Review

Latest Trends in Hemodiafiltration

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Abstract: This review provides a detailed analysis of hemodiafiltration (HDF), its progress from an emerging technique to a potential conventional treatment for chronic hemodialysis patients, and its current status. The article covers advances, methodologies, and clinical benefits of HDF, specifically focusing on its impact on cardiovascular health, survival rates, and overall well-being. The text also addresses concerns about the safety of HDF and provides evidence to dispel worries related to the elimination of beneficial substances and infection risks. Additionally, the article explores the potential implications of expanded hemodialysis (HDx) as an alternative to HDF, its classification, safety profile, and an ongoing trial assessing its non-inferiority to HDF. Supported by evidence from randomized controlled trials and observational studies, the review emphasizes the superiority of HDF as a hemodialysis modality, advocating for its positioning as the gold standard in treatment. However, it acknowledges the need for extensive research to define the role of HDx in comprehensive treatment approaches for individuals undergoing dialysis. The synthesis of current knowledge underscores the importance of ongoing exploration and research to refine hemodialysis practices for optimal patient outcomes.

Keywords: hemodiafiltration; dialyzer compatibility; survival; safety

1. Introduction

Hemodiafiltration (HDF) has evolved significantly since its inception in Europe in 1995. This review explores its trajectory from an emerging technique to a potentially conventional treatment for chronic hemodialysis patients. It delves into the advancements, methodologies, dialyzer compatibility, clinical advantages, current evidence, ongoing research, and the potential implications of expanded hemodialysis (HDx) as an alternative. Despite HDF's beginning in Europe in 1995, in 2015, the American National Kidney Foundation clinical practice guideline for hemodialysis (HD) adequacy only mentioned one paragraph for HDF[1]. This working group recognizes that this therapy is not widely available in the US. In 2018, more than 20 years after its introduction in Europe, the US formally stated regulatory considerations for HDF and whether HDF addresses unmet medical needs. In this review, we propose if HDF could currently be considered as the conventional treatment for HD patients.

2. Evolution of Hemodialysis

In the 1980s, conventional hemodialysis was considered dialysis with acetate dialysate, dialysis machines without volumetric control, low blood flow, and low-flux dialyzers. In the 1990s, the concept of conventional hemodialysis changed due to technological advances in dialysis machines, ultrafiltration control, and the widespread use of bicarbonate dialysate, which allowed an increase in blood flow and the use of synthetic high-flux dialyzers. To avoid backfiltration-induced adverse reactions, exogenous replacement fluid was promoted but was limited for technical and financial reasons.

This scenario changed in 1995 with the development of online hemodiafiltration (HDF) techniques using the dialysate as a replacement fluid. The concept of conventional hemodialysis has continuously evolved over the years and largely depends on each dialysis unit's possibilities and

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technological availability. However, after more than two decades of clinical experience and technological development with high-volume HDF, the question is whether HDF could currently be considered the conventional treatment for chronic hemodialysis patients. High convection volume HDF techniques constitute progress toward renal replacement therapy, which is most similar to the native kidney, and it can be indicated in all patients because there are no contraindications.

3. Characteristics of Hemodiafiltration

The European convective working group defined in 2013[2] HDF as hemodialysis with a high-flux dialyzer and ultrafiltration coefficient greater than 20 ml/mmHg/h/m², sieving coefficient ß2-microglobulin > 0,6 and effective convection volume of at least 20% of the total blood processed.

The convective volume comprises the substitution volume and the ultrafiltred interdialysis weight gain during the dialysis session. The substitution volume can be delivered to the patient, predilution (prefilter) or postdilution (postfilter).

The Eudial group specified that the effective convection volume is the total volume of undiluted ultrafiltered fluid. Therefore, it is necessary to calculate the dilution factor. Moreover, they suggest that infusion flow should be at least twice the postdilution for an equal clearance in predilution. We know that the predilution infusion can slightly decrease the clearance of small molecules and that it is the convective volume that favors the clearance of large molecules, but always somewhat lower than the postdilution. This is why the most used method is postdilution HDF in Europe, except for Japan, where they usually favor the use of predilutional HDF.

Blood flow is an important aspect in achieving an adequate convective volume. Modern dialysis machines deliver the substitution volume automatically, influenced mainly by the prescribed Qb, where, for instance, a substitution volume increased from 23 L to 35 L when the Qb increased from 250 ml/min to 450 mL/min. An interesting observation is how the auto substitution algorithm reaches 33% of the filtration fraction with a Qb of 250 ml/min, while it decreases progressively to 27% with a Qb of 450 ml/min [3]

4. Dialyzer Compatibility and Safety

In the year 2000, a study by Maduell et al. concluded that the symmetric cellulose triacetate (CTA) and polymethylmethacrylate (PMMA) dialyzers should be limited to HF-HD given their association with an elevated transmembrane pressure[4]

The former has found itself useful in hypersensitivity reactions to the use of synthetic HD membranes. These disappear when switching to a CTA dialyzer, making this the main reason for prescribing them[5]. It has been estimated that around 2% of dialysis patients have had a hypersensitivity reaction and require the use of a CTA dialyzer. In this context, the industry developed a new generation of CTA. The main modifications were to change from a homogeneous to an asymmetric structure and to decrease its roughness. The immediate question that arose was whether this new series of dialyzers would be adequate to perform HDF, unlike previous generations[6]. The new asymmetric cellulose triacetate dialyzer increased the ß2-microglobulin reduction ratio from 71% in HD to 80% with HDF, myoglobin from 70 to 82%, and prolactin from 61 to 74%. On the other hand, the previous generation of cellulose triacetate, despite achieving 20 liters of convective volume, underperformed, showing a decrease in the reduction ratio ß2-microglobulin, myoglobin, and prolactin in HDF mode compared to HD. Dialysate albumin losses were around 1 gram in HD and 1.7 grams in HDF in both dialyzers. This new asymmetric CTA generation dialyzer outperformed its predecessor, which indicated that could be used for both HD modality and postdilution HDF. The previous-generation CT prescription should be limited to HD [7].

The second dialyzer unsuitable for HDF was PMMA, a membrane with high adsorption properties. Again, the industry has evolved and created a new generation of PMMA, the NF series, designed to suppress platelet adhesion on the membrane and has adsorption properties similar to conventional PMMA[8]. When these were compared with polysulfone/helixone in HD mode and post-dilution HDF, the only difference was the convective volume, which was 29 L with PMMA and 34 L with polysulfone or helixone. However, the efficacy of PMMA NF series in HDF was higher than

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with HD treatment, and the albumin dialysate loss was less than 1 gram with NF series, significantly lower in comparison with both polysulfone and helixone dialyzers [9].

Regarding dialyzers, another point of debate is whether increasing the internal diameter generates a greater replacement volume and efficacy. A study comparing dialyzers with an internal diameter of 185 microns with ones of 210 microns found no differences in the convective volume achieved, 32 L with the 1.4 m^2 dialyzers and 34 L with the 1.8 m^2 dialyzers, while maintaining a similar efficacy in solute-clearance[10].

5. Clinical Advantages of HDF

HDF has demonstrated a spectrum of clinical benefits that profoundly impact the cardiovascular health and overall well-being of patients undergoing this treatment. HDF manages to reduce cardiovascular risk while enhancing survival rates among individuals. Notably, it provides superior control over several critical health parameters: effectively managing hyperphosphatemia, improving inflammatory status, and optimizing erythropoietin response for better anemia management. Moreover, HDF ensures enhanced hemodynamic stability and superior control over fluid overload, left ventricular hypertrophy, and arterial endothelial function, thereby reducing the propensity for serum calcification. Notably, neurological symptoms such as restless leg syndrome, polyneuropathy, and itching, which often arise due to the accumulation of medium to large-sized molecules, are substantially mitigated. HDF also contributes to the amelioration of joint pain and dialysis-related amyloidosis, thereby enhancing the overall quality of life and satisfaction among patients. Furthermore, the treatment demonstrates a significant reduction in DNA damage levels and an improvement in antioxidant status, underscoring its multifaceted positive impact on patient health and well-being.

Its safety has also been demonstrated. The fear that HDF could eliminate substances beneficial to patients, including vitamins and amino acids, has not been substantiated to date. There have been no case reports or published series of contamination or infection of patients in a dialysis unit due to the use of this treatment. What seems striking is that, after more than 25 years of the clinical application of HDF, no negative studies have been published.

6. Current Evidence and Ongoing Research

Observational studies have showcased numerous clinical benefits and enhanced survival among patients undergoing HDF compared to HF-HD. These benefits range between 22% to 50%, but the necessity for prospective randomized studies to validate these findings was evident.

Between 2010 and 2017, five RCTs were conducted, including the CONTRAST study[11], the Turkish study[12], and the ESHOL study[13], with mortality as the primary endpoint (Table 1). In the CONTRAST and Turkish studies, no survival differences were observed between the groups at the study's conclusion after an average follow-up of three years. However, the ESHOL study demonstrated the superiority of HDF over high-flux HD (HR 0.70 [0.53 to 0.92]). The main difference between the ESHOL study and its predecessors was the convective volume achieved. It was much greater in the former, with a median value of 23 L per session. In addition, a sub-analysis of the Turkish study found that those patients with a median convective volume greater than 17.4 L also had an increased survival compared to those who did not. A reanalysis of the ESHOL study incorporating patients who discontinued treatment and applying an intent-to-treat (ITT) approach revealed a 24% lower all-cause mortality in the HDF arm, compared to 30% when these patients were censored. Similarly, renal transplantation, as a competing event, produced consistent results.

Table 1. Comparison of the different HDF randomized control studies.

	Italian Trial	French Trial	Contrast Study	Turkish Study	ESHOL	CONVINCE
Country	Italian	French	Dutch	Turkish	Spain	Dutch

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Included patients	146	420	714	780	906	1360
Year started	2004	2005	2004	2007	2007	2019
Year of publication	2008	2010	2010	2010	2011	2023
Compared groups	Pre-OL-HDF HF LF-HD 1:1:2	Post-OL-HDF HF-HD 1:1	Post-OL-HDF LF-HD 1:1	Post-OL-HDF HF-HD 1:1	Post-OL-HDF HF-HD 1:1	Post-OL-HDF HF-HD 1:1
Follow-up	2 years	2 years	3 years	2 years	3 years	2.5 years
Primary endpoints	Cardiovascular stability and BP control	Intradialytic tolerance	Mortality	Mortality and cardiovascular events	Mortality	Mortality
Results	No difference between groups	No difference between groups	HR 0.95 (0.83–1.39)	HR 0.54 (0.31-0.93)	HR 0.70 (0.53-0.92)	HR 0.77 (0.65-0.93)

BP: Blood pressure; HF: hemofiltration; HF-HD: high-flux hemodialysis; HR: hazard ratio; LF-HD: low-flux hemodialysis; Post-OL-HDF: online postdilution hemodiafiltration; Pre-OL-HDF: online predilution hemodiafiltration.

The EuDial Pooling project analysis indicated significant reductions in all-cause and cardiovascular mortality by 14% and 33%, respectively, in the HDF arm[14]. These findings were corroborated by meta-analyses that supported the beneficial effects of HDF over HD in reducing mortality rates. National registries from various countries, including France [15], Australia, New Zealand[16], and Argentina[17], consistently exhibited reduced all-cause and cardiovascular mortality rates among patients undergoing HDF compared to those on HD. The French registry analyzed more than two thousand patients exclusively on HDF and found an HR of 0.77 (95% CI, 0.67-0.87) and 0.66 (95% CI, 0.50-0.86) for all-cause and cardiovascular mortality, respectively[15]. The Australia and New Zealand registry analyzed data of around four thousand patients on HDF and also found benefit all-cause mortality with HDF over conventional HF-HD with an adjusted HR of 0.79 (95% CI, 0.72-0.87) in Australia and 0.88 (95% CI, 0.78-1.00) for New Zealand[16]. Finally, the Argentinian registry also found a 53% reduction in mortality rates in patients on HDF compared to those on HF-HD[17].

Additionally, observational studies from Colombia [18] and Russia[19] further highlighted the advantages of HDF in reducing mortality. The Colombian study found a statistically significant reduction of 55% in all-cause mortality but not in cardiovascular mortality[18]. The Russian study reported a longer 5-year survival among patients on HDF with a substitution volume greater than 23-25 L[19]. Additionally, a study from Bulgaria showed an improvement in quality of life, a reduction in the annual number of hospitalizations, lower incidence of cardiovascular events, less itching, improved hypertension control, chronic joint pain, and nutritional status in patients on HDF.

Various studies underscored the association of high convective volumes in HDF with improved survival rates. The current recommendations suggest a minimum replacement volume in postdilution HDF to ensure optimal clinical benefits.

In 2023, the CONVINCE trial[20] replicated similar results to the ESHOL published ten years before[13] (Table 2), finding a significant 23% reduction in all-cause mortality, mostly driven by a decrease in infection-related mortality. The subgroup analysis showed that elderly patients, non-diabetics, those with a fistula as their vascular access, and those without a history of cardiovascular

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disease seem to benefit more. The lower overall risk of death found in the CONVINCE trial (7.13%) than reported in the European Renal Association registry[21] can be partly attributed to selection bias by enrolling patients who were likely to reach the highest convection volumes[20]. This makes the number needed to treat (NNT) was higher in the CONVINCE trial than in the ESHOL one (22 vs 10, respectively)[20,22].

Table 2. In-depth comparison of ESHOL and CONVINCE trials.

		ESHOL		**CONVINCE**
Age (years)		65.4±14.4		62.4±13.5
Male sex		606 (66.9%)		856 (62.9%)
Type 2 diabetes		226 (24.9%)		481 (35.4%)
Did not complete treatment		355 (39.2%)		314 (23.1%)
Censored in analysis		Yes (Per protocol)		No (ITT)
Reasons				
Kidney transplantation		180 (19.6%)		146 (10.7%)
Change of HD center		58 (6.4%)		95 (7%)
Change of HD modality		48 (5.3%)		58 (4.3%)
Other		69 (7.9%)		15 (1.1%)
Dialysis vintage (months)		28 (12–59)		33 (15-72)
Tunneled catheters		93 (10.3%)		184 (13.5%)
Qb (mL/min)		387		368
Convective volume (L)		23.9		25.2
Time of treatment (min)		236		244
Inclusion period (months)		16		30
Study duration (months)		52		52
Mean follow-up (years)		1.91±1.1		1.92±1.1
Mortality (100 patients/year)		11.95		7.13
All-cause mortality				
Hazard ratio		0.70 (0.53–0.92)		0.77 (0.65–0.93)
NNT		10 (6–41)		22 (12–268)
All-cause mortality subgroup analysis				
Age	Tertile 1	0.81 (0.36–1.81)	< 50 yr	0.25 (0.06–1.05)
	Tertile 2	0.82 (0.51–1.33)	50 to 65 yr	1.05 (0.75–1.49)
	Tertile 3	0.63 (0.43–0.92)	> 65 yr	0.68 (0.53–0.89)
Diabetes	No	0.68 (0.48–0.95)	No	0.65 (0.48–0.87)
	Yes	0.75 (0.46–1.21)	Yes	0.97 (0.72–1.31)
Vascular access	Fistula or graft	0.72 (0.53–0.97)	Fistula	0.77 (0.64–0.94)
	Catheter	0.83 (0.38–1.79)	Graft or catheter	0.78 (0.45–1.34)
Cardiovascular death		0.39 (0.16–0.93)		0.81 (0.49–1.33)
Other causes of death		0.45 (0.21–0.96)		0.76 (0.59-0.98)
Hospitalization		0.78 (0.67–0.90)		1.11 (0.98-1.25)

HD: hemodialysis; ITT: Intention-to-treat; NNT: number needed to treat; Qb: blood flow rate

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Currently, the H4RT is an ongoing British RCT[23] that seeks to definitively confirm the superiority of high-volume HDF versus HD not only clinically but also cost-effectively. The comparative efficacy between HDF and HD should be conclusive enough, although many specialists remain skeptical due to the cost of the therapy and the apparent lack of benefit in certain subpopulations. The H4RT study will offer a more comprehensive understanding of the advantages and disadvantages of high-dose HDF compared to high-flux HD in financial terms, thereby shaping treatment approaches for patients undergoing dialysis. There is still room for further study to determine which patient groups might derive the most benefit from HDF treatment.

Regarding the pediatric population, no RCTs have been performed to study the effects of HDF in contrast with HD[24]. However, the 3H is a prospective multicentric study across ten countries in Europe that found an improvement in blood pressure control, reduced ventricular mass, with a slower increase in carotid intima-media thickness; a reduction in inflammatory cytokines such as IL-6, TNF-α, and high sensitivity CRP in the HDF group[25,26]. Additionally, Fibroblast growth factor 23 decreased by 25% in the HDF group while it increased in every patient on HD[26]. Regarding quality of life, there were also fewer cramps, headaches, and lower post-dialysis recovery times, improving school attendance and physical activity[27]. Other studies have found similar results, such as the study by Fadel et al.[28] that found an improvement in systolic function in pediatric patients on HDF. Also, the study by Fischbach et al.[29] showed that HDF promoted the growth in children receiving growth hormone treatment.

7. Expanded Hemodialysis (HDx) as an Alternative

Expanded HD (HDx) requires the use of a medium cutoff dialyzer and appears to offer a new viable alternative to hemodiafiltration (HDF) raises questions about its efficacy compared to high-flux HD and HDF, especially in terms of dialyzer classification and clinical outcomes.

Dialyzer classification differs between Europe and Japan. In Europe, the classification includes low flux, high flux, medium cutoff (MCO), and high cutoff (HCO) based on specific coefficients and clearance rates. Conversely, Japan categorizes dialyzers based on their beta 2-microglobulin sieving coefficient, whereas those categorized as super high-flux or class V behave as MCO dialyzers [30].

Research comparing HDx to high-flux HD and HDF presents intriguing insights. A notable randomized controlled trial (RCT) involving 40 patients alternating between HF-HD and HDx for three months each demonstrated promising results [31]. Moreover, the study highlighted the importance of lambda-free light chains as potential markers for assessing depurative efficacy within the molecular weight range of 40-45 KDa [31].

Comparative studies involving myoglobin, prolactin, and Kappa-free light chain patterns further emphasized differences in depurative efficiency among HDx and other modalities [32]. Notably, despite differences in molecular weight removal rates, the Global Removal Score among MCO dialyzers was consistent, significantly higher than HD but lower than post-dilution HDF. Moreover, albumin dialysate loss remained clinically acceptable across these treatments [33].

Addressing safety concerns, long-term studies like REMOVAL demonstrated the stability of pre-dialysis albumin levels over a 6-month follow-up, affirming the safety profile of HDx [34]. Similar conclusions were drawn from a Korean study with a 12-month follow-up period, supporting the safety and viability of HDx in clinical practice [35].

However, cautionary observations from case reports underscore the importance of judicious use of MCO, HDx, or super high-flux dialyzers, specifically within the HD modality. Instances of significant albumin loss and hypoalbuminemia during postdilution HDF emphasize the need for careful patient selection and treatment modalities to prevent adverse outcomes [36].

Finally, while HDx shows promise as an alternative to HDF, there is an ongoing trial (NCT03714386)[37] seeking to determine HDx as non-inferior to HDF, looking to come forward as an alternative to those patients who cannot achieve a proper convective volume or to those hemodialysis centers that do not have access to an ultrapure water plant. Further studies will ascertain its efficacy, safety, and suitability for different patient profiles, ensuring optimal outcomes in renal replacement therapy.

8. Conclusion and future directions

In conclusion, the accumulating body of evidence overwhelmingly demonstrates that HDF stands as a superior modality, showcasing substantial clinical advantages and a clear impact on patient survival in comparison to high flux HD. This robust evidence strongly advocates for HDF's elevation to the status of the new 'conventional' hemodialysis technique, given its remarkable efficacy and proven benefits in enhancing patient outcomes.

However, amidst HDF's remarkable success, the emergence of HDx presents an intriguing alternative, particularly for those patients unable to receive optimal treatment with HDF. While initial studies suggest HDx as a viable option, deeper investigation is required to define its precise role and suitability across diverse patient profiles. More extensive research is indispensable to solidify its place as a genuine alternative, ensuring comprehensive treatment approaches for individuals undergoing dialysis.

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