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Review Article

Targeting large middle molecules: Clinical implications of expanded hemodialysis in hemodialysis care

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ABSTRACT

End-stage kidney disease (ESKD) presents a major clinical burden, with maintenance hemodialysis (HD) patients facing high cardiovascular mortality and impaired quality of life (QoL). Despite advances from low-flux to high-flux HD and the introduction of hemodiafiltration (HDF), clearance of large middle molecules (LMMs >25 kDa) remains inadequate. These molecules contribute to inflammation, oxidative stress, atherogenesis, and mineral-bone disorders, all of which worsen patient outcomes. Expanded hemodialysis (HDx), utilizing medium cutoff membranes, represents a novel approach that combines diffusion and enhanced internal convection to improve LMMs removal, without the need for substitution fluid. This review explores the limitations of conventional HD, the pathological roles of LMMs, and the evolution of dialysis strategies aimed at enhancing solute clearance. Evidence from observational studies, randomized trials, and meta-analyses shows that HDx improves the removal of inflammatory LMMs, reduces hospitalization burden, preserves residual kidney function, and enhances patient-reported outcomes such as recovery time and symptom relief. Furthermore, HDx offers a practical and cost-effective alternative to online HDF (OL-HDF), particularly in the resource-limited settings, achieving comparable efficacy with shorter sessions and lower blood flow requirements. By addressing the key shortcomings of traditional HD and approaching the solute clearance profile of the native kidney, HDx offers a promising advancement in the care of ESKD patients.

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INTRODUCTION

Chronic kidney disease (CKD) poses a growing global health burden, with a worldwide prevalence of 13.4% across all stages and 10.6% for stages 3 to 5 [1]. In Asia, the average prevalence of CKD stages 3 to 5 in 14 low- and middle-income countries is estimated at 11.2% [2], while in Taiwan, it reaches 11.9% [3]. End-stage kidney disease (ESKD), the terminal phase of CKD, requires renal replacement therapy (RRT). As of 2021, over 540,000 patients in the United States were receiving maintenance hemodialysis (HD) or peritoneal dialysis (PD) [4]. In Taiwan, the prevalence of dialysis patients reached 3806 per million in 2022, totaling 88,555 patients, with 92.5% receiving HD [5].

Despite advancements in RRT, ESKD remains associated with considerable morbidity and premature mortality, largely driven by cardiovascular (CV) disease, which accounts for 40%–50% of deaths among dialysis patients and is estimated to occur at rates up to 20 times higher than in the general population [4-8]. Five-year survival after dialysis initiation is approximately 40% in the U.S. and 55.1% in Taiwan (2013–2017 cohort) [4,5]. Beyond traditional CV risk factors such as obesity, insulin resistance, hypertension, and diabetes mellitus, nontraditional factors, including uremic toxins, inflammation, malnutrition, and endothelial dysfunction, critically influence outcomes [9,10]. ESKD significantly impairs quality of life (QoL), marked by symptom burden, functional decline, and psychological distress [11-13].

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A key limitation of conventional dialysis is its inability to adequately clear a wide spectrum of uremic toxins. Small solutes (<0.5 kDa) and smaller middle molecules (0.5–15 kDa) are effectively removed by high-flux HD (HF-HD). Hemodiafiltration (HDF) efficiently clears medium-middle molecules (15–25 kDa), including leptin, myoglobin, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-10, retinol-binding protein 4, prolactin, κ-free light chains (κ-FLC), complement factor D, IL-18, and IL-6. However, larger middle molecules (LMMs, >25 kDa), such as β-trace protein, adiponectin, fibroblast growth factor-23 (FGF-23), α1-microglobulin, vascular endothelial growth factor, chitinase-3-like protein 1 (YKL-40), pentraxin-3, advanced glycation end-products (AGEs), λ-FLC, visfatin, and albumin or protein-bound toxins, remain poorly removed, leading to accumulation [14-17]. These larger molecules include pro-inflammatory cytokines (e.g., IL-6 and TNF-α), immunoglobulin free light chains (κ-FLC, λ-FLC), mineral metabolism regulators (e.g., FGF-23), and oxidative stress mediators, which are implicated in malnutrition-inflammation-atherosclerosis syndrome and CV complications [9,18,19]. Oxidative stress is further amplified by HD-induced processes, including leukocyte activation and dialyzer membrane interactions [20]. AGEs correlate with cytokine production and oxidative stress markers [21], and skin autofluorescence – a noninvasive AGEs measure – predicts increased risks of CV events and mortality [22]. Inflammation-related biomarkers such as IL-6 and YKL-40 are the strong independent predictors of all-cause and CV mortality in HD patients [23], as are elevated combined free light chains (cFLCs) in both stage 3 CKD and HD populations [24,25]. In our study of 112 HD patients and 58 elderly (age >65 years old) HD patients, higher serum leptin levels were independently associated with increased arterial stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV >10 m/s) [26,27]. Arterial stiffness arises from multiple mechanisms, including oxidative stress, inflammation, uremic toxins, vascular calcification, and aging and is a key contributor to CV morbidity and mortality in patients with ESRD [28]. Our study also notes that cfPWV is an independent predictor of both all-cause and CV mortality in HD patients [29]. Pentraxin-3, a C-reactive protein (CRP)-related glycoprotein, is also elevated in HD patients and associated with inflammation, higher comorbidity, and malnutrition scores [30,31]. FGF-23 has emerged as a mortality predictor in both community and dialysis settings. In the Framingham Heart Study, higher FGF-23 levels were independently associated with all-cause mortality but not with incident CV disease [32]. Similarly, rising FGF-23 levels in HD patients correlated with higher mortality risk [33]. Together, these findings underscore the clinical significance of LMMs (25–58 kDa) and the unmet need to enhance their clearance. Accumulation of LMMs contributes to chronic inflammation, oxidative stress, vascular dysfunction, and mortality in HD patients. Addressing this gap represents a critical target for improving the long-term outcomes in ESKD. Table 1 summarizes the classification of uremic toxins by molecular weight.

This review article explores the clinical importance of removing LMMs in HD patients. While conventional HF-HD is limited in clearing these molecules, expanded hemodialysis (HDx) with medium cut-off (MCO) membranes is a promising, practical alternative to HDF. HDx improves toxin clearance, reduces inflammation, and enhances QoL, although the long-term outcome data are still needed.

The evolution of hemodialysis: An ongoing quest for enhanced solute removal

HD is a widely used the treatment for ESRD, utilizing semipermeable membranes to filter blood in an extracorporeal system [34]. The purification efficiency of various solutes in HD depends on the type of dialysis, treatment parameters, and the characteristics of the filtration membranes employed.

Limitations of conventional hemodialysis and the role of membranes

HD membranes differ in their biocompatibility, ability to clear medium-molecular-weight solutes, onset of molecular weight retention, and cutoff thresholds for molecules of varying sizes. Additional membrane properties, such as surface charge (Z potential), thickness, and solute-specific diffusion coefficients (Ko), also influence toxin clearance efficiency. Although prolonged dialysis sessions may enhance the clearance of certain solutes such as β2-microglobulin and phosphate, the removal efficiency for protein-bound toxins remains largely unchanged. Standard HD, the most widely used form of renal replacement therapy, primarily removes small molecules (<500 Da) through passive diffusion driven by concentration gradients between blood and dialysate. However, this method is ineffective for clearing medium and large molecules, while the use of HF membranes modestly improves the removal of medium-sized solutes, it still falls short of achieving comprehensive toxin clearance [35].

Classification of dialysis membranes by pore architecture

Pore size distribution curves are schematically depicted for four classes of dialysis membranes: low-flux (LF), HF, MCO, and high cutoff (HCO) [36,37]. LF membranes exhibit a narrow distribution with small pore sizes, restricting clearance to small solutes and excluding most middle molecules. HF membranes feature a broader pore size range, allowing for improved permeability to middle molecules such as β2-microglobulin, while still minimizing albumin loss. MCO membranes are designed with an optimized and steep pore size distribution curve, characterized by a narrow gap between the molecular weight retention onset (MWRO) and molecular weight cutoff (MWCO), to maximize the removal of large uremic toxins while preserving albumin. In contrast, HCO membranes have a very broad pore size distribution and high permeability, enabling extensive clearance of large molecules, including immunoglobulin light chains, but at the cost of significant albumin loss, which limits their use to specific short-term clinical indications [36,38].

Comparative profiles of dialysis modalities

LF-HD operates solely through diffusion using LF membranes, making it effective only for the removal of

Table 1: Uremic toxins by classification

Small protein-bound molecules (<0.5 kD)	MW (kD)	Small molecules (<0.5 kD)	MW (kD)	Small-middle molecules (0.5–15 kD)	MW (kD)	Medium-middle molecules (15-25 kD)	MW (kD)	Large-middle molecules (25-58 kD)	MW (kD)	Lorge molecules >58 kD	MW (kD)
Homocysteine	0.135	Urea	0.06	IGF-1	7.6	Leptin	16.0	β-Trace protein	26.0	Modified albumin	58.0
Phenylacetic acid	0.150	TMAO	0.075	IL-8	8.0	TNF-α	17.0	Adiponectin	30.0	Albumin	68.0
Indole acetic acid	0.175	Creatinine	0.113	Parathyroid hormone	9.5	Myoglobin	17.0	FGF-23	32.0		
Hippuric acid	0.179	Uric acid	0.170	β2-microglobulin	11.8	IL-1β	17.5	α1-microglobulin	33.0		
Kynurenic acid	0.189	ADMA	0.202			IL-10	18.0	VEGF	34.0		
p-Cresyl sulfate	0.190	SDMA	0.202			IL-6	20.0	YKL-40	40.0		
Kynurenine	0.208	PAG	0.264			RBT-4	21.2	Pentraxin-3	40.2		
Indoxyl sulfate	0.251					Prolactin	22.0	AGEs	45.0		
						Complement factor D	24.0	λ-FLC	45.0		
								Visfatin	55.0		

Modified albumin includes oxidized albumin, glycated albumin, and carboxymethyllysine albumin. MW: Molecular weight, KD: Kilodalton, IGF-1: Insulin-like growth factor 1, IL: Interleukin, TNF-α: Tumor necrosis factor-α, FGF-23: Fibroblast growth factor 23, YKL-40: Chitinase-3-like protein 1, AGEs: Advanced glycation end-products, λ-FLC: Lambda-free light chain, κ-FLC: κ-free light chain, TMAO: Trimethylamine N-oxide, ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, PAG: Phenylacetylglutamine, RBT-4: Retinol-binding protein 4, VEGF: Vascular endothelial growth factor

small water-soluble molecules (<500 Da), with limited biocompatibility and minimal effect on inflammation or CV stability. The clearance of middle and large molecules was negligible. It is the most accessible and cost-effective modality but offers no significant survival benefits [37]. HF-HD, in contrast, incorporates membranes with larger pores that allow both diffusion and limited convection, enhancing clearance of small and some middle molecules (~10–20 kDa) such as β2-microglobulin. It demonstrates improved biocompatibility, moderate CV stability, and some evidence of improved outcomes compared to LF-HD, while maintaining moderate cost and complexity [37]. The Membrane Permeability Outcome (MPO) study and the Multiple Interventions Related to Dialysis Procedures in Order to Reduce Cardiovascular Morbidity and Mortality in HD Patients (EGESTUDY) study provided evidence for survival and CV benefits favoring HF-HD over LF-HD, particularly pronounced in patient subgroups with hypoalbuminemia, diabetes mellitus, or extended dialysis vintage [39,40].

Online HDF (OL-HDF) combines diffusion with controlled convection by infusing sterile substitution fluid, thereby significantly improving the clearance of middle and some large molecules (~25–50 kDa), reducing inflammatory markers, and providing superior CV stability, particularly with high convective volumes [37]. In the CONTRAST (Convective Transport Study) study, which included 714 ESKD patients, online post-dilution HDF did not significantly reduce all-cause mortality or CV events compared to LF-HD over a mean follow-up of 3 years. However, on-treatment analysis suggested that patients receiving high-volume HDF may have a survival benefit [41]. The Turkish OL-HDF (comparison of postdilution online hemodiafiltration and hemodialysis) study, which included 782 ESKD patients, found no statistically significant difference in the composite outcome of all-cause mortality and nonfatal CV events between online post-dilution HDF (OL-HDF) and HF-HD over a 2-year follow-up. However, a *post hoc* subgroup analysis revealed that patients receiving high-efficiency OL-HDF (with substitution volumes >17.4 L/session) had significantly lower all-cause and CV mortality than those on HF-HD [42]. The Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL) study, which included 906 ESKD patients, high-efficiency postdilution OL-HDF significantly reduced all-cause mortality by 30% compared to standard HD, with additional trends toward lower CV and infection-related mortality. OL-HDF also improved treatment tolerability and reduced hospitalization and intradialytic hypotension [43]. The FRENCHIE (French Convective vs. HD in the Elderly) study, which included 381 elderly patients with ESKD, although overall patient-level outcomes such as mortality, morbidity, and quality of life were similar between groups, OL-HDF showed better intradialytic tolerance at the session level, with significantly fewer episodes of symptomatic hypotension and muscle cramps. In addition, OL-HDF was associated with lower β2-microglobulin levels and improved metabolic control, indicating better middle molecule clearance [44]. The *post hoc* analyses of four European randomized, controlled trials (CONTRAST, Turkish OL-HDF, ESHOL, and FRENCHIE) showed beneficial effects in patients with high convention volumes >23 L per session confers a significant reduction in all-cause mortality compared to HF-HD [45]. The definitive CONVINCE (Comparing Outcomes of Hemodiafiltration vs. HD in Kidney Failure) study, which included 1360 patients with ESKD, has established that high-volume HDF (typically defined by convection volumes >23 L per session) found that high-dose OL-HDF significantly reduced all-cause mortality compared to conventional HF-HD (hazard ratio, 0.77; 95% confidence interval, 0.65 to 0.93). While CV mortality and hospitalization rates were similar between groups, OL-HDF showed a notable reduction in infection-related deaths, including those linked to COVID-19 [46]. The prospective multicenter 3H (The HDF, Heart and Height Study) study in children, conducted across 10 European countries, demonstrated that patients receiving HDF experienced superior clinical outcomes compared to those on conventional HD. Specifically, HDF was associated with improved blood pressure control, reduced left ventricular mass, and a slower progression of carotid intima-media thickness [47]. In addition, significant reductions were observed in inflammatory markers, including IL-6, TNF-α, and high-sensitivity CRP. Notably, FGF-23 levels decreased by 25% in the HDF group, while they increased among HD patients in children. QoL also improved with HDF, evidenced by fewer post-dialysis symptoms such as cramps and headaches, shorter recovery times, and enhanced school participation and physical activity in children [47-49]. However, the CONVINCE trial was conducted in European centers that could deliver high blood flow rates (median blood flow 369 mL/min in OL-HDF and 367 mL/min in HF-HD) and maintain strict water quality standards, limiting generalizability to global practice.

Barriers to the widespread adoption of hemodiafiltration

Although online HDF offers enhanced removal of middle molecules through combined diffusion and convection, it is complex, costly, and dependent on high convection volumes and sterile substitution fluids, and its survival benefit over HF-HD requires high blood flow with high convection volumes (>23 L per session). Consequently, patients with vascular access limitations who are unwilling to extend their dialysis sessions are not ideal candidates for high-volume HDF [50]. This evolutionary path underscores a remaining therapeutic gap: the need for a modality that effectively addresses LMMs accumulation without the logistical and economic complexities associated with high-volume HDF. So, the HDx using MCO membranes achieved comparable dialysis efficacy to HDF, despite being delivered with shorter session durations, lower blood flow rates, reduced convective volumes, and lower instantaneous solute clearance, and was designed for clinical use [51-53].

EXPANDED HEMODIALYSIS

HDx utilizes MCO membranes that remove a broad range of solutes, including small, middle, and larger molecules (~15–60 kDa) without the need for substitution fluid [37,51,54]. HDx has emerged as a distinct RRT modality engineered specifically to enhance the clearance spectrum into the LMMs range.

Membrane structure, mechanism, and clearance profile

MCO membranes used in HDx are engineered with a higher MWRO than conventional HF membranes, allowing for improved passage of LMMs before retention begins. Their optimized MWCO enables effective LMMs clearance while minimizing albumin loss. Structural features – such as reduced internal fiber diameter and refined pore distribution – enhance internal filtration and back-filtration, generating significant convective transport without the need for external substitution fluid. This combination of diffusion and internal convection allows HDx to achieve superior clearance of solutes >25 kDa, with efficacy for some LMMs approaching that of high-volume HDF. Despite slightly greater albumin loss than HF-HD, long-term studies show serum albumin levels remain stable, indicating clinical safety [15,51,55-58].

Clinical benefits

Systematic reviews and meta-analyses of clinical evidence of expanded hemodialysis

HDx demonstrates strong biocompatibility and inflammation control similar to HDF, with simpler operations and lower cost, making it a practical alternative where HDF is not feasible [37,51,54]. It enables broader uremic toxin removal, particularly β2-microglobulin, cytokines, and FLCs, while preserving albumin [51]. Meta-analyses comparing HDx (e.g. Theranova) to HF-HD across 22 studies (1811 patients) showed improved quality of life, reduced symptoms (e.g., pruritus, restless legs syndrome), faster recovery time after dialysis, lower erythropoiesis resistance index and iron use, and fewer hospitalizations, with no increase in mortality or adverse events [59]. Another review of 18 studies found HDx achieved higher clearance of κ- and λ-FLCs than HF-HD and HDF, with comparable albumin loss was comparable to HDF, and no increase in adverse events was observed [60]. A broader synthesis of 79 studies confirmed HDF outperforms HF-HD in survival and hospitalization, while HDx shows promising but shorter-term benefits over HF-HD in middle- and LMMs clearance, symptom relief, and hospitalization reduction. However, no significant differences were found between HDx and HDF in terms of mortality, CV outcomes, or QoL [61]. Supplement Table 1 shows a summary of the comparative meta-analyses of HDx compared to HDF and HF-HD.

Evidence from controlled studies on expanded hemodialysis compared to high-flux hemodialysis and hemodiafiltration

Compared to HF-HD and OL-HDF, HDx shows improved clearance of inflammatory markers, better CV and vascular outcomes, and enhanced patient-reported QoL, including reduced fatigue and shorter recovery times, with no observed nutritional harm despite slightly higher albumin loss [51,54]. A study comparing four MCO dialyzers to HF-HD and HDF found superior removal of middle and large molecules and acceptable albumin loss (1.5–2.0 g/session) [62]. All MCO filters were well tolerated and safe for use. The global removal scores (GRS) of all four MCO dialyzers were superior to HF-HD and closely approached the efficacy of postdilution HDF [62]. A randomized trial in incident HD patients showed HDx better preserved residual kidney function and removed more middle molecules than HF-HD, with no difference in hospitalization or mortality [63]. In the CARTOON (Cardiovascular Risk Comparison between HDx Using Theranova and Online Hemodiafiltration) trial, HDx was noninferior to HDF for CV outcomes, although rising coronary artery calcium scores in the HDx group suggest caution in high-risk patients [64]. Other studies in heart failure and elderly populations demonstrated reduced inflammation, improved arterial stiffness, and lower erythropoiesis-stimulating agent resistance, supporting HDx's utility even in patients with low blood flow or poor vascular access [65,66]. Supplement Table 2 shows a summary of the evidence from controlled studies on HDx compared to HF-HD and HDF.

Special populations and extended applications of expanded hemodialysis

Effective removal of uremic toxins, particularly protein-bound uremic toxins (PBUTs) and inflammatory mediators, remains a key challenge in managing ESRD and acute kidney injury (AKI), especially in sepsis, COVID-19, and multiple myeloma. PBUTs such as p-cresyl sulfate and indoxyl sulfate (IS) are poorly cleared by conventional HD due to strong albumin binding, contributing to oxidative stress and CV disease [16,67]. A prospective crossover study in 12 ESRD patients compared the removal efficiency of IS among four dialysis modalities – HDx, pre-HDF, mixed-HDF, and post-HDF. Results showed no statistically significant differences in the reduction ratios for small, middle, large-middle, or protein-bound toxins (IS) across modalities. Although HDx and postHDF showed slightly better clearance of PBUTs like IS (mean reduction ratio 49% vs. 51%, respectively), the findings suggest all four techniques achieve comparable toxin removal under high-efficiency settings [68]. In sepsis and COVID-19, HDx achieves superior cytokine removal (e.g. TNF-α and IL-6) compared to HF-HD or OL-HDF, with possible mortality benefit in COVID-19 [69,70]. In myeloma-related AKI, HDx improves FLCs clearance, although evidence is limited [71]. Despite these promising findings, HDx's impact on oxidative stress and long-term outcomes remains uncertain, and current data are constrained by small sample sizes and variability in dialysis settings, highlighting the need for larger, controlled trials. Supplement Table 3 shows a summary of the potential advantages of HDx. Large-scale randomized controlled trials (RCTs) are needed to confirm their clinical benefits, such as dialysis independence and improved survival.

Clinical advantages and practical value of expanded hemodialysis in dialysis care

HDx, facilitated by MCO membrane technology, constitutes a significant conceptual and practical evolution in extracorporeal blood purification. It directly addresses the well-recognized deficiency of conventional HF-HD in clearing LMMs, achieving this through synergistic diffusive and enhanced internal convective transport. The principal advantage of HDx resides in its capacity to deliver augmented LMMs removal – potentially rivaling high-volume HDF for several key solutes – without the infrastructural demands (ultrapure water systems and dedicated HDF machines) and associated costs of online replacement fluid generation. The available clinical evidence provides robust support for the benefits of HDx in improving surrogate endpoints, notably reducing inflammatory biomarker levels and significantly lessening the burden of hospitalization. Furthermore, consistent reports of improvements in patient-reported QoL domains, such as recovery time and symptom severity, are clinically meaningful. Table 2 shows a summary of the comparison of LF-HD, HF-HD, HDF, and HDx. Figure 1 summarizes the comparison of the removal capabilities of different dialysis modalities by the molecular weight of uremic toxins.

CONCLUSION

The retention of LMMs represents a major contributor to the adverse clinical outcomes, including excessive CV mortality and diminished QoL, observed in the maintenance HD population. HDx, utilizing MCO membranes, offers a technologically advanced approach that significantly enhances the clearance of these deleterious solutes compared to conventional HF-HD. While HDx offers substantial benefits in middle and LMMs clearance, reduced inflammation, and simplified operational logistics, it is important to acknowledge clinical scenarios where high-volume OL-HDF may remain the superior modality. Large randomized controlled trials have demonstrated that HDF, particularly when delivered with convection volumes exceeding 23 L per session, is

Table 2: A comparison of low-flux hemodialysis, high-flux hemodialysis, hemodiafiltration, and expanded hemodialysis

Aspect	LF-HD	HF-HD	OL-HDF	HDx
Mechanism	Diffusion only	Diffusion+limited convection	Diffusion + controlled convection	Diffusion + enhanced convection (no substitution fluid)
Membrane type	Low-flux membrane	High-flux membrane	High-flux membrane with substitution fluid	Medium cut-off (MCO) membrane
Molecule clearance	Small molecules only (<500 Da)	Small molecules + Small-middle molecules + Some medium-middle molecules (~10–20 kDa)	Small molecules + Small-middle molecules + Medium-middle molecules + Some large-middle molecules (~25–50 kDa)	Small molecules + Middle molecules (~15–60 kDa)
Cardiovascular stability	Lower stability	Moderate improvement over LF-HD	Superior stability, particularly with high volumes	Good stability, approaching HDF
Inflammation reduction	Minimal	Moderate	Superior reduction	Good reduction, similar to HDF
Biocompatibility	Limited (especially cellulose membranes)	Good (synthetic membranes)	Excellent (advanced synthetic membranes, sterile fluid)	Very good (advanced synthetic membranes)
Survival benefit	Baseline standard	Moderate improvement versus LF-HD	Potentially superior, mixed evidence versus HF-HD	Promising evidence, potentially superior to HF-HD
Cost and complexity	Lowest cost, simplest technology	Moderate cost and complexity	High cost, requires sterile substitution fluid	Moderate cost, simpler than HDF, no substitution fluid
Vascular access requirement	Standard	Standard	High (needs higher blood flow rates)	Standard, similar to HF-HD
Global availability	Most widely available	Widely available	Limited availability	Increasingly available, newer technology

HD: Hemodialysis, LF: Low-flux, HF: High-flux, OL-HDF: Online hemodiafiltration, HDx: Expanded hemodialysis associated with significant reductions in all-cause and CV mortality. Therefore, HDF may be preferable in patients with high-CV risk profiles, such as those with significant coronary artery calcification, and in centers equipped with the infrastructure to support high-efficiency post-dilution HDF, including access to ultrapure water and high blood flow rates. Conversely, HDx is especially advantageous for patients with limited vascular access, low blood flow, or intolerance to high convective volumes, as well as in the resource-limited settings where HDF is not feasible. Moreover, patient subgroups such as those with advanced vascular calcification or minimal residual renal function may require individualized assessment, as current evidence for HDx in these populations remains limited. Figure 2 shows a pragmatic framework in which HDx serves as a practical and effective alternative when high-efficiency HDF is not available or not tolerated, while HDF may be favored in centers capable of delivering optimized therapy and in patients for whom long-term CV

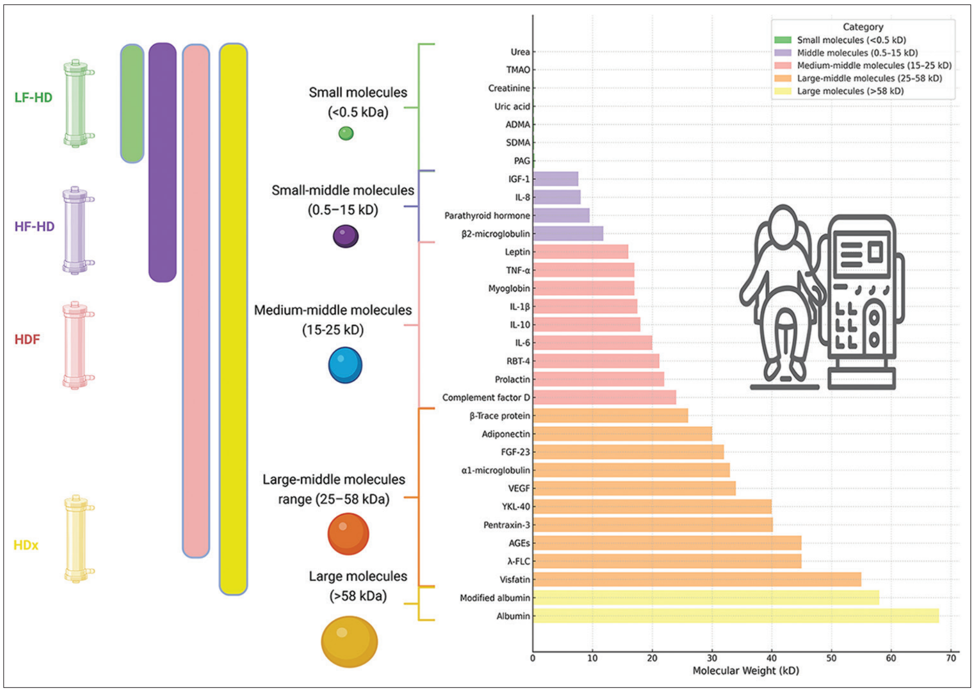

Figure 1: Comparative clearance of uremic toxins by dialysis modality. Compares the removal capabilities of different dialysis modalities – low-flux hemodialysis (LF-HD), high-flux hemodialysis (HF-HD), hemodiafiltration (HDF), and expanded hemodialysis (HDx) – against a spectrum of uremic toxins categorized by molecular weight. Uremic toxins are grouped into five categories: small molecules (<0.5 kDa), small-middle molecules (0.5–15 kDa), medium-middle molecules (15–25 kDa), large-middle molecules (25–58 kDa), and large molecules (>58 kDa). LF-HD is limited to small molecules, while HF-HD removes small molecules, small-middle molecules, and some medium-middle molecules. HDF removes small molecules, small-middle molecules, medium-middle molecules, and some large-middle molecules. HDx removes small molecules, small-middle molecules, medium-middle molecules, and large-middle molecules. Created in BioRender.com. TMAO: Trimethylamine N-oxide, ADMA: Asymmetric dimethylarginine, SDMA: Symmetric dimethylarginine, PAG: Phenylacetylglutamine, IGF-1: Insulin-like growth factor-1, IL-8: Interleukin-8, TNF-α: Tumor necrosis factor-α, RBP-4: Retinol-binding protein-4, FGF-23: Fibroblast growth factor-23, VEGF: Vascular endothelial growth factor, YKL-40: Chitinase-3-like protein 1, AGEs: Advanced glycation end-products, λ-FLC: Lambda free light chain, LF-HD: Low-flux hemodialysis, HF-HD: High-flux hemodialysis, HDF: Hemodiafiltration, HDx: Expanded hemodialysis

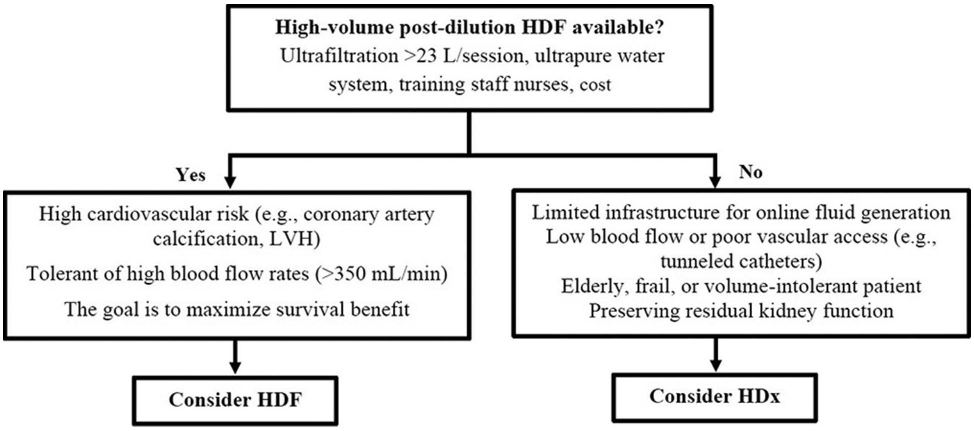

Figure 2: Clinical decision algorithm for selecting high-volume hemodiafiltration versus expanded hemodialysis (HDx). This flowchart outlines considerations for selecting between high-volume postdilution hemodiafiltration (HDF) and HDx using medium cutoff membranes. Factors include infrastructure availability, patient cardiovascular risk, blood flow tolerance, and clinical priorities such as residual kidney function preservation.

protection is a priority. Future research priorities must include adequately powered, prospective, long-term RCTs comparing HDx not only against HF-HD but also head-to-head against state-of-the-art high-volume HDF, utilizing hard clinical endpoints including cause-specific mortality and major adverse cardiovascular events. Continued investigation into the precise clinical sequelae of removing specific LMMs and the exploration of personalized dialysis prescriptions guided by individual uremic toxin profiles represent further important avenues for advancing the field. Future directions include nanotechnology-enhanced membranes, adsorptive mixed-matrix systems, and bioartificial kidneys that incorporate living renal epithelial cells – innovative strategies that hold promise for developing more physiological and effective dialysis treatments.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

Dr. Bang-Gee Hsu, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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Supplementary material

Supplement Table 1: Summary of recent meta-analyses comparing the clinical outcomes of expanded hemodialysis, hemodiafiltration, and high-flux hemodialysis

Study	Scope	Comparators	Key findings
Kandi *et al*., 2022 [59]	22 studies (6 RCTs, 16 non-RCTs), *n*=1811	HDx versus HF-HD	HDx improved QoL, reduced pruritus, restless legs, infection rates, and hospitalization; no significant difference in all-cause mortality or serious adverse events
Zhao *et al.*, 2022 [60]	18 studies, *n*=853	HDx versus HF-HD and HDF	HDx showed superior κ-FLC and λ-FLC removal versus both HF-HD and HDF; albumin loss comparable to HDF; no increase in adverse events
Mitchell *et al.*, 2023 [61]	79 studies (29 prioritized, including 13 RCTs)	HDx versus HF-HD and HDF	HDF outperforms HF-HD in mortality, CV risk, hospitalization, and QoL. HDx shows intermediate benefit – improves surrogate outcomes but no significant differences versus HDF in mortality or QoL

RCTs: Randomized controlled trials, QoL: Quality of life, λ-FLC: Lambda-free light chain, κ-FLC: κ-free light chain, CV: cardiovascular, HD: Hemodialysis, HF: High-Flux, HDx: Expanded hemodialysis, HDF: Hemodiafiltration

Supplement Table 2: Comparative performance of expanded hemodialysis in clinical studies

Study	Population	Comparison	Findings
Lee *et al*., 2021 [64]	80 HD patients	HDx versus OL-HDF, 12 months	No difference in CV outcomes, CAC increases in the HDx group
Maduell *et al*. 2022 [62]	23 HD patients	4 HDx filters versus HF-HD and HDF	All HDx filters outperformed HF-HD; nearly matched HDF in LMMs clearance
Ozarli *et al*., 2024 [65]	51 heart failure HD patients	HDx versus HF-HD, 12 weeks	Reduced IL-18, CRP, pentraxin-3, β2-microglobulin, improved vascular stiffness, and diastolic function
Aterini *et al*., 2024 [66]	10 elderly HD patients using tunneled central venous catheters with low blood flow	HDx versus HF-HD, 6 months	Improved β2-microglobulin, κ-FLC and λ-FLC, and prolactin clearance, decreased erythropoiesis-stimulating agent use, and stable albumin levels
Lim *et al*., 2025 [63]	80 new HD patients	HDx versus HF-HD, 12 months	Slower GFR decline, better LMMs removal, no difference in mortality/hospitalization

HD: Hemodialysis, HF-HD: High-flux hemodialysis, HDF: Hemodiafiltration, OL-HDF: On-line hemodiafiltration, LMMs: Larger middle molecules, CV: Cardiovascular, CRP: C-reactive protein, λ-FLC: Lambda-free light chain, κ-FLC: κ-free light chain, GFR: Glomerular filtration rate, CAC: Coronary artery calcium, HDx: Expanded hemodialysis, IL: Interleukin

Supplement Table 3: Clinical scenarios and evidence supporting expanded hemodialysis use

Study	Clinical scenario	Population	Key findings
Comoglu *et al*., 2022 [69]	Inflammation-driven conditions: Sepsis-AKI	38 septic AKI patients	HDx achieved higher TNF-α, IL-6, and IL-1β clearance versus HF membranes
Serrano Salazar *et al*., 2022 [70]	Inflammation-driven conditions: COVID-19	26 COVID-19 patients	HDx > OL-HDF in TNF-α and β2-microglobulin clearance; lower mortality observed
Koniman *et al*., 2023 [71]	Multiple myeloma-associated AKI	3 case series, 17 patients	MCO filters reduced FLCs effectively without significant albumin loss
Biedunkiewicz *et al*., 2024 [68]	PBUTs	12 HD patients	No significant difference in indoxyl sulfate reduction across HDx, pre-, mixed-, and post-HDF; PBUT removal is modest in all

AKI: Acute kidney injury, HF, High flux, HD: Hemodialysis, OL-HDF: On-line hemodiafiltration, MCO: Medium cut-off, FLCs: Free light chains, HDF: Hemodiafiltration, PBUTs: Protein-bound uremic toxins, IL: Interleukin, TNF-α: Tumor necrosis factor-α, calcium, HDx: Expanded hemodialysis