

REVIEW

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Development of online hemodiafiltration in Japan

Hideki Kawanishi*

Abstract

Evidence concerning online hemodiafiltration (ol-HDF) includes increased uremic toxin removal, prevention of dialysis-related hypotension, improved survival, and recovery of dialysis-related uncertain symptoms. In particular, evidence has been shown regarding prevention of dialysis hypotension and improvement of survival, but the mechanism of its manifestation is still unclear and its effects themselves are questionable. In Japan, pre dilution ol-HDF is mainly performed, and improvement in survival rate has been shown on the condition of convection volume is 40 L/session or more. In particular, the removal of α 1-microglobulin (α MG), which is a medium-middle solute, is targeted. The antioxidant action (Heme Scavenger) of α MG, is presumed, but in dialysis patients, the majority in serum are deteriorated (oxidized) α MG. It has been pointed out that removing the deteriorated α MG by ol-HDF may produce new α MG from the liver and lead to recovery of the original antioxidant effect. However, clinical evidence of this mechanism is desired. Obtaining evidence for the indicated α MG removal activity of ol-HDF will lead to advancement in HDF.

Keywords: Online HDF, Middle molecule, Convection volume, α 1microglobulin, Mortality

Background

Hemofiltration (HF) and hemodiafiltration (HDF) are used for the removal of middle molecular (MM) solutes of approximately 1 kDa molecular weight (MW) per the middle molecular hypothesis that was proposed in the 1970s [1, 2]. HF is a method of dialysis therapy in which transmembrane pressure is applied to the filter and solutes are removed as a filtrate by convection, and the same volume of substitution fluid is added. HF simulates the glomerular function in the kidney and is effective for removing even large solutes. In addition, HF avoids the risk of disequilibrium syndrome as there are no acute changes in blood osmolarity. However, since the so-called renal tubular function is absent, the electrolyte and acid–base balance are adjusted by administering substitution fluid containing electrolytes and alkaline agents. Therefore, a strict balance between the convection volume

and substitution fluid volume is required. In particular, replacement with a large volume of fluid is necessary to obtain solute removal effects.

Thus, HF is excellent in removing middle to large solutes, but small solute removal comparable to that using hemodialysis (HD) is difficult using convection alone. Therefore, to improve small solute removal, dialysis (diffusion) is included in HDF [3–7]. In general, in HDF, the convective flow is lesser than the dialysate flow, which tends to lead to the misunderstanding that HF is added to compensate for the low removal ability of HD. However, considering the development process of HDF, it should be understood that HD is added to achieve the adequate removal of small solutes. Thus, HF was developed first, and HD was incorporated into it, resulting in HDF establishment. However, in basic HDF, the dialysate flow rate is 500–700 mL/min, which is the same as in HD. Therefore, in terms of efficiency, HDF represents the addition of HF to conventional HD. As a result, small solutes are rapidly removed, but the prevention of disequilibrium syndrome as the effect of HF cannot be expected.

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A large amount of substitution fluid is required for stable large filtration HF/HDF. However, there is a limitation to the offline (bottle/back) method, and thus online HDF (ol-HDF) using a substitution fluid of aseptic/endotoxin-free membrane separation technology was developed [3]. Currently, ol-HDF is generally replaced with 15–26 L (50–100 mL/min) for post-dilution and 24–72 L (100–300 mL/min) for pre-dilution, and it is high enough to obtain sufficient amount of substitution fluid. Increasing the blood flow rate and total dialysate volume is necessary to compensate for the decrease in actual dialysate volume. Therefore, HF is clinically useful for dialysis-related distress syndromes, while the effects of HDF are due to improvement in removal efficiency. However, this increased removal efficiency does not produce adequate clinical differences when dialyzers themselves are highly efficient, and this aspect is important when evaluating the clinical significance of HDF.

A new concept of middle molecule solute

MM removal seems to begin with the following statement by Scriber BH at the American Society for Artificial Organs (ASAIO) in 1965 [8]. “The patients feel better on less dialysis, there is a chance that because the peritoneal membrane is leaky, we are removing with peritoneal dialysis certain higher molecular weight substances more efficiently than with hemodialysis,suggesting that we need a leaky membrane for a hemodialyzer”. After that, the significance of MM was established by the “square meter-hour hypothesis [1]” and the “middle molecular hypothesis [2]” by Babb AL.

MM has been expanded to show an MW of ≥ 0.5 kDa represented by β 2-microglobulin (β MG) in recent years. Furthermore, with the development of dialyzer and advancements in HDF, further large molecular solutes can be included in MM. In a recent review,

MM was defined as a solute that passes through the glomerulus, with a MW of 0.5–58 kDa, which is the limit of glomerular filtration, and following revisions in MM classification were proposed “small-middle 0.5–15 kDa,” “medium-middle >15–25 kDa” and “large-middle >25–58 kDa” (Fig. 1) [9]. In the future, the selection of blood purification therapy will follow this classification.

Pre-dilution ol-HDF (pre-ol-HDF) and post-dilution ol-HDF (post-ol-HDF)

In HDF, the removal characteristics differ depending on the dilution method. In post-ol-HDF, as the convection volume (CV) increases, the removal of small-to-large molecular solutes increases concurrently. When targeting small-MM solutes such as β MG (12 kDa), post-ol-HDF using a dialyzer with low protein leakage is effective. However, for a medium MM solute (for example, α 1-microglobulin [α MG], 33 kDa), a protein-leakage hemodiafilter must be used. However, it is difficult to separate albumin and α MG on post-ol-HDF due to the excessive albumin leakage. In such cases, pre-ol-HDF that can separate albumin and α MG can be selected. Although the biological activity of α MG itself is not yet clear. In Japan, pre-ol-HDF using a protein leakage hemodiafilter to increase the removal efficiency up to α MG has become the mainstream. On the other hand, in Europe, post-ol-HDF using a dialyzer with non-protein leakage to increase the efficiency of removing the MW up to β MG is the mainstream, for which uremic substance has been established as evidence. An increase in blood flow rate is essential for increasing CV in post-ol-HDF, and 300–400 mL/min is common in Europe. In Japan, blood flow rate is < 300 mL/min (average 250 mL/min), which is also one reason for choosing pre-ol-HDF (Fig. 1).

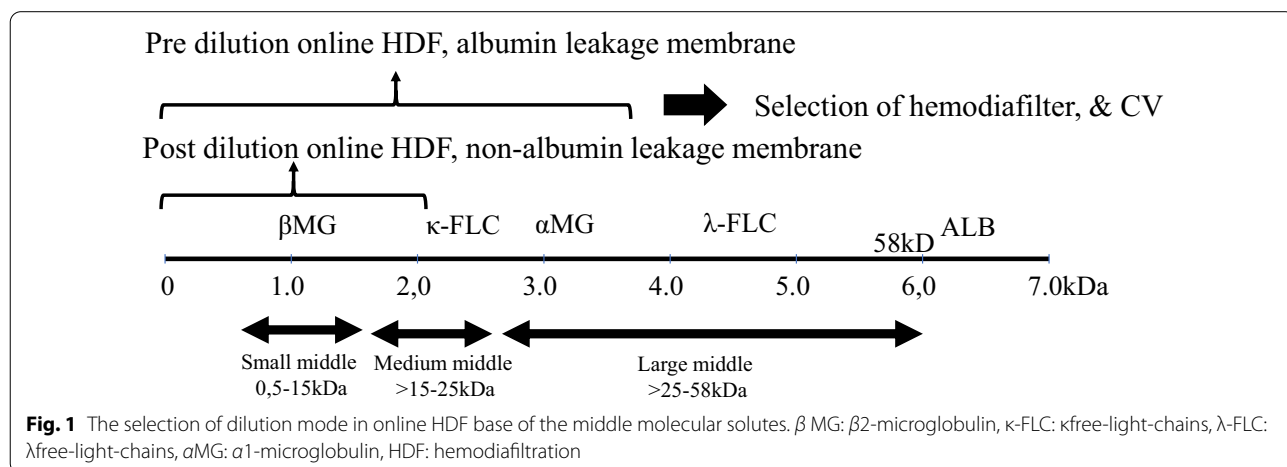


Fig. 1 The selection of dilution mode in online HDF base of the middle molecular solutes. β MG: β 2-microglobulin, κ -FLC: κ free-light-chains, λ -FLC: λ free-light-chains, α MG: α 1-microglobulin, HDF: hemodiafiltration

Clinical effects of HDF

ol-HDF was developed to remove MM substances that cannot be completely removed using HD. Furthermore, substitution fluid is free from bacteria/endotoxins, and its source, dialysis fluid, should be ultrapure; this requirement may be achieved through the purification of dialysis fluid. Dialysis fluid purification has demonstrated several clinical effects, including reducing anemia, preventing dialysis-related amyloidosis, maintaining residual kidney function, improving nutritional status, and relieving dialysis-related hypotension, have been demonstrated [10–14].

Recent evidence has focused on increasing removal efficiency, preventing dialysis-related amyloidosis, hypotension, improving survival, and improving dialysis-related indefinite complaints. These effects may be additively exhibited through an ol-HDF-related increase in the removal efficiency. However, it is difficult to indicate the effects separately. Furthermore, the presence or absence of synergistic effects remains to be clarified [15]. The clinical effects and mortality according to symptom (observational study and randomized controlled trial [RCT]) are shown in Table 1 and Table 2, respectively.

Prevention of dialysis-related amyloidosis has been established [16, 17]. However, mechanisms underlying the prevention of dialysis-related hypotension and survival improvement are still not clear. Furthermore, the effects of HDF are debatable [18].

One clinical effect of HDF is the prevention of dialysis-related hypotension. However, the volume of dialysate during HDF is larger than the amount of substitution fluid; therefore, the stabilization mechanism of circulatory dynamics observed in HF cannot be applied. This has been studied since the introduction of HDF. A recent study reported that dialysis-related hypotension could be reduced with pre-ol-HDF as well as pre HF [19]. Another study indicated that this effect occurred with post-ol-HDF [20]. RCTs and meta-analyses have proved the prevention of dialysis-related hypotension through ol-HDF [21]. However, although the Gibbs-Donnan effect [18] and low-temperature dialysis effect [22] was speculated, the mechanisms are not clear. Recently, Smith et al. conducted a randomized crossover study of high-flux HD (HFHD) and post-ol-HDF (CV 20 L) involving 100 subjects following a blinded method and found no difference in recovery time after dialysis and significantly more

Table 1 Clinical effect of HDF, symptoms

Study [Ref]	Study design	Modality/number	Results
<i>Dialysis related amyloidosis (DRA)</i>			
Locatelli [16], Lombardy/Italy	Prospective observation	HDF (HF) versus LFHD:1082/6298,	DRA:42.2%r reduction, Mortality:ns
Nakai [17], Japan	Retrospective observation	HDF 77 versus LFHD (total 1192)	DRA 97% reduction $P < 0.0001$
<i>Dialysis related hypotension (DRH)</i>			
Locatelli [19], Italian study	RCT	Pre-ol-HF/HDF versus LFHD: 150/75/75	DRH 54% reduction
ESHOL study [20], Catalonian/Spain	RCT sub-analysis	Post-ol-HDF versus HFHD: 450/456	DRH 28% reduction
Donauer [22], Germany	Crossover,, single center	Post-ol-HDF versus Cool HD: 25 session	DRH: prevention as same as post-ol-HDF & Cool HD
Smith [23], Glasgow/UK	Crossover, blind, single center	Post-ol-HDF versus HFHD: 50	Recovery time: longer DRH:52% higher
<i>Anemia</i>			
Locatelli [36], Italian study	RCT sub-analysis	Pre-ol-HF/HDF versus LFHD: 150/75/75	ns
Pedrini [37], Italy, Czech, Slovenia,	Retrospective cohort	mixed dilution HDF versus post-ol-HDF; 87/87	Mixed HDF:Hgb up ($p = 0.0124$)
<i>Quality of life (QOL)</i>			
Karkar [38], Saudi Arabia	RCT	Post-ol-HDF versus HFHD:32/32	Better
<i>Restless legs syndrome (RLS)</i>			
Sakurai 2013 [45], Japan	Retrospective, observation	Pre-ol-HDF 17	RLS prevention: α MG removal rate > 35%
<i>Inflammation</i>			
Ariza [34], Spain	Crossover study	HFHD versus post-ol-HDF versus mid-dilution HDF:12	HDF: decrease CD14, CD16, monocyte
Dutch CONTRAST [35], The Netherlands	RCT sub-analysis	Post-ol-HDF versus LFHD: 356/358	Decrease CRP

HDF, hemodiafiltration; LFHD, low flux hemodialysis; HFHD, high flux hemodialysis; post ol-HDF, post dilution online HDF; pre-ol-HDF, pre dilution online HDF

Table 2 Clinical effect of HDF, mortality

Study [Ref]	Study design	Modality/number	Results
<i>Observation study</i>			
Canaud [24] (Euro-DOPPS-1) Germany, France, Italy, Spain, UK	Prospective observation	LFHD 1366 (63%), HFHD 546(25.2%) Low-HDF 156 (7.2%) High-HDF 97 (4.5%)	High-HDF versus LFHD: mortality reduction 35%
Panichi [25] (RISCAVID), Italy	Prospective observation	LFHD 424 (56%) ol-HDF 129 (17.7%) off-HDF 204 (27%)	ol-HDF versus LFHD: mortality reduction 22%
Vilar [26], UK	Retrospective	HFHD 626 ol-HDF 232(27%)	ol-HDF versus HFHD: mortality reduction 34%
European Clinical Database (EUCLID) [27], Czech, France, Italy, Portugal, Romania, Spain, Turkey	Retrospective	Post-ol HDF CV < 54.6L/wk versus > 64.8L/wk: 204/204	CV > 70.1 L/wk: survival 64% increase Survival and CRP/ β 2MG reduction depend on CV
Euro-DOPPS [31] (DOPPS-4,5), Sweden, France, Belgium, Italy, UK, Spain, Germany	Prospective observation	Post-ol-HDF versus HD: 2012/6555	ns
Kikuchi [32], JRDR, Japan	Retrospective	Pre-ol-HDF \geq 40L session versus < 40L & HD: 2548/2424/5000	Pre-ol-HDF \geq 40L: mortality reduction 29.1%
<i>Randomized controlled trial (RCT)</i>			
Dutch CONTRAST [28], The Netherlands	RCT	Post-ol-HDF versus LFHD: 356/358	ns, higher CV (> 21.95L): reduction 38%
Turkish study [29], Turkey	RCT	Post-ol-HDF versus HFHD: 391/391	ns, higher CV (> 17.4L): mortality reduction 46%
ESHOL study [20], Spain	RCT	Post-ol-HDF versus HFHD: 450/456	Mortality Reduction 30%, higher CV (23-25L): 40%, CV (> 25L): 45%
French study [30], France	RCT	Post-ol-HDF versus HFHD, > 65y.o: 190/191	ns

HDF, hemodiafiltration; LFHD, low flux hemodialysis; HFHD, high flux hemodialysis; post-ol-HDF, post dilution online HDF; pre-ol-HDF, pre dilution online HDF; CV, convection volume

dialysis hypotension with HDF [23]. The fact that the superiority of HDF was denied in a strict crossover study such as this is an objection to the prevention of dialysis-related hypotension.

To overcome the limitations of previous observation studies [24–27] for survival, large RCTs have been conducted in Europe, such as the Dutch CONTRAST [28] (comparison between post-ol-HDF and low flux HD [LFHD]), the Turkish Study [29], the ESHOL study [20], and the French study [30] (the latter three compared post-ol-HDF and HFHD). These RCTs showed similar results, indicating that post-HDF with high-CV have a favorable influence on survival rates. However, a high blood flow rate is essential for obtaining a high CV with post-ol-HDF, suggesting that survival rates were good when a high blood flow rate could be obtained.

A recent clinical study involved an analysis of survival with HDF using Euro-DOPPS 4–5 [31]. Unlike the study using Euro-DOPPS 1 [24], the superiority of HDF was not shown. However, as the research and analysis styles were comparable, the effects of HDF on survival are not established.

In Japan, pre-ol-HDF is used for 90% of patients. Therefore, the Japanese Renal Data Registry (JRDR)

compares the 1-year prognosis of pre-ol-HDF and HD using the propensity score-matched method based on the national database [32]. Pre-ol-HDF with a higher CV (\geq 40 L) decreased all-cause mortality and cardiovascular diseases (CVD) mortality unlike HD or HDF with a small CV. These RCTs and observational studies have shown the efficacy of ol-HDF for survival, but its superiority is small. The hazard ratio (HR) in the “pooled individual participant data analysis,” which was analyzed by combining all the cases of CONTRAST, Turkish Study, ESHOL study, and French study, was 0.86 (CI 0.75–0.99), which is close to 1.0 [33].

Factors of clinical efficacy of ol-HDF include improving dialysis-related indefinite complaints. In particular, it is expected to be effective for restless legs syndrome (RLS), pruritus, inflammation control, and quality of life (QOL).

Regarding inflammation control in ol-HDF, in a crossover study by HFHD and post-ol-HDF/mid-dilution HDF, ol-HDF reduced the expression of CD14, CD16 on the surface of monocyte and decreased endothelial microparticles [34]. In addition, Dutch-CONTRAST [35] and EUCLID study [27] also showed a decrease in C-reactive protein (CRP) levels. Therefore, it can be inferred that

ol-HDF led to controlled inflammation and improved survival rate.

The effect of HDF on improving anemia has also been discussed. It was denied in the sub-analysis of the Italian study by Locatelli et al. [36]. In a recent comparison between post-ol-HDF and mixed-ol-HDF, mixed-ol-HDF showed an increase in hemoglobin [37], but the mechanism is unclear.

Regarding QOL, an RCT from Saudi Arabia migrated patients controlled by low flux HD (LFHD) to HFHD or ol-HDF using the same dialyzer, and ol-HDF not only has good solute removal but also well QOL evaluated by KDQOL-SF [38].

Based on the evidence of the clinical effects of HDF, the guidelines prepared by the Japanese Society for Dialysis Therapy (JSDT) also recommend the following: "HDF should be considered as a measure against indefinite complaints (itchiness, arthralgia, malaise, loss of appetite, etc.) and dialysis-related hypotension in patients who do not improve HFHD" [39].

Japanese online HDF

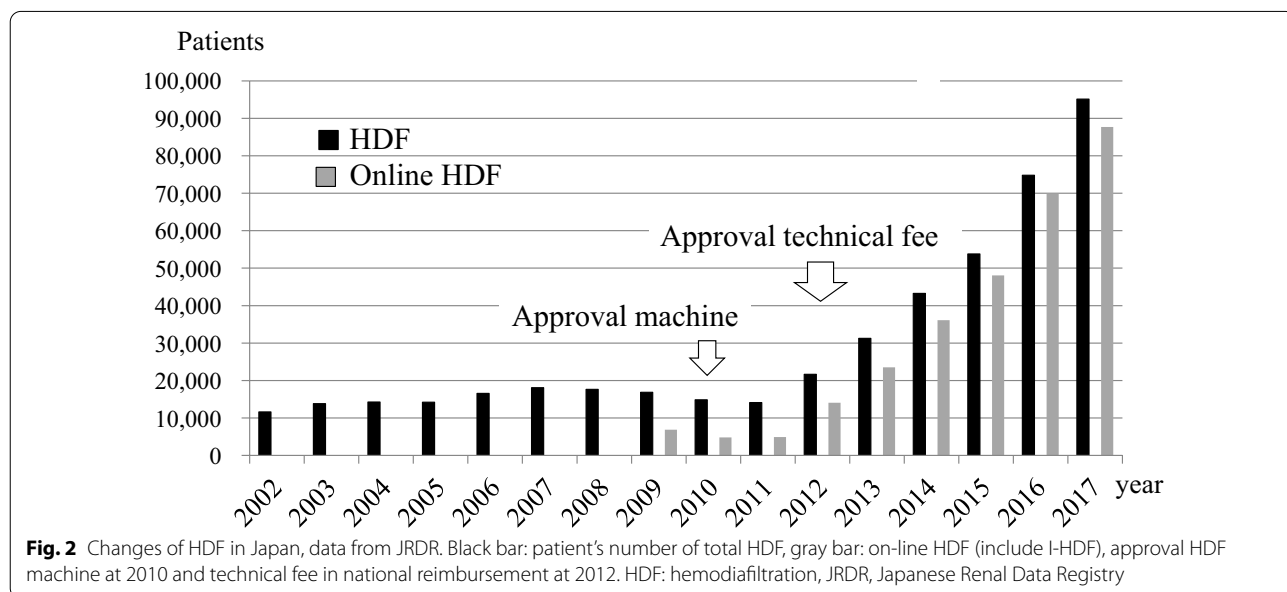
Canaud et al. reported on the "Global trends in HDF," which shows that Japan has the highest HDF patients as of 2017 [40].

Although in Japan, ol-HDF started in 1993, concerning payment for medical services, inaccurate circumstances persisted [15]. At the beginning of 2010, an ol-HDF machine for a central dialysis fluid delivery system was approved as a multi-purpose dialysis system, thus ol-HDF became a general procedure in dialysis therapy. After the revision of the reimbursement for medical services in

2012, a technical fee for ol-HDF was newly established and separated from off-HDF. This was the first time a technical fee was established for ol-HDF in the world. Furthermore, as a facility requirement, the "maintaining dialysis fluid quality [41]" was added. In particular, it became possible to maintain dialysis fluid quality in all patients (including those undergoing HD) in facilities in which the ol-HDF system is maintained. Moreover, the use of an approved "hemodiafilter" is required for ol-HDF to be reimbursed. Furthermore, there are no restrictions on indications in terms of medical fees, and it can be used for all dialysis patients. Since then, the number of HDF patients has increased rapidly, reaching 144,717 (43.5% of HD patients) at the end of 2019 (Fig. 2). In particular, ≥ 90% of ol-HDF is pre-ol-HDF. The reasons why pre-ol-HDF became mainstream in Japan are as follows: (1) Relatively low blood flow (average 224 mL/min) [42] and failure to achieve high CV post-ol-HDF; (2) Since the target substance to be removed was α1MG with a MW of 33 kDa, a protein leakage hemodiafilter was used to measure the separation of albumin and α1MG. Recently, use of post-ol-HDF has been gradually increasing.

What is α1-microglobulin, a recent topic about HDF in Japan?

There are many reviews on the clinical effects of HDF [18, 40, 43]. A recent topic is the improvement of survival by higher CV in Europe [20, 27–30, 33]. In addition, many studies suggest that post-ol-HDF improves survival proportional to the increase in CV (>18–24 L) [40]. However, although the amount of CV is shown in these studies, the target solute removal is not shown.



Therefore, the theoretical relationship between the survival and the increase of solute removal is unclear. Also, the upper limit of the CV is not presented.

Pre-ol-HDF in Japan specifically aims to remove α MG, and Sakurai et al. reported that achieving high efficiency of α MG removal rate of ≥ 35 –40% resulted in improvement of RLS [44]. Therefore, it is clinically significant that this target has been determined. At present, the goal is to set therapeutic conditions that maximize the removal of α MG while suppressing albumin leakage (≤ 5 g/session). Sakurai et al. [45], showed that an excessive increase in the removal volume can be obtained even with a slight increase in the removal rate in the higher removal rate region (Fig. 3). Furthermore, according to the JRDR, a pre-ol-HDF with a ≥ 40 L substitution fluid volume improved the 1-year survival rate. The substitution fluid volume that most contributed to the survival rate was 50.5 L pre-ol-HDF, which is the prognosis of survival [32]. It was shown that a U-shaped curve is estimated in relation to the amount of substitution fluid. Sakurai et al. also showed that high-efficiency HDF releases the platelet surface marker CD62P, suggesting the stress on blood cell components [46]. From this result, the conditions of blood flow 250–300 mL/min and substitution fluid volume 200–240 mL/min (48–58 L/session) are recommended for pre-ol-HDF in Japan (Table 3). However, the

Table 3 Characteristics of standard online HDF in Japan

Pre-dilution online HDF
Blood flow rate: 200–250 mL/min
Substitution fluid volume: 48–60L/session
Dialysate flow: 500–600 mL/min
Dialysis time: 4–5 h
Hemodiafilter: protein leakage member
Mainly central dialysate delivery system
Target removal rate of α MG 35–40% and β MG 80%

functions of α MG are not clear, and until recently, it was regarded as a marker for MM.

One of the founders of ol-HDF in Japan, Kim ST, explained the significance of α MG removal [47]. In serum, the ratio of free form and high molecular IgA bound form α MG is almost same, and the target of removal is about 50% free form α MG. Therefore, the removal rate per HDF is limited to 60%. As its physiological function, both cell differentiation inhibitory action and antioxidant action (Heme Scavenger) [48, 49] are presumed. Nevertheless, in dialysis patients, the serum concentration α MG is more than ten times higher than normal, and most of them are deteriorated (oxidized)

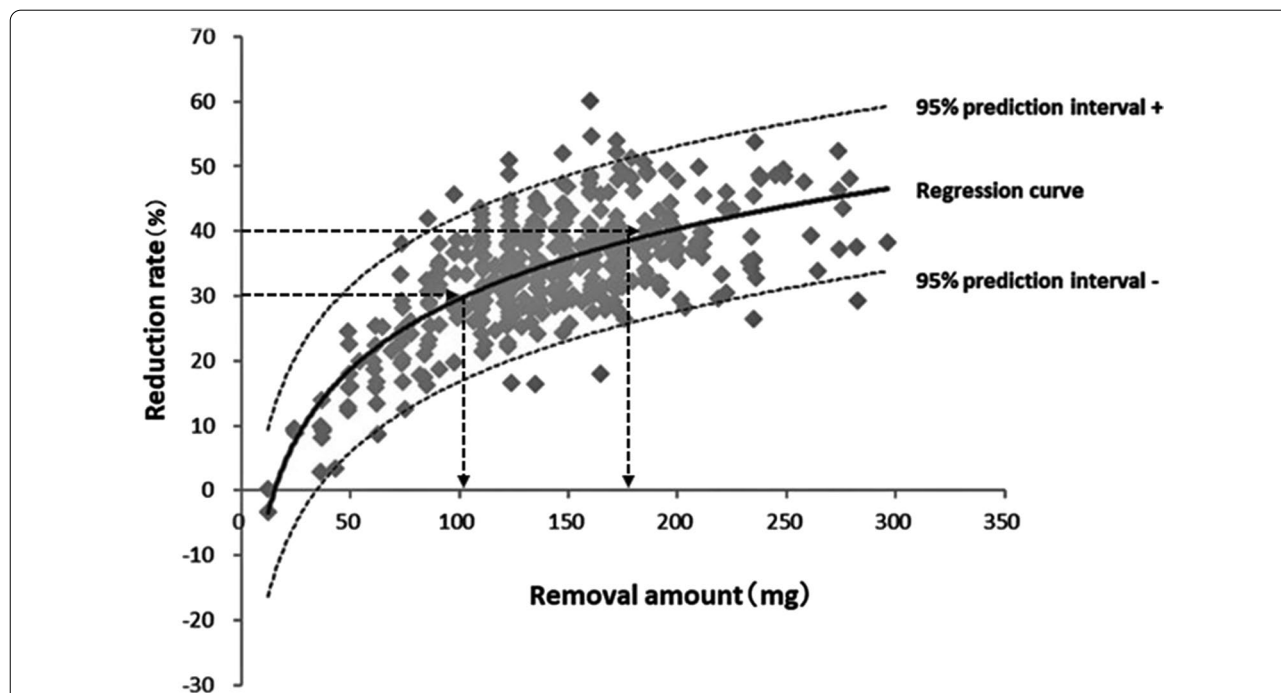


Fig. 3 Relationship between α 1-microglobulin removal rate (%) and removal volume (mg). Modified reference 45, Fig. 3, Sakurai K et al., *Renal Replacement Therapy* 2021 with consent from the author. This graph shows that an excessive increase in the removal volume (mg) can be obtained even with a slight increase in the removal rate (%) in the higher removal rate region

α MG. Therefore, it is presumed that the turnover is also suppressed. It has been suggested that removing the deteriorated α MG through HDF may produce new α MG from the liver and aid recovery of the original antioxidant effect (Fig. 4). However, clinical evidence of this mechanism is required.

A prospective observational cohort study “Japanese Study of the effects of α MG (α 1-microglobulin) reduction rates on the survival, complications, and prognosis in dialysis patients (JAMREDS)” has been started to prove the clinical efficacy of α MG removal, led by the Japanese Society for HDF (Fig. 5) [50]. This study includes 4000 uncomplicated outpatients with HD at a registered facility for 3 years to examine the relationship between α MG removal rate and prognosis. The dialysis modality includes all HD and HDF. It is expected that the relationship between MM removal efficiency and prognosis will be clarified by investigating the prognosis of dialysis patients and CVD events.

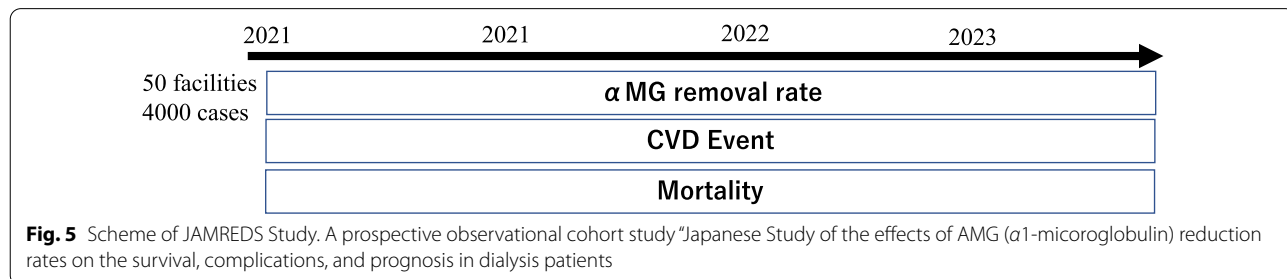
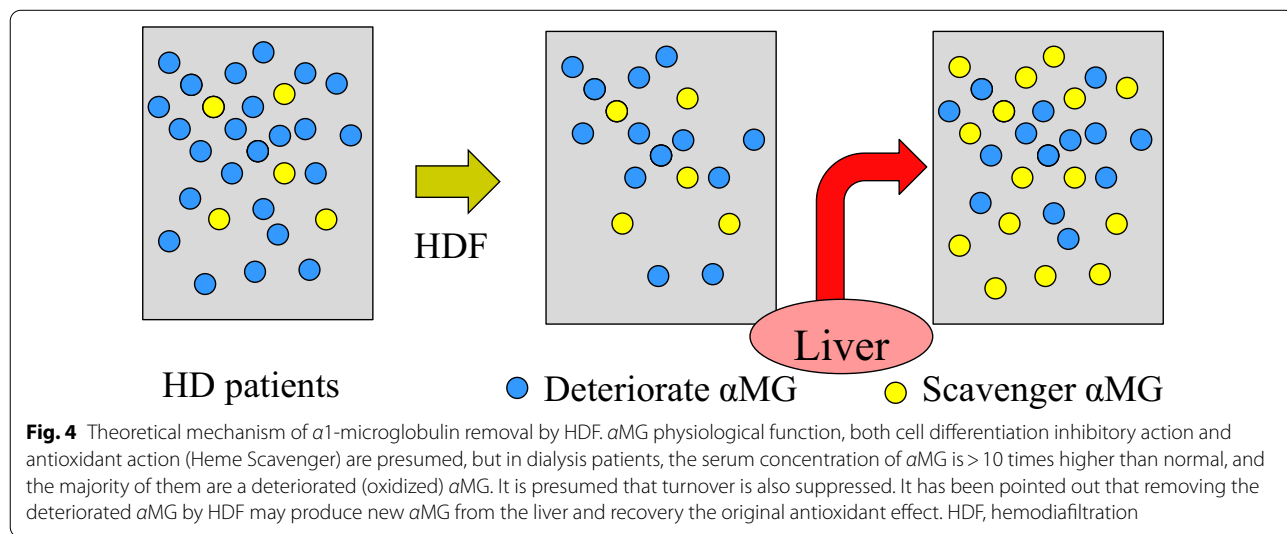
Intermittent Infusion Hemodiafiltration (I-HDF)

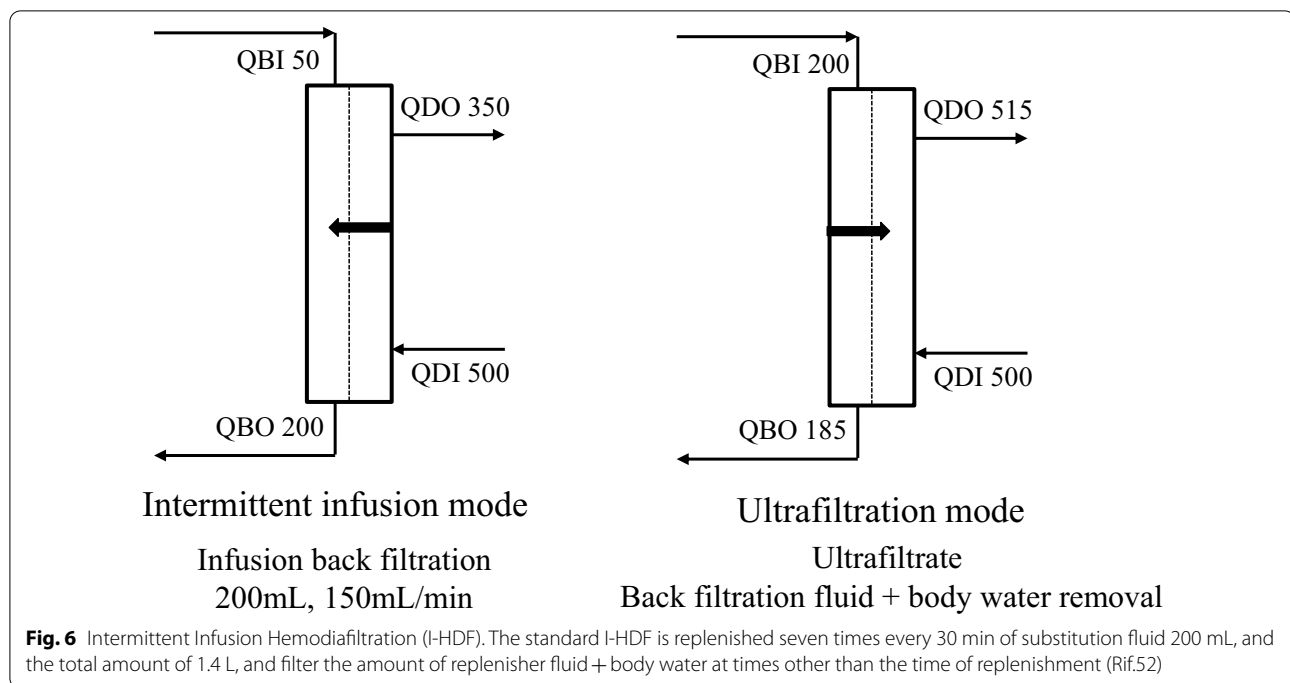
I-HDF was developed in Japan as a division of ol-HDF and accounted for about 27% of ol-HDF. It is mainly

positioned to prevent complications, i.e., dialysis related-hypotension and correcting peripheral circulatory disorders by HD itself [51, 52].

By systematically replenishing the blood side with purified dialysate or substitution fluid, blood pressure can be maintained by suppressing hypovolemia due to body water removal, and plasma refilling rate (PRR) can be achieved by improving peripheral circulation. Furthermore, it is thought to be effective in reducing the number of treatments for hypotension during HD by increasing the amount and promoting the movement of fluid from the interstitial space to the blood vessels.

I-HDF using back-filtration and replenished ultrapure dialysate through the membrane can suppress the gradual decrease in membrane performance. The standard I-HDF is replenished seven times every 30 min of substitution fluid 200 mL, and the total amount of 1.4 L, and filter the amount of replenisher fluid + body water at times other than the time of replenishment (Fig. 6). It is positioned as an ol-HDF for a small amount of replacement. Although ol-HDF has been shown to prevent dialysis-related hypotension, further studies are needed to clarify its other effects.





Conclusions

Evidence of the effectiveness for ol-HDF is gradually accumulating. Although dialysis amyloidosis has been established, the prevention of dialysis-related hypotension and dialysis-related indefinite challenges remains unclear. Moreover, the apparent benefit for survival has not yet been determined. The prescription of ol-HDF varies from country to country and each facility, including the selection of hemodiafilter. Obtaining sufficient evidence for α MG removal by ol-HDF will lead to further advancement in HDF.

Abbreviations

α MG: α 1-Microglobulin; β MG: β 2-Microglobulin; CRP: C-reactive protein; CVD: Cardiovascular diseases; DRA: Dialysis related amyloidosis; DRH: Dialysis related hypotension; HD: Hemodialysis; HFHD: High flux Hemodialysis; HF: Hemofiltration; HDF: Hemodiafiltration; I-HDF: Intermittent infusion hemodiafiltration; JRDR: Japanese Renal Data Registry; LFHD: Low flux hemodialysis; MW: Molecular weight; MM: Middle molecular; ol-HDF: Online hemodiafiltration; off-HDF: Offline hemodiafiltration; pre-ol-HDF: Pre-dilution online hemodiafiltration; post-ol-HDF: Post-dilution online hemodiafiltration; QOL: Quality of life; RCT: Randomized controlled trial; RLS: Restless legs syndrome.

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Authors' contributions

HK contributed to the intellectual discussion during manuscript drafting, revision, and the approval of the final version.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The author declares that they have no competing interests.

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