figure 1). The substitution volume was smaller in postdilution online HDF in Japan compared with previous reports emphasizing that a larger substitution volume of >23 L/session was needed to achieve good clinical results [39, 40]. However, MCO and HCO membranes are occasionally used for online postdilution HDF in Japan, so the removal patterns of middle molecules are quite different from those of postdilution HDF performed in Europe. In Japanese-style postdilution HDF, the RRs of B2M and A1M are >80% and 20–40%, respectively, and albumin leakage can be controlled to >10 g/session [64].

Dialysis fluid quality

Dialysis fluid quality is an indispensable element for high-efficiency dialysis because bacteriological contamination of dialysis fluid deteriorates the biocompatibility of dialysis therapy.

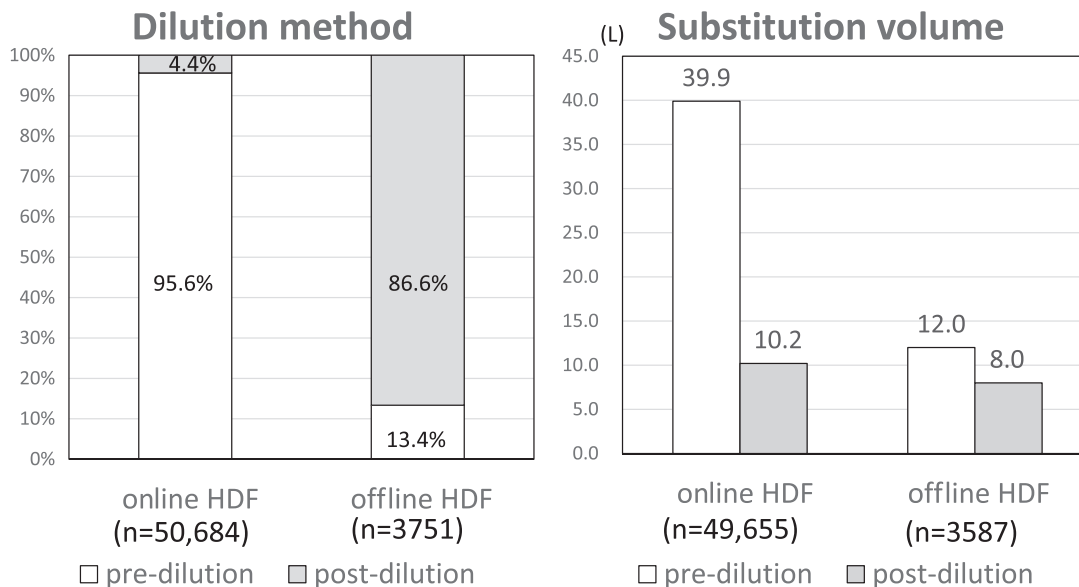


FIGURE 1: HDF prescription in Japan [62].

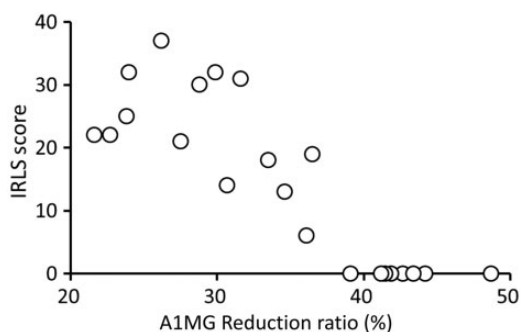


FIGURE 2: Relationship between IRLS score and A1M RR. The relationship between the RRs of A1M and IRLS scores during the treatment courses of seven dialysis patients are shown. A1M RR >35% was closely related to the amelioration of IRLS [17]. IRLS, International Restless Legs Syndrome Study Group.

The JSDT’s standard recommendations are that all dialysis modalities, including online HDF, should be performed with ultrapure dialysis fluid [65]. In the 2016 JSDT Renal Data Registry survey, ultrapure dialysis fluid had been achieved in 2863 facilities out of the 4008 that responded (71.4%) and the percentage of ultrapure dialysis fluid that had been achieved had been gradually increasing [62]. Hasegawa *et al.* [66] reported that patients treated with dialysis fluid with endotoxin levels >0.100 EU/mL had a higher mortality risk compared with patients treated by with ultrapure dialysis fluid.

Parameters for middle molecule removal

In Japan, the efficacies of middle molecule removal are usually evaluated by the RRs of B2M, A1M and albumin leakage during a dialysis sessions [17, 67]. In the JSDT guidelines, it is recommended that predialysis serum B2M concentration should be kept at <30 mg/dL, but the target value for A1M and the RRs of B2M and A1M are not shown [13]. Unfortunately, there have been few studies that have evaluated middle molecule removal in relation to patient survival or symptoms.

Sakurai [17] reported the improvement of severe restless legs syndrome by the aggressive removal of larger LMWPs >35% of the RR of A1M and 3–5 g of albumin leakage during a dialysis session (Figure 2). When we try to remove larger LMWPs, we have to accept ~3–5 g of albumin leakage and, occasionally, this may be >10 g in some circumstances [67]. Nagai *et al.* [68] reported that dialysis modalities with ≥3 g of albumin loss during a dialysis session had better survival rates than those with <3 g. They also reported that protein-leaking dialysis was favorable to maintain the serum level of the reduced form of albumin, which was recognized as having protective effects on dialysis patients from cardiovascular events [69]. However, large amounts of albumin leakage should be avoided because this leads to hypoalbuminemia and lipoprotein metabolism abnormalities. The relationship is different in each dialysis prescription, based on pore size and the density of the membrane, predilution or postdilution, substitution flow rate and so on. We can predict albumin leakage based the relationship between the A1M removal rate and albumin leakage on various dialysis prescriptions, as shown in Figure 3.

DAILY PRACTICE PATTERNS OF DIALYSIS IN RELATION TO MIDDLE MOLECULE REMOVAL

Many reports have evaluated the retention and toxic effects of middle molecules on chronic dialysis patients, however, we have not yet established enough evidence for removal targets for middle molecules in relation to patient survival. So what should we prescribe for dialysis in daily practice? It is not easy to choose a proper prescription that will give each patient a longer survival rate with a higher quality of life (QOL).

Recently several dialysis-related symptoms have also come to be known as mortality risk factors, such as a depressive state [70], sleep disturbance [71], skin itchiness [72], intradialytic hypotension [73] and delayed recovery from postdialysis fatigue [74]. There are other dialysis-related uncomfortable symptoms

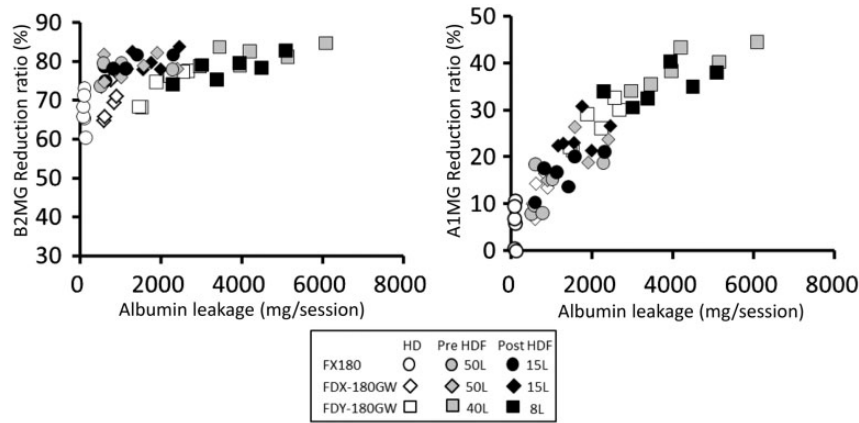


FIGURE 3: Relationship between the RRs of B2M and A1M and albumin leakage. The relationship between albumin leakage and the RRs of B2M and A1M under various dialysis prescriptions are plotted [17].

that have not been recognized as mortality risk factors, such as restless legs syndrome, irritability, skin pigmentation and so on. If a certain symptom is identified as a mortality risk factor, can we improve the survival rate by ameliorating the symptom with some interventions? As we all know, these are two different things. However, if we can ameliorate a certain symptom via the aggressive removal of middle molecules or some PBUTs, it would need to be under conditions that are acceptable to the patient and might finally lead to the improvement of survival rates through the amelioration of the QOL of dialysis patients. As previously addressed, it has been reported that aggressive removal of A1M improves severe restless legs syndrome [17]. Skin hyperpigmentation is usually observed in chronic dialysis patients and it has been postulated that it may be associated with the accumulation of middle molecules in uremia. Moon *et al.* [75] reported that skin color was well preserved in HDF patients compared with low- and high-flux HD, and predialysis serum B2M concentrations and the RRs of B2M were significantly higher in HDF patients than in others [75].

We started a dialysis prescription system according to the patient's symptoms and nutritional status as a patient-oriented dialysis (POD) system [76]. We have two basic tests in the POD system: the POD sheet, which evaluates the QOL of the dialysis patient, and the malnutrition inflammation score sheet originally composed by Kalantar-Zadeh *et al.* [77], which evaluates the nutritional status of the patient. On the POD sheet, 20 dialysis-related or daily symptoms and feelings are evaluated by a four-grade scoring system (Table 3). If any problems are observed in these two tests, dialysis prescriptions and nutritional approaches are changed to monitor the target symptom. Under this therapeutic concept, >90% of our patients have been treated by protein-permeable membranes such as EVAL, PMMA and PAN membranes and predilution online HDF. Uremic skin itchiness is one of the most frequent symptoms and is occasionally accompanied by sleep disturbance, which have both been recognized as a mortality risk factors [71, 72]. The prevalence of more than moderate itching was reported to be relatively high, at 40–50% [72], but only 15% of patients complained about itching in our facilities [76]. The prevalence of sleep disturbances rated as poor or bad sleep was 18% [76],

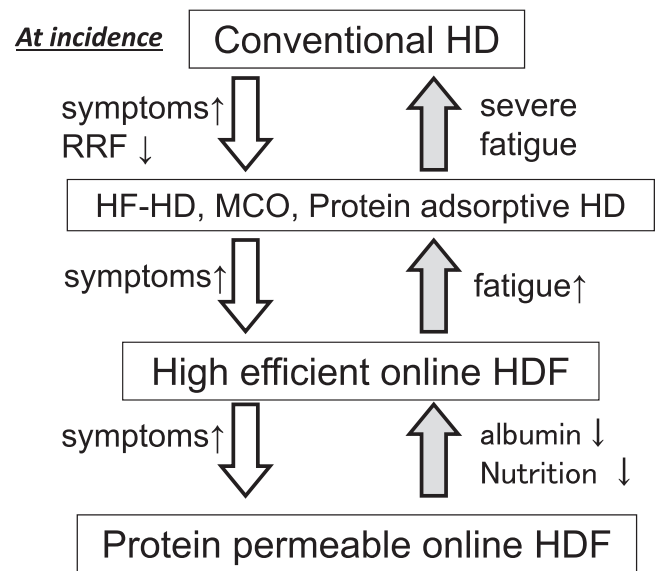


FIGURE 4: Daily practice patterns for dialysis prescription [34]. HF-HD, high-flux hemodialysis; RRF, residual renal function.

and was one-third less frequent than the result in the dialysis outcomes and practice patterns study [71]. In our practice pattern, the total amount of albumin leakage is one of the most important parameters for dialysis prescription. If a patient has serious symptoms such as restless legs syndrome or itchiness, we modify the dialysis prescription to online HDF or protein absorptive HD. First, we recommend the patient extend the dialysis time without changing the dialysis modality or membranes. Second, we start protein-permeable dialysis with mild albumin leakage set as 1–3 g/session and monitor the changes of the targeted symptom. If the symptom does not improve, we increase the albumin leakage by changing membranes. When obvious hypoalbuminemia occurs, we attenuate the albumin leakage again [34] (Figure 4).

The POD system is one of the platforms of person-centered care or patient-centered medicine and especially focuses on chronic dialysis patients. There have been several

Table 3. Questionnaire items on the POD sheet

Questions	Grading (score)
Symptoms in daily life	
1. Do you have any pains in your joints?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
2. Do you have skin itchiness?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
3. Do you have irritability?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
4. Do you have fatigue?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
5. Do you have palpitations or shortness of breath?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
6. Are you constipated?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
7. Do you fall asleep just after you go to bed?	Always (0), frequently (1), sometimes (2), rarely (3), no (4)
8. Do you have comfortable sleep until the morning?	Always (0), frequently (1), sometimes (2), rarely (3), no (4)
Symptoms related to dialysis	
9. Do you have any pains during cannulation?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
10. Do you get headache around your dialysis session?	No (0), rarely (1), sometimes (2), frequently (3), always (4)
11. Do you have painful hypotension during your dialysis session?	No (0), rarely (1), sometimes (2), frequently (3), always (4)
12. Do you have muscle cramps during your dialysis session?	No (0), rarely (1), sometimes (2), frequently (3), always (4)
13. Can you get up from your bed just after your dialysis session?	Quickly possible (0) to need a long time (4)
Dietary life	
14. Do you have an appetite?	Always (0), frequently (1), sometimes (2), rarely (3), no (4)
15. Do you enjoy your meals?	Always (0), frequently (1), sometimes (2), rarely (3), no (4)
16. Do you have thirst?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
17. Do you have any difficulties with your dietary life?	No (0), somewhat (1), moderate (2), very much (3), extreme (4)
Feelings	
18. Do you have any depressive feelings?	No (0), yes (4)
19. Are you motivated?	Yes (0), no (4)
20. Are you satisfied with life?	Very much (0) to not at all (4)

comprehensive assessment tools for the QOL of dialysis patients, however, there are no tools except for the POD system that directly link the QOL of dialysis patients to the practice patterns for dialysis prescription. The POD system could ameliorate the QOL of dialysis patients and finally improve their survival rates. Furthermore, it may also encourage the maturation of patient-centered care in the chronic dialysis field.

CONCLUSIONS

Aggressive removal of middle molecules or larger LMWPs has been a growing concern due to their toxic effects with regard to the development of complications and the deterioration of survival rates. However, membrane pore size-dependent removal, such as the use of HCO membranes, increases the risk of massive albumin leakage during a dialysis session. MCO membranes, predilution HDF by HCO membranes with high substitution volumes and postdilution HDF by MCO membranes with lower substitution volumes are recommended to remove larger LMWPs without massive albumin leakage. Nevertheless, even with all of these efforts we cannot remove all PBUTs, but protein adsorptive membranes are useful to reduce some PBUTs as well as middle molecules.

The performance of dialysis therapy is usually evaluated by solute removal, and the quality of dialysis therapies should be evaluated by clear outcome studies such as randomized control trials (RCTs). However, there have been few studies that have evaluated the relationship between solute-removal properties and clinical outcome. If we design an RCT of a certain intervention with mortality as the primary outcome, recruitment of a huge number of subjects and long follow-up periods are needed to eliminate various confounding factors, and this will also require a large budget. As previously postulated, some dialysis-

related symptoms are good surrogate markers of dialysis quality, and the improvement of these symptoms could directly improve the QOL of dialysis patients. Further studies evaluating the relationship between middle molecule or PBUT removal and the improvement of patient symptoms should be performed in well-designed RCTs.

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