Development of online hemodiafiltration in Japan

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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 α1-microglobulin (αMG), which is a medium-middle solute, is targeted. The antioxidant action (Heme Scavenger) of αMG, is presumed, but in dialysis patients, the majority in serum are deteriorated (oxidized) αMG. It has been pointed out that removing the deteriorated αMG by ol-HDF may produce new αMG 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 αMG removal activity of ol-HDF will lead to advancement in HDF.

Keywords: Online HDF, Middle molecule, Convection volume, α1-microglobulin, 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. However, since the so-called renal tubular function is absent, 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 less 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 β2-microglobulin (βMG) 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 βMG (12 kDa), post-ol-HDF using a dialyzer with low protein leakage is effective. However, for a medium MM solute (for example, α1-microglobulin [αMG], 33 kDa), a protein-leakage hemodiafilter must be used. However, it is difficult to separate albumin and αMG on post-ol-HDF due to the excessive albumin leakage. In such cases, pre-ol-HDF that can separate albumin and αMG can be selected. Although the biological activity of αMG itself is not yet clear. In Japan, pre-ol-HDF using a protein leakage hemodiafilter to increase the removal efficiency up to αMG 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 βMG 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).

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**Fig. 1** The selection of dilution mode in online HDF base of the middle molecular solutes. βMG: β2-microglobulin, κ-FLC: κ-free-light-chains, λ-FLC: λ-free-light-chains, αMG: α1-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 |
|-------------|--------------|----------------|---------|
| **Dialysis related amyloidosis (DRA)** | | | |
| Locattelli [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 $P<0.0001$ |
| **Dialysis related hypotension (DRH)** | | | |
| Locattelli [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 |
| **Anemia** | | | |
| Locattelli [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 ($p=0.0124$) |
| **Quality of life (QOL)** | | | |
| Karkar [38], Saudi Arabia | RCT | Post-ol-HDF versus HFHD:32/32 | Better |
| Restless legs syndrome (RLS) | | | |
| Sakurai 2013 [45], Japan | Retrospective, observation | Pre-ol-HDF 17 | RLS prevention: $\alpha$MG removal rate > 35% |
| **Inflammation** | | | |
| 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 | Decease CRP |

HDF, hemodialfiltration; LFHD, low flux hemodialysis; HFHD, high flux hemodialysis; post ol-HDF, post dilution online HDF; pre-ol-HDF, pre dilution online HDF
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 (≥ 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 micro-particles [34]. In addition, Duch-CONTRAST [35] and EUCLID study [27] also showed a decrease in C-reactive protein (CRP) levels. Therefore, it can be inferred that

| Study [Ref]                | Study design          | Modality/number                                                                 | Results                                                                 |
|---------------------------|-----------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Observation study          |                        |                                                                                |                                                                        |
| Canaud [24] (Euro-DOPPS-1) | Prospective observation | LFHD 1366 (63%), HFHD 546(25.2%)                                               | High-HDF versus LFHD: mortality reduction 35%                           |
| Panichi [25] (RISC-AVID)   | Prospective observation | LFHD 424 (56%) ol-HDF 129 (17.7%)                                                  | 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/β2MG 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 ≥ 40L session versus < 40L & HD: 2548/2424/5000                      | Pre-ol-HDF > 40L: mortality reduction 29.1%                             |
| Randomized controlled trial (RCT) |                        |                                                                                |                                                                        |
| 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, hemodialfiltration; 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.
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.

![Fig. 2 Changes of HDF in Japan, data from JRDR. Black bar: patient's number of total HDF, gray bar: on-line HDF (include I-HDF), approval HDF machine at 2010 and technical fee in national reimbursement at 2012. HDF: hemodiafiltration, JRDR, Japanese Renal Data Registry](image)
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 αMG, and Sakurai et al. reported that achieving high efficiency of αMG 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 αMG 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 functions of αMG 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 αMG removal [47]. In serum, the ratio of free form and high molecular IgA bound form αMG is almost same, and the target of removal is about 50% free form αMG. 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 αMG is more than ten times higher than normal, and most of them are deteriorated (oxidized)

### 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 αMG 35–40% and βMG 80% |

![Fig. 3 Relationship between α1-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.](image-url)
αMG. Therefore, it is presumed that the turnover is also suppressed. It has been suggested that removing the deteriorated αMG through HDF may produce new αMG 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 (α1-microglobulin) reduction rates on the survival, complications, and prognosis in dialysis patients (JAMREDS)” has been started to prove the clinical efficacy of αMG 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 αMG removal rate and prognosis. This study 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.

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**Fig. 4** Theoretical mechanism of α1-microglobulin removal by HDF. αMG physiological function, both cell differentiation inhibitory action and antioxidant action (Heme Scavenger) are presumed, but in dialysis patients, the serum concentration of αMG is > 10 times higher than normal, and the majority of them are a deteriorated (oxidized) αMG. It is presumed that turnover is also suppressed. It has been pointed out that removing the deteriorated αMG by HDF may produce new αMG from the liver and recovery the original antioxidant effect. HDF, hemodiafiltration

**Fig. 5** Scheme of JAMREDS Study. A prospective observational cohort study “Japanese Study of the effects of AMG (α1-microglobulin) reduction rates on the survival, complications, and prognosis in dialysis patients”
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 αMG removal by ol-HDF will lead to further advancement in HDF.

Abbreviations
αMG: α1-Microglubulin; βMG: β2-Microglobulin; CRP: C-reactive protein; CVD: Cardiovascular diseases; DRA: Dialysis related amyloidosis; DRH: Dialysis related hypotension; DRA: 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.

Acknowledgements
Not applicable.

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

Funding
None.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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

Received: 25 June 2021   Accepted: 16 September 2021
Published online: 02 October 2021

References
1. Babb AL, Popovich RP, Christopher TG, Scribner BH. The genesis of the square meter-hour hypothesis. Trans Am Soc Artif Intern Organs. 1971;17:81–91.
2. Babb AL, Ahmad S, Bergstrom J, Scribner BH. The middle molecule hypothesis in perspective. Am J Kidney Dis. 1981;1:46–50.
3. Henderson LW, Besarab A, Michaels A, Bluemle LW Jr. Blood purification by ultrafiltration and fluid replacement (dialfiltration). Trans Am Soc Artif Intern Organs. 1967;13:216–26.
4. Henderson LW, Sanfelippo ML, Beans E. ‘On-line’ preparation of sterile pyrogen-free electrolyte solution. Trans Am Soc Artif Intern Organs. 1978;24:465–7.
5. Henderson L. Current status of hemofiltration. Artif Organs. 1978;2(suppl):1–5.
6. Asaba H, Bergström J, Furst P, Lindh K, Mion C, Oulès R, et al. Sequential ultrafiltration and diffusion as alternative to conventional hemodialysis. Proc Clin Dial Transplant Forum. 1976;6:129–35.
7. Leber HW, Wizemann V, Goubeaud G, Rawer P, Schütterle G. Hemodiafiltration: a new alternative to hemofiltration and conventional hemodialysis. Artif Organs. 1978;2(suppl):408–11.
8. Scriber BH. Discussion. Trans Am Soc Artif Int Organs. 1965;11:29.
9. Rosner M, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, et al. Classification of uremic toxins and their role in kidney failure. Clin J Am Soc Nephrol. 2021. https://doi.org/10.2215/CIN.02660221.
Kawanishi H. Is there enough evidence to prove that hemodiafiltration is superior? Blood Purif. 2018;46:3–6.

Locatelli F, Alphei P, Andruilli S, Bolasco P, Sau G, Pedrini LA, et al. Hemodiafiltration and mortality in hemodialysis patients. Am J Nephrol. 2000;21:526–56.

Schiffl H, Lang SM, Fischer R. Ultrafiltration dialysis fluid slows loss of residual renal function in new dialysis patients. Nephrol Dial Transplant. 2002;17:1814–8.

Izuhara Y, Miyata T, Saito K, Ishikawa N, Nakamura T, Nangaku M, et al. Ultrafiltration dialysate decreases plasma pentosidine, a marker of 'carbonyl stress'. Am J Kidney Dis. 2004;43:1024–9.

Kawanishi H. What can we expect from on-line hemodiafiltration? Blood Purif. 2013;33(suppl 1):1–5.

Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D. Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. Kidney Int. 1999;55:286–93.

Nakah I, Iseki K, Tabei K, Kubo K, Masakane I, Fushimi K, et al. Outcomes of hemodiafiltration based on Japanese dialysis patient registry. Am J Kidney Dis. 2001;38(4 Suppl 1):S212–6.

Kawanishi H. Is there enough evidence to prove that hemodiafiltration is superior? Blood Purif. 2018;46:3–6.

Locatelli F, Alphei P, Andruilli S, Bolasco P, Sau G, Pedrini LA, et al. Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. Am J Nephrol. 2010;21:1798–807.

Maduell F, Moreso F, Pons M, Ramos R, Mora-Maciá J, Carreras J, et al. High-efficiency post-dilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol. 2013;24:487–97.

Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. Am J Kidney Dis. 2014;63:954–67.

Donauer J, Schweiger C, Rumberger B, Krumme B, Böhler J. Reduction of convective transport and endothelial dysfunction independently of the technique. Blood Purif. 2013;35(4):270–8.

den Hoedt CH, Bots ML, Grooteman MP, van der Weerd NC, Mazarach AH, Penne EL, et al. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. Kidney Int. 2014;86:423–32.

Locatelli F, Alphei P, Andruilli S, Sau G, Bolasco P, Pedrini LA, et al. Predictors of haemoglobin levels and resistance to erythropoiesis-stimulating agents in patients treated with low-flux haemodialysis, haemofiltration and haemodiafiltration: results of a multicentre randomised and controlled trial. Nephrol Dial Transplant. 2012;27:3594–600.

Pedrini LA, Zawada AM, Winter AC, Pham J, Klein G, Wolf M, et al. Effects of high-volume online mixed-hemodiafiltration on anaemia management in dialysis patients. PLoS ONE. 2019;22(14):e0212795.

Karkar A, Abdelrahman M, Locatelli F. A randomized trial on health-related patient satisfaction level with high-efficiency online hemodiafiltration versus high-flux dialysis. Blood Purif. 2015;40:84–91.

Watanabe Y, Kawanishi H, Suzuki K, Nakai S, Tsushima K, Tabei K, et al. Maintenance hemodialysis: hemodialysis prescriptions” Guideline Working Group, Japanese Society for Dialysis Therapy. Japanese Society for Dialysis Therapy clinical guideline for “Maintenance hemodialysis: hemodialysis prescriptions. Ther Apher Dial. 2015;19(Suppl 1):67–92.

Canaud B, Köhler K, Sichert JM, Möller S. Global prevalent use, trends and practices in hemodiafiltration. Nephrol Dial Transplant. 2020;35:398–407.

Mineshima M, Kawanishi H, Ase T, Kawasaki T, Tomo T, Nakamoto H. Update Japanese Society for Dialysis Therapy Standard of fluids for hemodiafiltration and related therapies. Renal Replacement Therapy. 2018;4:15. https://doi.org/10.1186/s41100-018-0155-x.

Nitta K, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, et al. Annual dialysis data report 2017, JSDT renal data registry. Renal Replacement Ther. 2019;5:53. https://doi.org/10.1186/s41100-019-0248-1.

Schiffl H. High-volume online haemodiafiltration treatment and outcome of end-stage renal disease patients: more than one mode. Int Urol Nephrol. 2020;52:1501–6.

Sakurai K. Biomarkers for evaluation of clinical outcomes of hemodiafiltration. Blood Purif. 2013;35(Suppl 1):164–8.

Sakurai K, Hosoya H, Kunihara Y, Saito T. Suitability of α₁-microglobulin reduction rate as a biomarker of removal efficiency of online hemodiafiltration: a retrospective cohort study. Renal Replacement Therapy. 2021;7:10. https://doi.org/10.1186/s41100-021-00326-y.

Sakurai K, Saito T, Yamachi F, Hosoya H, Kunihara Y, Kurosawa K, et al. Comparison of the effects of pre- and post-dialysis on-line hemodiafiltration on the cell surface and other inflammatory markers. Nephrol Dial Transplant. 2016;31(suppl 1):493.

KimST ArchivesRelease. https://www.youtube.com/user/KimSTArchivesRelase.

Magnum G, Olsson M, et al. Pathological conditions involving extracellular hemoglobin: molecular mechanisms, clinical significance, and novel therapeutic opportunities for alpha(1)-microglobulin. Antioxidants Redox Signal. 2012;17(5):813–45.

Krüttmann A, Bergwirth AL, Alattar AG, Flygare J, Gram M, Hansson SR, et al. Human radical scavenger α₁- microglobulin protects against hemolysis in vitro and α₁-microglobulin knockout mice exhibit a macrocytic anemia phenotype. Free Radic Biol Med. 2021;162:149–59.

JAMIRES Study. https://rtcportal.niph.go.jp/s/detail/um/trial_id=UMIN0038457.

Kovács Y, Aiko I, Hasegawa S, Osawa Y, Nakagawa Y, Iwabuchi F, et al. Feasibility of intermittent back-filtrate infusion hemodiafiltration to reduce intradialytic hypotension in patients with cardiovascular instability: a pilot study. Clin Exp Nephrol. 2017;21:324–32.
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52. Mineshima M, Takahashi S, Tomo T, Kawanishi H, Kawaguchi H, Minakuchi J, et al. A clinical significance of intermittent infusion hemodiafiltration using backfiltration of ultrapure dialysis fluid compared to hemodiafiltration: a multicenter randomized controlled crossover trial. Blood Purif. 2019;48:368–81.