Impact of Expanded Hemodialysis Using Medium Cut-off Dialyzer on Quality of Life: Application of Dynamic Patient-Reported Outcome Measurement Tool

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Rationale & Objective: Current hemodialysis (HD) treatments have limited ability to clear larger-molecular-weight uremic toxins. Retention is associated with increased symptom burden, low health-related quality of life (HRQoL), and high mortality. Improved clearance, using novel medium cut-off dialyzers, termed expanded HD (HDx), may be associated with improved subjective experience. We have previously developed a dynamic patient-reported outcome measure (PROM) instrument to allow iterative recording to better appreciate the overall burden of disease and assess the impact of therapy changes.

Study Design: Single-center interventional pilot study.

Setting & Participants: 28 patients established on maintenance HD, London, Ontario, Canada.

Intervention: Initial study consisting of 2-week observation (baseline-conventional high-flux HD) followed by 12 weeks of HDx. HRQoL was assessed using the dynamic PROM instrument thrice weekly (enabled in a dedicated app as the London Evaluation of Illness [LEVIL]). Extension phase; 2-week baseline with 24 weeks of HDx and 8-week washout.

Outcomes: Principal aim was to establish whether HDx therapy was associated with improved HRQoL, evidence of dose-dependant response, and whether effects were durable over time, using LEVIL.

Results: Patients with lower LEVIL scores (<70/100) at baseline showed improvement in overall HRQoL after 8 weeks of therapy with similar carryover effect. General well-being, energy, and sleep quality were improved significantly as a consequence of HDx therapy. There were no detrimental effects of HDx detected in patients with higher baseline HRQoL.

Limitations: Small nonrandomized sample size. The coronavirus disease 2019 pandemic interfered with the extension phase.

Conclusions: Dynamic PROM assessment effectively identified patients with lower HRQoL and higher symptom burden, demonstrating durable time/dose-dependent improvements across a range of symptom domains. The use of this instrument may allow targeted selection of patients most likely to benefit from HDx therapy and assist in monitoring response and defining effect size and treatment duration to allow optimal design of further definitive randomized controlled trials of this newly introduced technology.

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Chronic kidney disease (CKD) leads to the accumulation of waste products.[1-3] Retained toxins are important in the pathophysiology of cardiovascular disease and the high level of chronic systemic inflammation characteristic of patients requiring maintenance hemodialysis (HD).[4-6] In addition, many patients experience significant symptom burden, impaired health-related quality of life (HRQoL), and excessively high rates of mortality.[1-3,6-9] The inadequate removal of larger middle-molecular-weight uremic toxins with conventional HD highlights an unmet clinical need, which until recently was largely unaddressed.

Medium cut-off dialyzers have been developed in an attempt to meet the need for improved clearance of larger middle-molecular-weight molecules, largely rejected by conventional high-flux HD and without the need for added resources, infrastructure, and patient criteria required by hemodiafiltration.[8,10] The combination of HD with medium cut-off dialyzers has been termed "expanded HD" (HDx). This allows more effective targeting of molecules of a molecular weight up to 45 kDa without the risk for removing essential proteins (principally albumin).[4,5,8,11-17]

Patient-reported outcome measures (PROMs) provide information relating to the patient's subjective experience of disease and treatment and can be important in supporting and evaluating health care quality and decision making.[18-22] Traditionally, PROMs specific to patients with CKD are largely used to provide cross-sectional assessment, have long recall periods (2-4 weeks), and are not intended to be used repeatedly. This is particularly important in the setting of HD because it is an inherently intermittent treatment with cyclical variation of symptoms and HRQoL that fluctuate to extremes during the treatment week (Fig 1C). Conventional questionnaire-based "snapshot" PROMs of the subjective state fail to appreciate the area under the curve of symptoms and reduced HRQoL and further hamper sensitivity to detect signal of need or

PLAIN-LANGUAGE SUMMARY

Maintenance hemodialysis patients experience symptom burden resulting in poor health-related quality of life and consequently extremely high rates of mortality due to retained uremic toxins. Inefficiencies of currently used dialysis membranes with their limited clearance of larger uremic toxins could be part of the reason why hemodialysis patients experience worse outcomes. Our aim was to evaluate patient response (using a dynamic patient-reported outcomes measurement tool; London Evaluation of Illness [LEVIL]) to a new medium cut-off dialysis membrane (HDx) that is able to clear toxins of larger size in the conventional hemodialysis population. We found that patients who experience symptoms including poor general well-being, low energy levels, and poor sleep quality have suboptimal health-related quality of life, which improves significantly with HDx after 8 weeks. The combination of LEVIL and HDx is capable of identifying patients in need and individualizing treatments to improve care in a constrained health care system.

monitor response to treatment.[22,23] From a patient perspective, these tools are arduous and time consuming to complete, increasing disease burden.

The London Evaluation of Illness (LEVIL) is an example of a dynamic PROM instrument, developed specifically (in conjunction with user input) to domains relevant for patients with CKD. LEVIL evaluates general well-being, energy level, sleep quality, bodily pain, appetite, and shortness of breath using visual analogue scales (Fig 1A). LEVIL has a very short recall period (24 hours), is intended for repeated use, and takes only seconds to complete, automatically uploading patient data for real-time monitoring, response, and subsequent analysis. Initial study has proven patient acceptability and ease of use, with evidence demonstrating sensitivity to detect clinically relevant changes over both short and longer periods, correlating to biomarkers of significance.[22]

The principal aim of this pilot study was to establish whether HDx is associated with changes in HRQoL/ symptom burden, evidence of dose-dependent response, and whether effects were durable over time.

METHODS

This study was conducted according to Good Clinical Practice/ International Conference on Harmonisation guidelines and the principles of the Declaration of Helsinki, with appropriate ethical approvals (REB #1589). All patients gave their written informed consent before participating in this study.

Study Design

This was a single-center, unblinded, exploratory pilot study in the prevalent adult HD population within the London Health Sciences Centre Renal Program, Ontario, Canada. Baseline data were obtained over a 2-week duration in which patients completed the app-based LEVIL PROM with each HD session while dialyzing with their usual high-flux dialyzer. After this baseline period, HD treatment was continued using an identical HD prescription; however, a medium cut-off dialyzer (Theranova; Baxter Healthcare) was substituted for the high-flux membrane with maintained surface area (smaller surface area high-flux converted to Theranova 400, larger surface area high-flux converted to Theranova 500). Patients continued to complete the LEVIL PROM with each HD treatment for 12 weeks of HDx intervention.

Blood work including complete blood cell count, electrolytes, urea, creatinine, calcium, phosphorus, albumin, C-reactive protein, β_2-microglobulin (B2M), κ free light chains (K-FLCs), λ free light chains (L-FLCs), and free light chain ratio was obtained before and after HD, midweek, and at baseline and repeated after 12 weeks of HDx.

To further evaluate an extended course of HDx therapy, a 24-week extension was conducted. A washout phase was added in which patients returned to high-flux HD while completing LEVIL for an additional 8 weeks to assess the presence of any carryover effect.

Study Population
Initial Study (12 weeks of HDx)

Patients were included if they were older than 18 years and receiving maintenance thrice-weekly HD for more than 3 months. Twenty-eight patients were consented to participate. One patient died before initiation of the study and another died during the study (due to overwhelming sepsis), 1 patient was removed from study procedures for not attending HD regularly, and 3 participants chose to withdraw consent. Twenty-two patients completed all study procedures to contribute to the full 12-week analysis.

Extension (24 weeks of HDx)

Due to the coronavirus disease 2019 (COVID-19) pandemic and inability of research staff to access patients, a vast amount of data collection was unattainable. However, 6 participants were able to use their personal smartphones for LEVIL PROM data collection. See Consolidated Standards of Reporting Trials chart of study flow in Fig S1.

Outcomes

The primary outcome was change in iteratively recorded symptoms (using LEVIL) and HRQoL associated with conversion to HDx therapy and by comparison to treatment with conventional high-flux HD. Secondary outcomes included comparison of middle-molecule biomarkers from baseline to 12 weeks of HDx therapy, as well as middle-molecule reduction ratios. Reduction ratios were calculated as: $[1 - (concentration_{post}/concentration_{pre})] \times 100$.
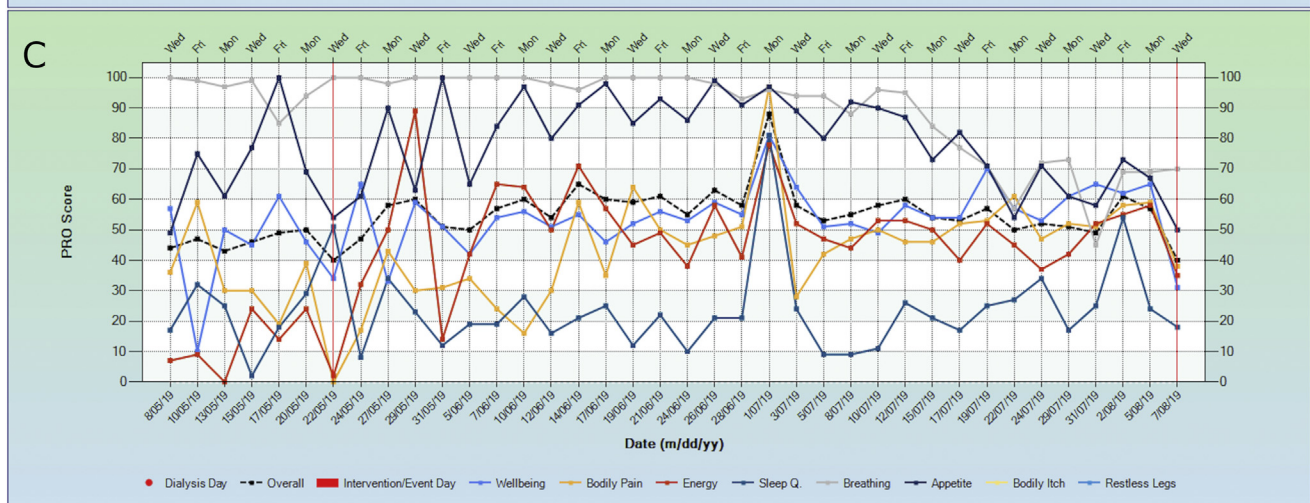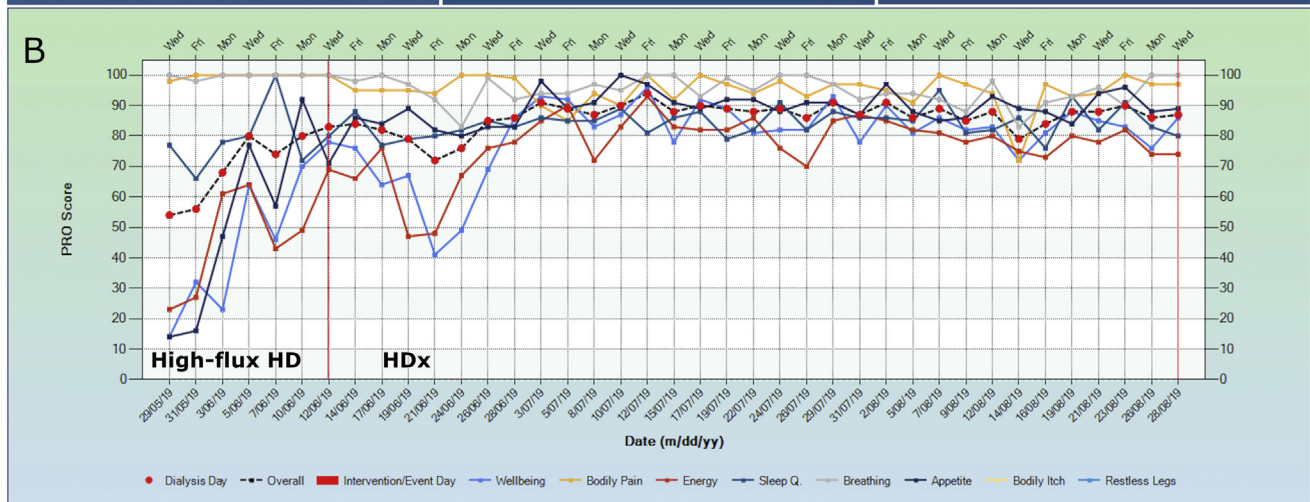
Table 1. Patient Demographics for Total Population and Stratified Groups

	Total Population (N = 22)	Low Overall QoL (N = 16)	High Overall QoL (N = 6)	P
Age, y	65.6 ± 14.6	64.9 ± 16	67.3 ± 11.3	0.84
HD vintage, mo	55 (27,93)	78 (37,122)	27 (12,56)	0.06
Male sex	11 (50%)	8 (50%)	3 (50%)	>0.99
Diabetes mellitus	9 (41%)	6 (38%)	3 (50%)	0.66
AVF	14 (64%)	9 (56%)	5 (83%)	0.35
CVC	8 (36%)	7 (44%)	1 (17%)	0.35
Kt/V	1.4±0.2	1.4±0.2	1.3±0.2	0.13
RRF, mL	0 (0, 606)	0 (0, 400)	450 (32, 1,150)	0.08
RRF	9 (41%)	5 (31%)	4 (67%)	0.18
Theranova 400	11 (50%)	7 (44%)	4 (67%)	0.64
Theranova 500	11 (50%)	9 (56%)	2 (33%)	0.64
Causes of kidney disease				0.11
Diabetes mellitus	7 (32%)	5 (31%)	2 (33%)	—
Reflux nephropathy	3 (14%)	2 (13%)	1 (17%)	—
Glomerulonephritis	3 (14%)	3 (19%)	0 (0%)	—
Hypertension	2 (9%)	1 (6%)	1 (17%)	—
IgA nephropathy	2 (9%)	0 (0%)	2 (33%)	—
Other	5 (23%)	5 (31%)	0 (0%)	—

Note: Continuous values are represented as mean ± standard deviation or median (25th, 75th) categorical values represented as whole numbers (percent).
Abbreviations: AVF, arteriovenous fistula; CVC, central venous catheter; HD, hemodialysis; IgA, immunoglobulin A; QoL, quality of life; RRF, residual renal function.

Dialysis Treatments

Dialysis treatments were delivered using Fresenius 5008 dialysis monitors. Treatment times ranged from 3.5 to 4 hours thrice weekly, dialysate sodium concentration ranged from 134 to 140 mmol/L, dialysate potassium concentration was either 1.5 or 3.0 mmol/L, dialysate calcium concentration was 1.25 mmol/L, bicarbonate concentration was 35 to 40 mmol/L, and dialysate flow was 500 mL/min. All patients received low-molecular-weight heparin for intradialytic anticoagulation. Net ultrafiltration was calculated on an individual basis according to each patient's ideal dry weight. Patients dialyzed using their prescribed HD treatment with a high-flux polysulfone dialyzer for the first 2 weeks of study (baseline) before changing to HDx therapy for the intervention phase of the study (with appropriate choice of effective surface area informed by previous adequacy requirements). No other changes were made to the dialysis prescription.

Dynamic PROM LEVIL

The LEVIL application was installed onto a study-dedicated iPad. Patient-specific identifiers were assigned to each participant and entered into the application by the study coordinators/researchers. The iPad was then handed to each participant to complete the questionnaire and submit results immediately. If a patient was not able to complete the survey independently (visual impairment, positioning, or dominant hand restrictions), assistance was provided at the most minimal level required to allow completion.

Participants answered 6 questions with each HD session, consisting of feeling of general well-being from very poor to excellent, presence and severity of bodily pain from extreme to no problem, feeling washed out or drained from extremely fatigued to full of energy, sleep quality from very poor to excellent, difficulty breathing or shortness of breath from extreme to no problem, and last, appetite from very poor to excellent (Fig 1A). Baseline symptom measures were established after 2 weeks of thrice-weekly LEVIL entries (high-flux HD). Patients continued completing LEVIL PROM with each HDx treatment throughout the remaining 12 (initial study) and 24 weeks (extension) of intervention. Additionally, extension participants continued completing the LEVIL PROM for an 8-week washout period on return to high-flux HD.

LEVIL Outputs

Each LEVIL PROM entry resulted in an embedded numeric output between 0 (poor) and 100 (excellent) for each of the 6 questions. The system automatically calculated an "overall" score for each entry (average of all 6 domain-specific scores).

Figure 1 (previous page). (A) London Evaluation of Illness (LEVIL) application questions. (B) Example of a patient's response to expanded hemodialysis (HDx); LEVIL graphical output. (C) Variability in symptoms day to day using LEVIL (conventional high-flux hemodialysis [HD]). Abbreviation: PRO, patient-reported outcome.

Table 2. Perceived HRQoL Acceptable/Unacceptable Patient Scores

N = 11	Acceptable Scores			Unacceptable Scores		
	Mean ± SD	Median (25th, 75th percentile)	Range	Mean ± SD	Median (25th, 75th percentile)	Range
Well-being	81.4±8.7	80 (75, 90)	70-95	59.1±12.8	55 (50, 70)	40-80
Energy	75.9±11.4	80 (70, 80)	50-90	52.7±15.6	50 (50, 70)	30-80
Sleep	76.8±16.9	80 (75, 90)	40-95	55±14.3	60 (40, 70)	30-75
Pain	82.7±10.1	85 (75, 90)	60-95	65±15	60 (50, 80)	50-90
Appetite	82.3±9.3	80 (70, 90)	70-95	60.5±13.5	60 (50, 70)	40-85
Breathing	85±16	90 (80,90)	40-100	64.6±15.9	60 (50,80)	40-90
Overall	80.7±12.4	80 (75,90)	40-100	59.5±14.7	60 (50,70)	30-60

Note: Scores for patient-perceived acceptable/unacceptable scores.
Abbreviations: HRQoL, health-related quality of life; SD, standard deviation.

For the baseline (high-flux HD), each participant's entries for the first 2 weeks of study were collectively averaged to calculate a baseline measurement. Baseline scores were used for stratification (overall and domain specific). During the intervention phase (HDx), each participant's entries were collectively averaged every 4 weeks throughout the study for both the initial (4, 8, and 12 weeks of HDx) and extension phase (4, 8, 12, 16, 20, and 24 weeks). In the washout phase (extension only), on return to high-flux HD, LEVIL scores were averaged for the 4-week washout and 8-week washout. This was intended to assess the carryover effect of HDx.

Statistical Analysis

Descriptive statistics are reported as mean ± standard deviation or median with interquartile range for continuous variables and as frequency and percentage for categorical variables. Mean differences between groups were analyzed using paired t test and within groups using analysis of variance for repeated measures. Analyses were performed using GraphPad Prism, version 8.4.2 (GraphPad Software).

RESULTS

Baseline Characteristics

Baseline clinical characteristics are summarized in Table 1. Participants' mean age was 65.6±14.6 years, median HD vintage was 55 months, 50% of participants were men, 41% had diabetes mellitus type 2, 64% dialyzed using an arteriovenous fistula, mean Kt/V was 1.4±0.2, and 41% of patients had some degree of residual kidney function. Documented causes of kidney disease include diabetes mellitus (32%), reflux nephropathy (14%), glomerulonephritis (14%), hypertension (9%), and immunoglobulin A nephropathy (9%); other causes included polycystic kidney disease, lithium toxicity, and glomerulosclerosis.
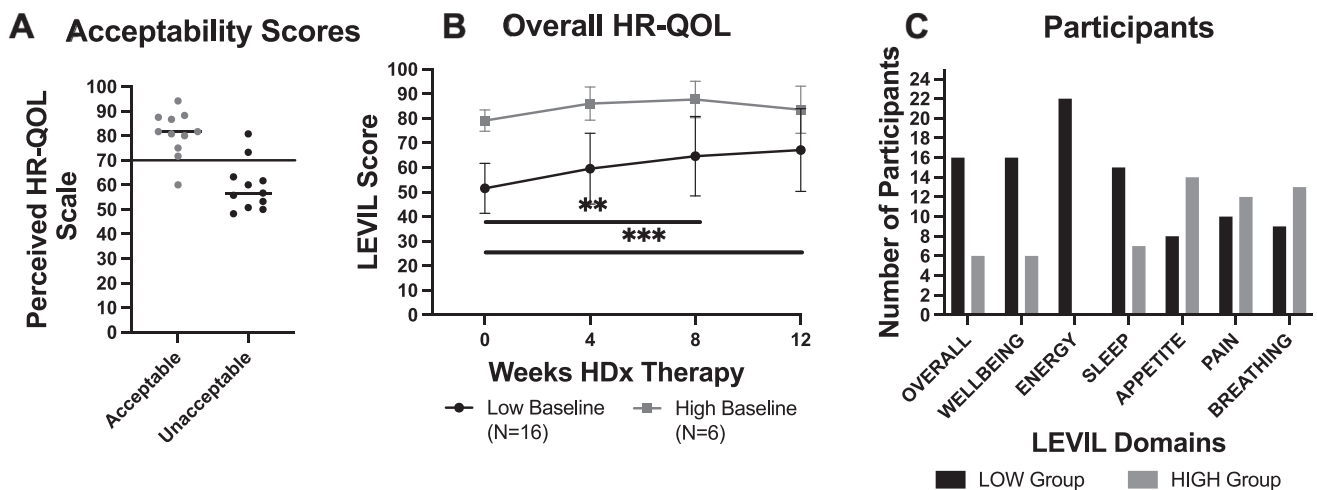

Figure 2. Stratification. (A) Individual participant's scores for acceptable versus unacceptable overall quality of life. (B) Overall quality-of-life scores over course of study. (C) Number of participants with high/low baseline scores for each symptom domain. Abbreviations: HDx, expanded hemodialysis; HR-QOL, health-related quality of life; LEVIL, London Evaluation of Illness.

Stratification of LEVIL Outputs

Group stratification was determined using baseline LEVIL scores. Patients with an average baseline score < 70 were grouped as low, while those with an average baseline score ≥ 70 were grouped as high. This method of stratification was used for all analyses. Primary analysis was based on overall scores (6 domains combined), whereas subgroup analysis was domain specific.

Rationale for Stratification

Justification for group stratification was based on input from our study participants. A survey was designed in which study participants were asked their perspective on an "acceptable" score for each symptom domain, and alternatively, what they thought an "unacceptable" score was for each symptom domain. Patient ratings for each symptom domain were ranked using the same scale as used with LEVIL PROM, 0 (very poor) to 100 (excellent). Eleven (50%) study participants were randomly selected to complete the survey (poststudy/preanalysis; 55% of those surveyed fell into the low group poststratification, 45% fell

into the high group poststratification). As with LEVIL PROM, domain-specific results were combined for an overall score.

Patients were asked "What would be an acceptable score for you in regards to…" well-being (mean score, 81.4 ± 8.7), energy (mean, 75.9 ± 11.4), sleep quality (mean, 76.8 ± 16.9), bodily pain (mean, 82.7 ± 10.1), appetite (mean, 82.3 ± 9.3), and difficulty breathing/shortness of breath (mean, 85 ± 16). Patient responses resulted in an overall acceptable score of 80.7 ± 12.4 (Table 2; Fig 2A).

When patients were asked "What would be an unacceptable score for you in regards to…" well-being (mean score, 59.1 ± 12.8), energy (mean, 52.7 ± 15.6), sleep quality (mean, 55 ± 14.3), bodily pain (mean, 65 ± 15), appetite (mean, 60.5 ± 13.5), and difficulty breathing/shortness of breath (mean, 64.6 ± 15.9). Overall unacceptable score was 59.5 ± 14.7 (Table 2; Fig 2A). The midpoint between overall acceptable and unacceptable values was 70. Therefore, we chose this as the threshold for stratification to high (≥70) and low (<70) groups at baseline.

Table 3. LEVIL Scores at Baseline and 4, 8, and 12 Weeks of HDx Therapy; – Total Population, Stratified Groups

Initial Study	Total Population							
	N	Baseline	4-wk HDx	P	8-wk HDx	P	12-wk HDx	P
Overall HRQoL	22	59.1±14.4	66.8±17.5	0.12	70.9±17.6	<0.001	71.9±16.8	<0.001
Subgroup analysis								
General well-being	22	52.2±19.6	60.9±23	0.28	69±21.1	0.001	71±17.9	0.002
Energy	22	40.3±20.5	53.4±23.3	0.16	59.9±22.8	0.001	64.7±19.6	<0.001
Sleep quality	22	49.4±26.8	62.2±27.9	<0.001	65.6±24.2	<0.001	68.9±24.5	<0.001
Bodily pain	22	67.3±25.5	68±26.8	>0.99	72.5±25.2	>0.99	71.5±22.1	>0.99
Appetite	22	70.3±21.8	77.9±21.6	>0.99	81.1±21.2	0.28	78.0±22.5	>0.99
Breathing	22	78.2±27.5	77.4±25.8	>0.99	75.9±22.9	>0.99	49.6±22.2	>0.99

Scores < 70 at Baseline: Low								
	N	Baseline	4 wk HDx	P	8 wk HDx	P	12 wk HDx	P
Overall HRQoL	16	51.5±10.2	59.5±14.4	0.33	64.6±16.2	0.001	67.2±16.9	<0.001
Subgroup analysis								
General well-being	16	43±14.1	52.9±21.4	>0.99	65.2±21.9	<0.001	66.3±17.7	0.002
Energy	22	40.3±20.5	53.4±23.3	0.16	59.9±22.8	0.001	64.7±19.6	<0.001
Sleep quality	16	37.2±20.1	52.8±26.7	0.01	57±22.2	0.002	61.7±24.5	<0.001
Bodily pain	10	43.2±12.3	47.4±24	>0.99	56.2±25.7	0.23	57.3±20.5	0.15
Appetite	8	46.1±14.8	63.8±28	>0.99	67±30.8	0.05	66.9±31.8	0.39
Breathing	9	49.6±22.2	53.7±27.3	>0.99	53.7±23.5	>0.99	61.6±24.6	0.11

Scores ≥ 70 at Baseline: High								
	N	Baseline	4 wk HDx	P	8 wk HDx	P	12 wk HDx	P
Overall HRQoL	6	79.2±4.3	86.1±6.8	>0.99	87.7±7.4	0.15	83.6±9.6	>0.99
Subgroup analysis								
General well-being	6	76.6±5.6	82.1±9.7	0.71	78.9±16.6	>0.99	83.5±12.2	>0.99
Energy	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sleep quality	6	81.8±8.3	87.3±10.4	0.15	88.8±9.8	0.01	89.2±6.3	0.04
Bodily pain	12	87.4±12.1	85.2±13.8	>0.99	86.1±15.3	>0.99	82.9±16.1	0.68
Appetite	14	84.3±8.8	85.9±11.9	>0.99	88±8.6	>0.99	84.4±12.4	>0.99
Breathing	13	92±9	95.2±8.4	>0.99	93.8±9.2	>0.99	85.8±16	>0.99

Abbreviations: HDx, expanded hemodialysis; HRQoL, health-related quality of life; LEVIL, London Evaluation of Illness.

Overall Quality of Life

On stratification, there were no differences in baseline characteristics between groups (Table 1). Sixteen participants (73%) had low overall HRQoL (mean, 51.5±10.2; range,36.1-69.3), with statistically significant improvement after 8 weeks of HDx therapy (mean, 64.6 ± 16.2; P = 0.001) as well as after 12 weeks of HDx therapy (67.2 ± 16.9; P = 0.001) when compared with baseline. Six (27%) participants had a high overall HRQoL score at baseline (mean, 79.2 ± 4.3; Table 3), with no significant changes throughout the course of study (Table 3; Fig 2B).

Circulating Levels of Middle Molecules

B2M, K-FLC, L-FLC, free light chain ratio, and albumin were measured at baseline and again after 12 weeks of HDx therapy. HDx therapy had no impact on hemoglobin levels, with similar changes to small- and middle-molecular clearance (urea/creatinine) as high-flux HD. After 12 weeks of HDx, there was no change in albumin levels (P = 0.73; Table 4).

β₂-Microglobulin

There were no significant changes in predialysis serum B2M levels with high-flux HD compared with HDx after 12 weeks (total population, 28.8 ± 6.8 vs 28.6 ± 5.9 mg/L; P = 0.91; low overall HRQoL, 29.4 ± 7.4 and 29 ± 6.4 mg/L; P = 0.63; and high overall HRQoL, 27.3 ± 5.2 and 27.6 ± 4.4 mg/L; P = 0.44, respectively). However, there was significance in the reduction ratio of B2M between high-flux-HD and HDx (total population, 54.2% ± 9.4% and 70.6% ± 6.3%; P < 0.001; low overall HRQoL, 55.3% ± 10.1% vs 71.5% ± 6.4%; P < 0.001; and high overall HRQoL, 51.5% ± 8.1% and 68.3% ± 5.9%; P = 0.03, respectively; Table 4). Although HDx was

Table 4. Laboratory Values at Baseline Compared With 12-Week HDx

	Baseline	12-wk HDx	Baseline to 12-wk HDx *P*
Total Population Overall HRQoL (N=22)			
Alb, g/L	41±3.8	40.8±2.8	0.73
Alb RR, %	3.9±6.4	4.3±7.1	0.78
B2M, mg/L	28.8±6.8	28.6±5.9	0.91
B2M RR, %	54.2±9.6	70.6±6.3	<0.001
K-FLC, mg/L	183.6±126.7	164.1±100.4	0.002
K-FLC RR, %	27±22.1	53.3±12.7	<0.001
L-FLC, mg/L	119.2±40.1	111.6±36.8	0.02
L-FLC RR, %	3±9.1	29.5±10	<0.001
FLC-R	1.7±1.3	1.6±1.1	0.15
FLC-R RR, %	24.9±21.1	34.1±13.3	0.05
Low Overall HRQoL Group (N=16)			
Alb, g/L	40.6±2.9	40.6±2.9	0.96
Alb RR, %	3.1±6.3	3.8±8	0.88
B2M, mg/L	29.4±7.4	29±6.4	0.63
B2M RR, %	55.3±10.1	71.5±6.4	<0.001
K-FLC, mg/L	198.9±145.1	178.2±113.3	0.02
K-FLC RR, %	25.8±25.9	54.2±14.1	<0.001
L-FLC, mg/L	118.6±36.5	111.7±36.1	0.07
L-FLC RR, %	3.6±8	32.5±10.1	<0.001
FLC-R	1.8±1.5	1.7±1.2	0.37
FLC-R RR, %	23.5±24.6	32.8±14.9	0.23
High Overall HRQoL Group (N=6)			
Alb, g/L	41.8±4.6	41.2±2.9	0.69
Alb RR, %	6.6±6.7	6±2.3	>0.99
B2M, mg/L	27.3±5.2	27.6±4.4	0.44
B2M RR, %	51.1±8.1	68.3±5.9	0.03
K-FLC, mg/L	142.8±38.5	126.6±38	0.16
K-FLC RR, %	30±8	50.9±9.1	0.03
L-FLC, mg/L	120.8±52.6	111.3±42.2	0.22
L-FLC RR, %	1.7±12.1	22.1±4	0.03
FLC-R	1.3±0.3	1.2±0.2	0.22
FLC-R RR, %	28.4±7.9	37.1±8	0.31

Note: Values are represented as mean ± standard deviation.
Abbreviations: Alb, albumin; B2M, β₂-microglobulin; HDx, expanded hemodialysis; HRQoL, health-related quality of life; K-FLC, κ free light chains; L-FLC, λ free light chains; FLC-R, free light chain ratio; RR, reduction ratio.

superior at clearing B2M incidentally, there were no serum reductions over time, possibly due to interdialytic rebound into the circulation (potentially with significant depuration of tissues).

Free Light Chains

A significant reduction in serum K-FLC was noted between high-flux HD and 12 weeks of HDx in those with low baseline scores (total population, 183.6 ± 126.7 vs 164.1 ± 100.4 mg/L; $P = 0.002$; low overall HRQoL, 198.9 ± 145.1 and 178.2 ± 113.3 mg/L; $P = 0.02$; and high overall HRQoL, 142.8 ± 38.5 and 126.6 ± 38 mg/L; $P = 0.16$; Table 4). Serum reductions in L-FLC were noted after 12 weeks of HDx in the total population (baseline, 119.2 ± 40.1 mg/L; HDx, 111.6 ± 36.8 mg/L; $P = 0.02$); however, statistical significance was not reached within groups (low overall HRQoL, 118.6 ± 36.5 vs 117.7 ± 36.1 mg/L; $P = 0.07$; and high overall HRQoL, 120.8 ± 52.6 and 111.3 ± 42.2 mg/L; $P = 0.22$ respectively; Table 4).

Consistently, reduction ratios comparing high-flux-HD with HDx were significant throughout the entire population. K-FLC reduction ratio; total population, $27\% \pm 22.1\%$ vs $53.3\% \pm 12.7\%$; $P < 0.001$; low HRQoL, $25.8\% \pm$ 25.9% at baseline compared to $54.2\% \pm 14.1\%$ HDx; $P < 0.001$; and high HRQoL, $30\% \pm 8\%$ baseline compared to $50.9\% \pm 9.1\%$ with HDx ($P = 0.03$). L-FLC reduction ratio; total population, $3\% \pm 9.1\%$ versus $29.5\% \pm 10\%$; $P < 0.001$; low HRQoL, $3.6\% \pm 8\%$ at baseline versus $32.5\% \pm 10.1\%$; $P < 0.001$; and high HRQoL, $1.7\% \pm 12.1\%$ versus $22.1\% \pm 4\%$; $P = 0.03$ (Table 4).

Subgroup Analysis; Domain Specific
Feeling of General Well-being

Sixteen (73%) participants had a low score at baseline (mean, 43 ± 14.1; range, 19.7-69.5), which significantly improved after both 8 (65.2 ± 21.9; $P < 0.001$) and 12 weeks (66.3 ± 17.7; $P = 0.002$) of HDx therapy. The remaining 6 participants with a high score at baseline (mean, 76.6 ± 5.6) saw no change, positive or negative, with HDx (Table 3; Fig 3A).

Feeling Washed Out/Drained

All participants experienced lack of energy with high-flux HD (mean, 40.3 ± 20.5; range, 8.7-67.4). The initial response to HDx was seen at 8 weeks (59.9 ± 22.8; $P = 0.001$) with continued improvement after 12 weeks (64.7 ± 19.6; $P < 0.001$; Table 3; Fig 3B).
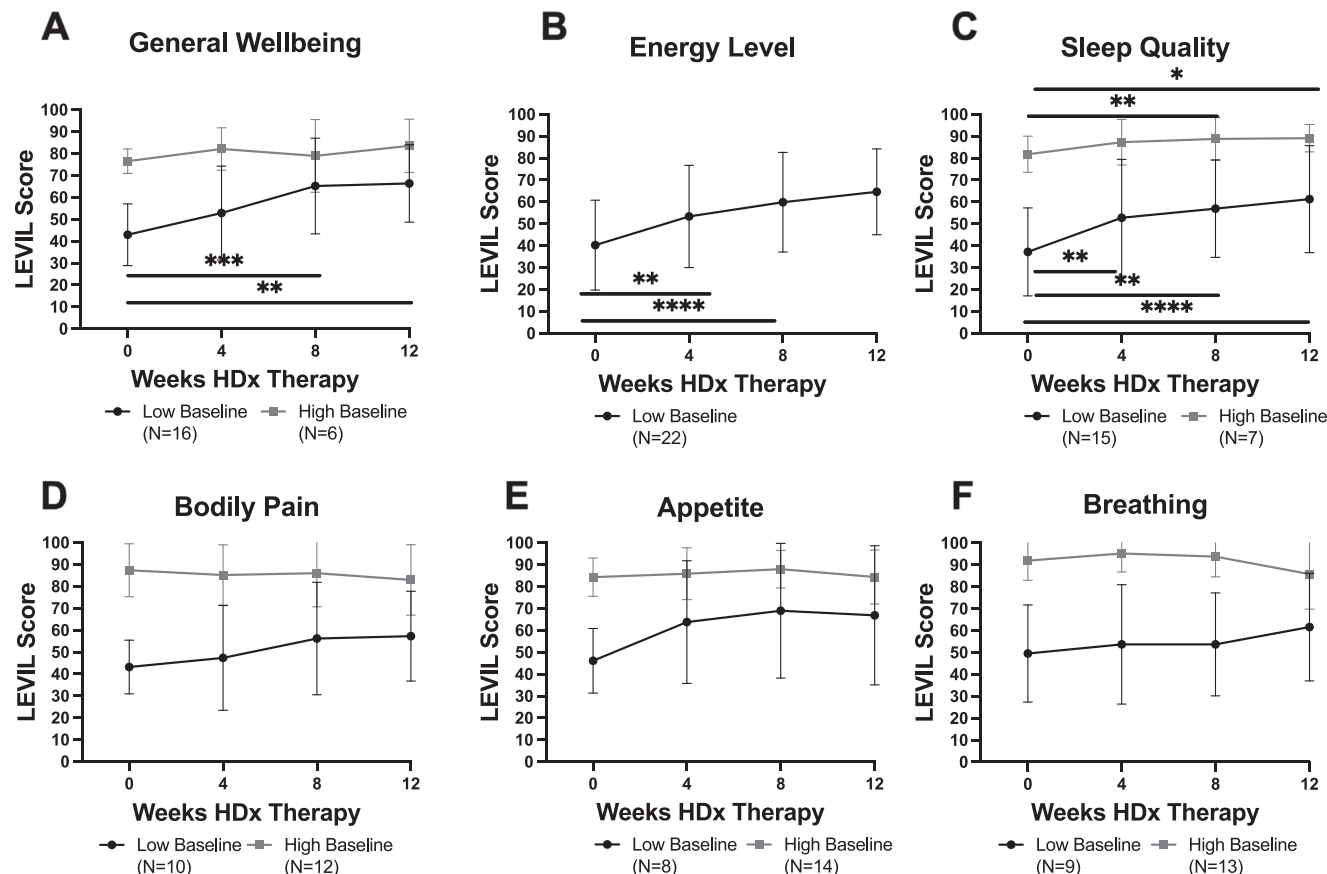

Figure 3. Subgroup analysis: domain specific analysis. (A) General well-being, (B) energy, (C) sleep, (D) pain, (E) appetite, and (F) breathing. Abbreviations: HDx, expanded hemodialysis; LEVIL, London Evaluation of Illness.

Sleep Quality

Seventy-three percent of participants experienced poor sleep quality (baseline: mean, 37.2 ± 20.1; range, 7.2-66.2). Improvement in sleep was initially seen after only 4 weeks of HDx (mean, 52.8 ± 26.7; $P = 0.01$) and continually improved throughout our investigation (8 weeks: mean, 57 ± 22.2; $P = 0.002$; 12 weeks: mean, 61.7 ± 24.5; $P < 0.001$). Additional benefit was seen in the 6 participants with already acceptable levels of sleep quality (mean, 81.8 ± 8.3) with improvement after 8 and 12 weeks of HDx (88.8 ± 9.8; $P = 0.001$; and 89.2 ± 6.3; $P = 0.04$, respectively; Table 3; Fig 3C).

Presence and Severity of Bodily Pain

HDx did not affect pain (Table 3; Fig 3D).

Appetite

There was no consistent improvement in appetite with HDx (Table 3; Fig 3E).

Difficulty Breathing/Shortness of Breath

HDx therapy did not affect breathing scores (Table 3; Fig 3F).

Extension Evaluation

Although our study population was smaller than expected due to the COVID-19 pandemic and significance could not be reached, Fig 4A-D visually shows a similar effect profile consistent with the 12-week study results (Table S1). General well-being, energy, and sleep quality were the drivers of poor HRQoL, experienced by most patients with some response to therapy consistently after 8 weeks in these domains. The washout period provided carryover profiling trending similar to effect profile.

DISCUSSION

This study demonstrated that HDx therapy improves HRQoL and reduces symptom burden in the prevalent HD population, with the most significant improvement in participants with poorer HRQoL at baseline. Furthermore, there was no decline in HRQoL or exacerbation of symptoms for participants with pre-existing higher HRQoL at baseline. Use of a dynamic PROM instrument (LEVIL) established an effect profile for HDx therapy and identified
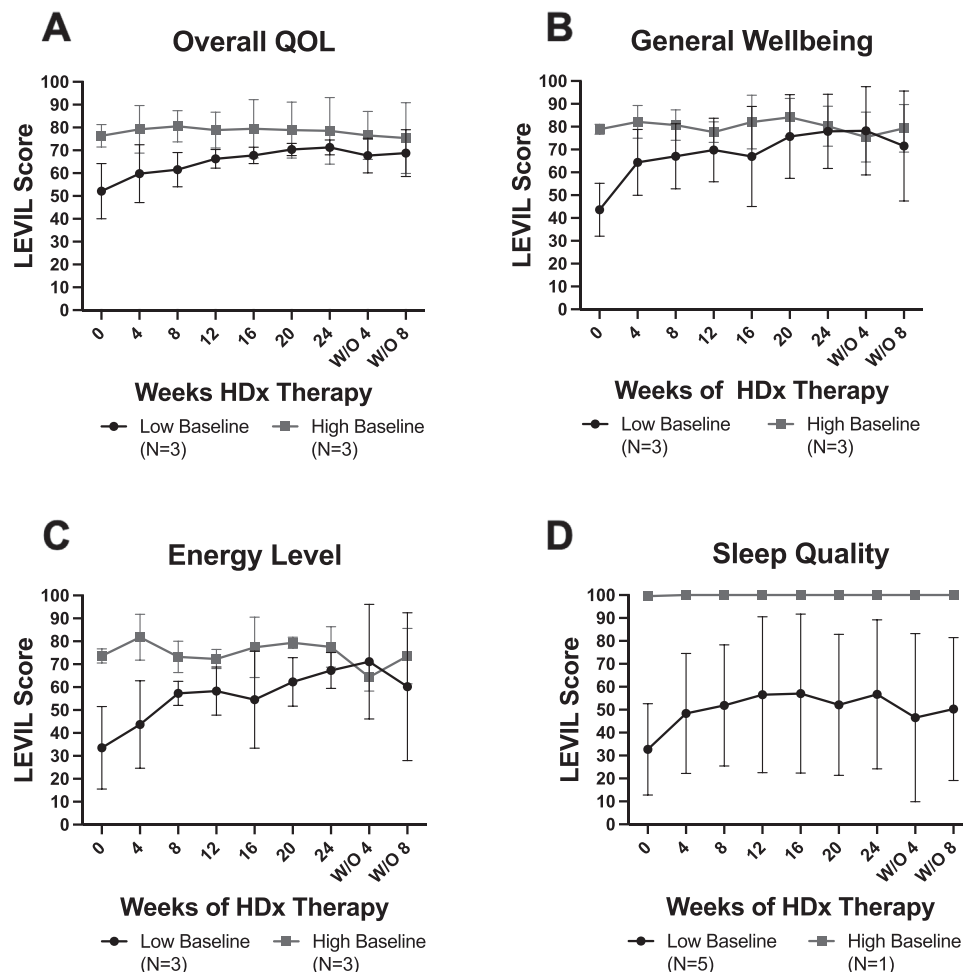

Figure 4. Extension phase; 24 weeks of expanded hemodialysis (HDx) therapy with 8 weeks of washout (W/O). (A) Overall and (B-D) domain-specific quality of life (QOL). Abbreviation: LEVIL, London Evaluation of Illness.

a population that should receive the most benefit. A dose-dependent response was sustainable with a similar timeline to return to previous status after HDx therapy suspension, these changes being consistent with an improved middle-molecule removal profile.

The efficacy and safety of HDx has been well established.[8,15-17,19,24,25] The literature suggests the reduction ratio of larger middle molecules in HDx therapy to be similar to hemodiafiltration,[8,10] resulting in improved health-related physical functioning scores.[26,27] Recent studies using pre-existing cross-sectional PROM tools for CKD report that HDx therapy also has a positive impact on HRQoL, improving physical function and reducing the severity and frequency of symptoms and disease burden.[16,19]

However, to date, there is no available information on the onset timing, scale, or durability of effect of HDx therapy on HRQoL. Additionally, there has been no direct interrogation into the characteristics of populations that may benefit from HDx therapy to assist in clinical decision making and resource allocation. With the substantial fluctuations in day-to-day symptoms that intermittent HD induces (Fig 1C), knowledge on targeted therapy is crucial.

This study enhances current knowledge and highlights valuable details relating to the effect profile of HDx therapy, targeted symptoms, and population framework. Our findings suggest that HDx therapy has a profound influence on patients with HRQoL scores < 70 (poorer HRQoL measured using LEVIL), which tend to be patients with longer HD vintage, higher prevalence of central venous catheter, low residual kidney function, and higher K-FLC levels. HDx therapy effectively targets a range of common symptoms that conventional high-flux HD appears to manage less well. In terms of dose response, improved general well-being and energy is evident by 8 weeks, whereas sleep quality has an earlier response profile, all of which proved to be sustained over time (12- and 24-week evaluations; Fig 1B). On return to high-flux HD, the loss of effect and return to baseline appeared to be very similar in terms of delayed onset of effect, although further investigation is required. This is in keeping with a putative clearance-based explanation of symptom improvement with HDx therapy.[16,19]

Dynamic PROM measurement with LEVIL may aid in the selection and continuous maintenance of patients most in need, if resources are constrained. Biological plausibility, effect size, duration, and potential assessment methods have now been established for the design and implementation of a definitive large-scale, multicenter, randomized, controlled trial as the final crucial step in the implementation of this new dialysis therapy.

Our study has a number of limitations, including small sample size in a single-center setting and nonrandomized unblinded design. The lack of a control group warrants caution in evaluating the study results; however, the delayed improvement in HRQoL in response to HDx therapy and the carryover effect after its suspension support the possibility of a direct effect of HDx therapy on HRQoL based on improved middle-molecule removal. The definition of domain acceptability thresholds by a random study subsample may have introduced bias in the definition of these thresholds. Increasing restrictions due to the COVID-19 pandemic also challenged the conduct of elements of this study.

This study using dynamic PROM (LEVIL) assessment effectively identified patients with lower HRQoL and higher symptom burden, demonstrating durable time/dose-dependent improvements across a range of symptom domains. The use of this instrument may allow targeted selection of patients most likely to benefit from HDx therapy to allow intelligent use of limited resources. By defining populations likely to benefit, effect size, and required treatment duration,this study will allow optimal design of further definitive randomized controlled trials of this newly introduced technology.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Study Consolidated Standards of Reporting Trials (CONSORT) chart

Table S1: LEVIL scores for extension phase (24 weeks)

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What is the impact of expanded dialysis using medium cut-off dialyzer on quality of life?

Kidney Medicine

Methods

Single center pilot study

n = 28
Age > 18 yrs

Maintenance Hemodialysis

Intervention

Initial study
✦ 2 week observation
✦ Conventional high flux HD

12 weeks of expanded dialysis (HDx, Medium cut-off dialyzer)

Extension phase
✦ 2 week observation with 24 weeks HDx
✦ 8 week wash out

HR-QoL assessed thrice weekly using dynamic patient related outcome measurement *(PROM-LEVIL)*

Findings

In patients with "Low" HR-QoL (*PROM-LEVIL* score < 70/100)

Outcomes	Baseline PROM-LEVIL score	At 8 weeks	At 12 weeks
Overall QoL	51.5 ± 10.2	64.6 ±1 6.2 $P = 0.001$	67.2 ± 16.9 $P = 0.001$
General wellbeing	43 ± 14.1	65.2 ± 21.9 $P < 0.001$	66.3 ± 17.7 $P = 0.002$
Energy	40.3 ± 20.5	59.9 ± 22.8 $P = 0.001$	64.7 ± 19.6 $P < 0.001$
Sleep	37.2 ± 20.1	57 ± 22.2 $P = 0.002$	61.7 ± 24.5 $P < 0.001$

There were no detrimental effects of HDx detected in patients with higher baseline HR-QoL (*PROM-LEVIL* score > 70).
Extension phase not reported in table above

Conclusion: Dynamic PROM assessment with PROM-LEVIL identified patients with lower HR-QoL and higher symptom burden, and, in this non-controlled study among those with lower baseline QoL, quality of life scores improved with HDx. PROM-LEVIL is a promising tool for use in subsequent RCTs of HDx.