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REVIEW ARTICLE

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Clinical performance, intermediate and long-term outcomes of high-volume hemodiafiltration in patients with kidney failure

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Abstract

Hemodiafiltration (HDF), in which both convective and diffusion methods are combined, yields an increased overall solute clearance compared with hemodialysis (HD), specifically for medium and larger molecular weight uremic toxins. Due to uncertainty in the treatment effects, the nephrology community still perceives the implementation of HDF and the achievement of high convective volume as complex. In this article, we review practical aspects of the implementation of HDF that can effectively deliver a high-volume HDF therapy and assure clinical performance to most patients. We also present an overview of the impact of high-volume HDF (compared to HD) on a series of relevant biochemical, patient-reported, and clinical outcomes, including uremic toxin removal, phosphate, Inflammation and oxidative stress, hemodynamic stability, cardiac outcomes, nutritional effects, health-related quality of life, morbidity, and mortality.

1 | INTRODUCTION

The expansion of dialysis into a form of long-term kidney-replacement therapy (KRT) has transformed nephrology. Dialysis performed with conventional diffusion methods, such as hemodialysis (HD), has improved quality of life and increased longevity of patients with end-stage kidney disease (ESKD) since its introduction in the 1960s and until recently was considered the standard form of KRT across the globe.[1] Hemodiafiltration (HDF), a technique that combines both convective and diffusion methods, yields an increased overall solute clearance with a broadened spectrum of solute removal for medium and larger molecular weight uremic toxins. The clinical benefits of HDF appear to be dependent on the achievement of high convective volume. The nephrology community still perceives the implementation of HDF and the achievement of high convective volume as complex; hence, the utilization of HDF varies across different countries. In this article, we review practical aspects of the implementation of HDF that can effectively deliver a high-volume HDF therapy and assure clinical performance to most patients. We also present an overview of the impact of high-volume HDF (compared to HD) on a series of relevant biochemical, patient-reported, and clinical outcomes.

Murilo Guedes and Robin W.M. Vernooij shared first author and contributed equally.

2 | PRACTICAL ASPECTS OF THE IMPLEMENTATION OF HIGH-VOLUME HDF

Patient and treatment-related factors are important to achieve high-volume HDF. It has long been debated that the benefit of higher convective volume achievement may reflect some degree of residual confounding, since healthier patients may successfully tolerate (and therefore achieve) higher convective volume.[2] Thus, patient-related factors—often non-modifiable—could be drivers of higher convective volume achievement and survival, rather than treatment-dependent factors. This perspective has been questioned by post-hoc analyses of

large randomized controlled trials (RCTs) comparing HDF to standard HD.[3] These studies report that achieved blood flow, rather than comorbidity status, age, vascular access type, and body mass index, is the most important predictor of convective volume achievement.[3] These findings suggest that modifiable treatment-related factors are essential determinants of improved outcomes in high-volume HDF.

Particularly, a stable vascular access and the right patient population are prime factors to ensure adequate blood flow and thus convective volume. High blood flow can be achieved in patients with arterio-venous fistulas, grafts, or permanent catheters, although catheters tend to provide lower and irregular flow rates. Vascular accesses with blood flows rates of 350–400 mL/min will be most likely successful in achieving the high convective volume associated with improved outcomes without the need to increase the dialysis treatment time.[4] Additionally, solute clearance in HDF depends on effective water flow, which varies inversely with blood viscosity. Hence, patients with hemoconcentration will achieve less solute clearance per unit of time under HDF. In a recent example, in the *Impact of Hemodiafiltration on Physical Activity and Self-Reported Outcomes (HDFit)*, which enrolled stable ESKD individuals, 99% of patients consistently achieved the target convective volume of 22 L/min, and the monthly mean achieved convective volume in the population varied from 27.1 L to 27.5 L through the 6-month follow-up period.[4] Mean achieved blood flows varied from 364 mL/min for AV fistula to 345 mL/min for permanent catheter, while median treatment time was 235 min across groups.

In sum, patient selection in HDF entails securing an adequate vascular access to achieve optimal blood flow through a sufficient treatment time. Treatment factors seem to be more important than patient-specific limiting conditions. Thus, HDF can be implemented in a broad population of patients.

2.1 | Modalities (predilution and postdilution)

The convective clearance in HDF requires the concomitant infusion of fluid during the session to replace the ultrafiltrate. In chronic HDF, the infusate is generated by the dialysis machine, often referred as online HDF. This replacement volume, or infusate, can be delivered before the ultrafiltration (predilution) or after it (postdilution). In the mixed-dilution HDF, the infusate is delivered into the blood via two lines, before and after the dialyzer; in mid-dilution HDF, replacement fluids flow into the dialyzer. Postdilution methods tend to yield better solute clearance, albeit they increase the risk of clotting and protein deposition inside the dialysis membrane surface.

2.2 | HDF components, technology, and microbiological safety

HDF and high-flux HD use the same high-flux dialyzer. Also, most dialysis machines generate the ultrapure fluid by filtering the dialysis fluid. A key distinction between HDF and HD is the generation of a sterile infusion volume in the former. This is achieved by an additional filter in the infusate port, within the HDF system. After this filtration process, the resulting sterile volume is infused in the patient, dependent on specific modalities as described above.

The generation of a sterile fluid is warranted in HDF due to the infusion of large replacement volumes in this modality, which can increase risks of microbial contamination. In fact, strict monitoring and maintaining of the dialysis equipment is needed to ensure the infusate remains free of contaminants. This is achieved by two main processes, specific to distinct HDF systems. The infusate filter can either be changed for each treatment or be disinfected along with the dialyzer and thus reused multiple times. Ensuring adequate processes for generating the sterile infusion fluid is fundamental for a safe implementation of HDF.

Implementing HDF requires that the dialysis technology complies with the Electrotechnical Commission standards 60601-2-16, which determine manufacturers are responsible for equipment-associated risk analysis and management.[5] Additionally, the International Organization for Standardization 11663:2009 states that HDF infusate must be sterile; the process of obtaining infusate volumes through ultrapure dialysis fluid filtration must be validated by the manufacturer.[6] Despite the manufacturer responsibilities and risk control processes, the clinician must be aware of several adverse reactions that may arise from the HDF processes, such as pyrogen reactions and leaks.

2.3 | Importance of staff training in the implementation of HDF

HDF implementation is feasible and can be achieved with short-term training programs—even in clinics that were not exposed to the HDF modality. In the HDFit trial, a 3-day staff training protocol using a standardized *train-the-trainer* framework was implemented.[4] In brief, a single nurse certified in HDF recruited a group of five nurses, who were responsible for the HDF training, implementation, and oversight at the recruitment sites.[4] Site dialysis staff enrolled in a standardized in-person 3-day training program that was implemented the day before site activation in the study. The program included a mix of theoretical and practical activities, with a continuous oversight by the training nurse and final knowledge assessment in structured tests. All sites were able to successfully complete training and adequately enroll patients in the study. Key elements of a safe and efficient HDF prescription are summarized in Table 1.

3 | SHORT- AND INTERMEDIATE-TERM OUTCOMES

Short-term outcomes of high-volume OL-HDF may be defined as those related to immediate intradialytic or interdialytic effects, such as uremic toxin removal, intradialytic hemodynamic stability or complications, postdialysis fatigue, changes in interdialytic volume status, and blood pressure control. Intermediate-term outcomes may be a direct or indirect consequence of repetitive short-term effects

TABLE 1 Suggestions of technical specification for HDF

Parameter	Specification
Dialyzer	High flux
Anticoagulation	Per clinic protocol
Needle size	15G
Arterial pressure	−200 mmHg
Blood flow	400 mL/min
Target convective volume	22 L
Dialystate composition	
Sodium (mmol/L)	138
Potassium (mmol/L)	2
Calcium (mmol/L)	1.5
Bicarbonate (mmol/L)	32
Glucose (mmol/L)	5.5

becoming evident only after a period of steady treatment. These include phosphate control, nutritional status, arterial stiffness, chronic inflammation, oxidative stress, eyrhtopoetin stimulating agent (ESA) responsiveness, insomnia, and response to vaccinations, such as hepatitis, influenza, or recently SARS-CoV-2. Eventually, both short- and intermediate-term outcomes may mediate long-term outcomes. Following the new concept of "goal-oriented dialysis prescription," short- and intermediate-term outcomes may become even more relevant from a medical as well as a patient perspective.

3.1 | Middle molecules and protein bound uremic toxins

Solute elimination can be longitudinally assessed by repeated measures of predialysis concentrations or at a single dialysis section via mass removal. Substance removal depends on membrane characteristics, convective volume, treatment time, and frequency. Mass removal is generally a better indicator of solute removal than predialysis or postdialysis blood concentrations. Many studies on high-volume OL-HDF have demonstrated a superior removal of higher molecular weight substances—such as b2MG, myoglobin, free immunoglobulin light chains Kappa, β-trace protein, orosomucoid, indoxyl-sulfate, and p-cresyl-sulfate—as compared to HD.[7,8] Higher fluid substitution rates are associated with higher b2MG clearances in post-HDF therapies.[9] The maximum benefit of OL-HDF on middle molecule removal may be achieved with 24 L substitution volume per 4-h treatment.[10]

The removal of protein bound uremic toxins (PBUT), such as p-cresylglucuronide, hippuric acid, indole acetic acid, indoxyl sulphate, p-cresyl sulphate, and 3-carboxy-4-methyl-5-propyl-furanpropionic acid, may not be improved by high-volume OL-HDF with high-flux membranes, although new evidence may suggest otherwise.[11] An explanation for the limited additive PBUT removal by post-HDF is their multicompartmental distribution with markedly low inter-compartmental clearance, which reflects slow inter-compartmental transport into the plasma.[12] Removal of protein bound substances may be increased with the use of protein/albumin leaking membranes in HDF, which is not considered a standard.

3.2 | Phosphate

Superior phosphate clearance and phosphate mass removal have consistently been shown for high-volume OL-HDF compared with HD.[13,14] However, this may not directly translate into lower serum phosphate levels due to improved protein and phosphorous intake or lower phosphate binder dose in patients treated with HDF. This may explain why some other studies[15–17] found no difference in phosphate level in predilution or postdilution OL-HDF versus low- or high-flux HD.

3.3 | Inflammation and oxidative stress

Earlier studies demonstrated an improvement of inflammatory parameters and cardiovascular outcomes in dialysis patients treated with OL-HDF.[18,19] Although similar results were reported of the CONTRAST trial, the clinical impact of the observed reduction of high sensitivity CRP remains unclear because the change was only 1 mg/L over 3 years.[20] Others described a reduction of pro-inflammatory CD14+, CD16 + monocyte derived dentritic cells in HDF patients.[21] Most of the differences with HD disappeared when ultrapure dialysis fluid was used in both modalities.

3.4 | Intradialytic and peridialytic hemodynamic stability

Many efforts to improve the prospects of chronic dialysis patients aim at reducing hemodynamic instability during (intradialytic) and around (peridialytic) the dialysis procedure. Clinical and subclinical intradialytic hypotension (IDH) are related to myocardial stunning and hypoperfusion of other vital organs, such as brain, gut, and kidneys. Several observational studies have indicated that HDF reduces the incidence of symptomatic IDH compared with HD, and these findings have been corroborated in several RCTs, where blood pressure stability during predilution OL-HDF was superior to HD.[15,16,22,23] The effect of OL-HDF on intradialytic organ perfusion was recently examined in a prospective study in 12 stable, non-hypotension-prone HD patients. Switching from high-flux HD with cooled dialysate to predilution OL-HDF did not reduce the extent of myocardial stunning, and both modalities were associated with similar short-term intradialytic cardiac events.[24] However, so far, no such studies have been performed in vulnerable IDH-prone dialysis patients, where results may differ. In relation to peridialytic blood pressure patterns, which per se are less affected by dialysis modality than intradialytic patterns, no differences were observed between patients treated with OL-HDF and HD.[25]

3.5 | Volume status and cardiac outcomes

Volume status and predialysis blood pressure very much depend on interdialytic fluid intake and residual renal function. As OL-HDF requires large amounts of dialysate infusion, it may be associated with a positive intradialytic sodium balance resulting in increased interdialytic fluid accumulation. In a recent cross-sectional study, there was no indication that OL-HDF per se and average convective or infusion volumes were associated with fluid overload or high predialysis systolic blood pressure. Thus, there appears to be no association between the use of postdilution OL-HDF and markers of fluid volume excess.[26] Among only a few studies that have addressed the loss of residual kidney function in HD versus OL-HDF patients, neither a large observational study nor a recent RCT showed any longitudinal differences in this respect.[27]

3.6 | Arterial stiffness and PWV

Development of arterial stiffness has been related to oxidative stress, CKD-MBD, as well as chronic inflammation in dialysis patients. Potential benefits of OL-HDF on endothelial function and vascular calcification may be mediated by reduced oxidative stress.[28] Some studies have suggested improved conduit artery endothelial function and reduced arterial stiffening following OL-HDF.[29] So far, there is no convincing data that HDF improves left ventricular mass (LVM) or vascular stiffness. In a meta-analysis comparing cardiac outcomes of HD and HDF, in terms of LVM and ejection fraction, a similar improvement of left ventricular hypertrophy was found in patients receiving HD or OL-HDF.[30] Similarly, in a study comparing HD and OL-HDF, vascular stiffness, as assessed by pulse wave velocity, was not affected by dialysis modality.[31]

3.7 | Anemia, Epo responsiveness

Considering anemia control, conflicting results are found. While observational and crossover studies suggested improvements in ESA resistance and iron use, three OL-HDF-RCTs were inconclusive. In the CONTRAST trial, there was a trend toward a lower consumption of ESA in OL-HDF, but the differences did not reach statistical significance.[18] The mean dose of iron supplementation tended to be slightly higher in the OL-HDF group as compared to HD. In the Turkish OL-HDF study, the weekly ESA dose was significantly lower, and the erythropoietin resistance index (ERI) was reduced in OL-HDF versus HD.[17] In the ESHOL study, no differences in hemoglobin levels, transferrin saturation index, and ferritin levels were reported, and ESA doses were comparable between the two treatment groups.[15] In a small crossover, randomized study of the ERI was significantly reduced in HV-OL-HDF patients.[32] An improvement in ERI may be mediated by an increased convective removal of hepcidin, thus facilitating iron mobilization.[33]

3.8 | Immune response to vaccination

There are no conclusive data on the effects of increased middle molecule removal on response to vaccination. A better sustained seroprotection and higher lymphocyte proliferation in response to influenza A vaccination was shown in dialysis patients treated with OL-HDF compared to those treated by HD.[34] So far, no data are available on the effects of OL-HDF on the response toward SARS-CoV-2 vaccination.

3.9 | Nutritional effects of HDF

The patients with ESKD treated by dialysis are at increased risk of sarcopenia and protein energy wasting.[35] The demographics of the dialysis population in economically developed countries has changed over time, with increasing numbers of older, diabetic, and more frail patients.[36] As such, nutrition and preservation of nutritional status including body composition are now key elements of dialysis adequacy. On one hand, HDF, by increasing the spectrum of cleared waste products of metabolism, may be beneficial but could also lead to the removal of small protein and other nutrient losses.

There have been many studies which have compared the effect of HDF and high-flux HD. One prospective randomized controlled trial of 33 adult patients reported that those treated by HD had a reduction in both lean tissue and body cell mass compared to HDF after 12 months, with an increased estimate of dietary protein intake in the HDF cohort.[37] Not all interventional or observational studies have reported an advantage with HDF. For example, an observational study of more than 1000 patients reported HDF only had a beneficial effect for middle-aged patients with a low serum albumin.[38] Observational studies in children have reported both improvements in nutritional status,[39] growth, and physical activity.[40]

Studies which have investigated albumin losses with HDF have reported sessional losses ranging from around 2–3 g, with losses according to convective volume exchange and transmembrane pressure.[41,42] These protein losses are similar to those with high-flux HD, HD with higher permeability dialyzers, and peritoneal dialysis.[43,44] However, other studies have demonstrated that the amount of albumin lost per session also depends on the type of dialyzer used, with some loosing 5 g or more.[45]

4 | PATIENT REPORTED OUTCOMES

The effects of HDF on patient-reported outcomes (PROs), such as health-related quality of life (HRQoL and fatigue), remain unclear. Where some studies suggest no differences in HRQoL scores between HDF and HD patients,[7–10,46] conversely, others have demonstrated a beneficial effect of HDF on HRQOL, including social, physical, and professional domains in association with fewer episodes of hypotension, cramps, itching, fatigue, joint pain, and stiffness.[8,12–14] However, this evidence is limited in terms of sample size and

follow-up. PROs are important because if there are no difference in mortality or morbidity, any benefit in HRQoL would be highly relevant. For example, a change in nutritional status alone might be a reason to prefer one dialysis modality over the other.[15]

The actual body of evidence fails to demonstrate a real improvement in cognitive function or physical or mental fitness when comparing OL-HDF versus HD.[47] However, these findings may strongly depend on the length of follow-up, as significant improvement in the various HRQoL aspects might not be achieved in short periods. The few studies that have assessed postdialysis fatigue and recovery time from dialysis treatment did not report a significant association between dialysis modalities and prevalence or severity of fatigue[48,49] or differences in recovery time.[50] Physical activity was somewhat increased in patients treated with OL-HDF vs HD in the HDFit trial, as documented by a higher step count between two dialysis treatments.[5] In the same trial, the dialysis modality (HDF vs. HD) had no effect on self-reported sleep duration,[51] or progression of peripheral neuropathy, an indicator of chronic uremic intoxication and dialysis quality.[52]

5 | LONG-TERM AND HARD OUTCOMES

The question whether the improved uremic environment followed by HDF, compared with HD, will translate ultimately into better mortality and morbidity outcomes on the longer term remains largely unanswered. Several studies have tried to answer this vexing question, nevertheless no consensus has been reached. This might be due to the clinical differences in terms of patient and treatment characteristics and also methodological differences across the studies that compared HD versus HDF.

5.1 | Mortality and morbidity

Mixed results on the comparison of HDF versus HD regarding mortality have been reported in several large recent observational studies.[16–19] Focusing on RCTs instead, in a Cochrane review with 35 studies and 4039 dialysis participants, no significant beneficial effect on all-cause mortality for convective dialysis compared with HD was found.[19] Nevertheless, an individual participant data (IPD) meta-analysis, including four RCTs comparing HDF with HD, suggested the existence of a dose–response effect for convection volumes on all-cause and cardiovascular mortality.[20,21]

Different techniques of both HD (low-flux and high-flux) and HDF are used across the previous studies.[20,21] As a result, differences in vascular access, blood flow, treatment times, and achieved convection volumes are identified across the studies. These variables, including a higher achieved convection volume, are also associated with better outcomes,[4,20–22] which introduces the possibility of confounding by indications (i.e., higher convection volume is achieved in patients with less comorbidities, with thus a lower mortality risk).[4] These discrepancies might be partly explained by differences in achieved blood flows and treatment times across the studies. Consequently, the positive effects of higher convection volumes might not be extrapolated to the overall dialysis population.

6 | ONGOING STUDIES ON HDF VERSUS HD

Since there is no consensus that HDF is superior to high-flux HD, two studies were started recently. Firstly, the CONVINCE (high convective volume versus high flux HD) study, which recruited 1360 patients in 61 dialysis centers in seven European countries.[23] CONVINCE was designed with a follow-up time of at least 24 months and will run up to 2023. Another ongoing key patient-centric study is the high-volume HDF versus High-flux HD Registry Trial, including over 30 centers in the United Kingdom, with 32–50 months of follow-up.[24]

7 | CONCLUSIONS

Current HDF techniques and equipment can effectively deliver a high-volume convective therapy to most patients and assure clinical performance associated with improved outcomes. High-volume HDF can be easily and safely implemented in different settings, resulting in demonstrations of improved clearance of relevant uremic solutes. There are several studies showing improvements in intermediate, patient reported and clinical outcomes compared to standard HD, but the definitive studies that will provide answer about the superiority of the modality compared to standard methods are underway.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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