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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BACKGROUND

Many patients with chronic kidney disease (CKD) have retained toxins, particularly larger molecular weight toxins, despite maintenance hemodialysis (HD). These toxins have been associated with cardiovascular disease, chronic systemic inflammation, and increased mortality. Not surprisingly, patients receiving maintenance HD often report significant symptom burden and impaired health-related quality of life (HRQoL). To address this need, medium cut-off dialyzers have been developed that offer the opportunity to remove middle-molecular-weight molecules without removing essential proteins such as albumin and without the need for high-flux hemodiafiltration and its added requirements of infrastructure, costs, and patient selection criteria. Patient-reported outcome measures (PROMs) may help guide clinicians in determining when traditional HD has not sufficiently managed patient symptoms and improved their HRQoL. Theoretically, the use of a rapid, relevant, and repeated PROM tool could guide clinical decisions about the most appropriate dialyzer for a specific patient. The London Evaluation of Illness (LEVIL), is such a PROM instrument. Developed with user input, this tool measures well-being, energy level, sleep quality, bodily pain, appetite, and shortness of breath using visual analog scales. LEVIL takes only seconds to complete, provides real-time monitoring, allows a 24-hour recall period, and is intended for repeated use. An initial study has proven that LEVIL is easy to use, acceptable to patients, and sensitive to clinical changes in the short- and long-term.

OBJECTIVE

This pilot study's main purpose was to establish whether expanded hemodialysis utilizing medium cut-off dialyzers may be associated with changes in HRQoL/symptom burden, whether there may be a dose-dependent response, and whether effects were durable over time, as assessed using LEVIL.

METHODOLOGY

This single-center, unblinded, exploratory pilot study was conducted in the prevalent adult HD population within the London Health Sciences Centre Renal Program in Ontario, Canada. All patients had been receiving thrice-weekly HD for > 3 months. During the 2-week baseline period, patients completed the app-based LEVIL assessment during each of their usual high-flux dialyzer sessions. During the 12-week test period, patients completed LEVIL while receiving HD with a medium cut-off dialyzer that maintained the surface area of the membrane that had been used during the baseline period (i.e., smaller-surface-area dialyzers converted to **Theranova** 400 dialyzer; larger surface dialyzers to **Theranova** 500 dialyzer). Blood work included complete blood cell count, electrolytes, C-reactive protein, β2-microglobulin (B2M), κ- and λ-free light chains (K-FLC, L-FLC), and the free light chain ratio.

A 24-week extension was planned to include a washout phase and a return to high-flux HD for 8 more weeks.

Dialysis treatments were delivered using Fresenius 5008 dialysis monitors, with treatment times between 3.5 and 4 hours. Net ultrafiltration was calculated on an individual basis according to each patient's ideal dry weight. Dialysis prescriptions were unchanged except for the switch between high-flux polysulfone dialyzers and **HDx** therapy. Patients answered 6-question LEVIL surveys via iPad app during each dialysis session. Each participant's LEVIL scores during the first two weeks (i.e., baseline) were averaged to create a collective baseline score that was used to stratify patients into those with high- or low-HRQoL scores. High HRQoL scores were those with an overall average score ≥70; determination of an "acceptable" HRQoL score was based on a survey of 11 study patients.

Primary outcomes were changes in HRQoL and symptoms when patients were treated with **HDx** therapy vs baseline conventional high-flux HD. Secondary outcomes included middle-molecule biomarkers and middle-molecule reduction ratios.

RESULTS

Study Population

Twenty-eight patients consented to participate. One died before study initiation, another died of overwhelming sepsis during the study, one patient was removed due to poor dialysis attendance, and three patients withdrew consent, leaving 22 patients to be analyzed over 12 weeks. Due to limited patient access during the COVID-19 pandemic, only 6 patients were able to complete the 24-week extension program.

Participants' mean age was 65.6 ±14.6 years, with a median time on HD of 55 months. Half of the participants were men, 41% had diabetes mellitus type 2, and 41% of patients had some degree of residual kidney function. Half of the population was treated with **Theranova** 400 dialyzer, half with **Theranova** 500 dialyzer.

Stratification

Sixteen of 22 patients (73%) had a low overall HRQoL baseline. Figure 1A shows how individual participants' HRQoL fell on what survey participants deemed "acceptable" or "unacceptable" for HRQoL scores. Figure 1C shows, at baseline, how many participants had "low" vs "high" HRQoL scores for each domain. Note, for example, that none of the participants ranked energy levels as being at a high HRQoL level. When domain sub-analyses are shown, high and low QoL classifications refer to baseline rankings specific to that domain.

HR-QoL Changes

For the overall HRQoL, the 16 patients with "low" initial overall HRQoL scores and the 6 patients with high initial scores (as shown in Figure 1C) are tracked in Figure 1B and in Table 1 as they received 12 weeks of **HDx** therapy:

- **Low HRQoL group:** The average HRQoL among those with low initial HRQoL increased significantly from baseline to week 8 ($P = 0.001$) and week 12 ($P = 0.001$).
- **High HRQoL group:** Patients who had high initial HRQoL saw no significant changes in HRQoL throughout the study.

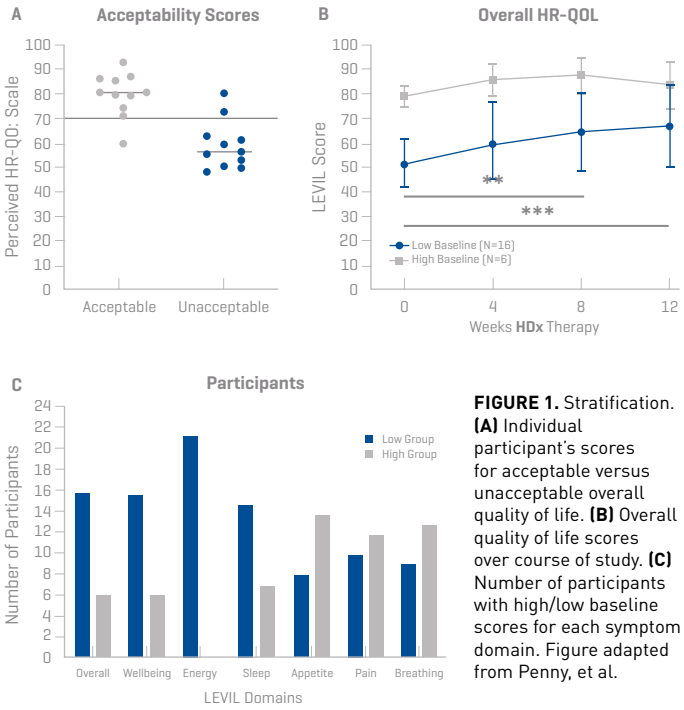


FIGURE 1. Stratification. **(A)** Individual participant's scores for acceptable versus unacceptable overall quality of life. **(B)** Overall quality of life scores over course of study. **(C)** Number of participants with high/low baseline scores for each symptom domain. Figure adapted from Penny, et al.

TABLE 1. LEVIL scores at baseline and 4, 8, and 12 weeks of **HDx** therapy; Total population and stratified groups. Adapted from Penny, et al.

	Total Population							
Initial Study	**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								
Initial Study	**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	>0.99
Appetite	8	46.1±14.8	63.8±28	>0.99	67±30.8	0.05	66.9±31.8	>0.99
Breathing	9	49.6±22.2	53.7±27.3	>0.99	53.7±23.5	>0.99	61.6±24.6	>0.99
Scores ≥ 70 at Baseline: High								
Initial Study	**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	70.9±17.6	0.15	83.6±9.6	>0.99
Subgroup analysis								
General well-being	6	76.6±5.6	82.1±9.7	.71	69±21.1	>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	.15	65.6±24.2	<0.01	89.2±6.3	0.04
Bodily pain	12	87.4±12.1	85.2±13.8	>0.99	72.5±25.2	>0.99	82.9±16.1	0.68
Appetite	14	84.3±8.8	85.9±11.9	>0.99	81.1±21.2	>0.99	84.4±12.4	>0.99
Breathing	13	92±9	95.2±8.4	>0.99	75.9±22.9	>0.99	85.8±16	>0.99

Laboratory Values

Table 2 shows laboratory values for the total population and for the two HRQoL subpopulations at baseline and after 12 weeks of **HDx** therapy:

- **Proteins:** Circulating levels of albumin did not change during therapy ($P = 0.73$); this was also true of the subpopulations (low HRQoL, $P = 0.096$; high HRQoL, $P = 0.69$).
- **B2M:** There was no significant change in serum B2M level, but there was significance in the reduction ratio of B2M between high-flux HD and **HDx** therapy ($P < 0.001$), and this was true of the subpopulations (low HRQoL, $P < 0.001$; high HRQoL, $P = 0.03$).
- **Free light chains:** A significant reduction in serum levels of K-FLC was noted in the overall population ($P < 0.001$) and the low HRQoL subpopulation ($P = 0.02$) but not the high HRQoL population ($P = 0.16$). For L-FLC, the overall population showed a significant decrease over 12 weeks ($P = 0.02$) even though subpopulations did not reach statistical significance (low HRQoL, $P = 0.07$; high HRQoL, $P = 0.22$). Reduction ratios were consistently significant higher with **HDx** therapy for K-FLC and L-FLC in the total population and the subpopulations.

TABLE 2. Laboratory values at baseline compared with 12-Week HDx. Table adapted from Penny et al.

	Baseline	12-wk HDx	Baseline to 12-wk HDx
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

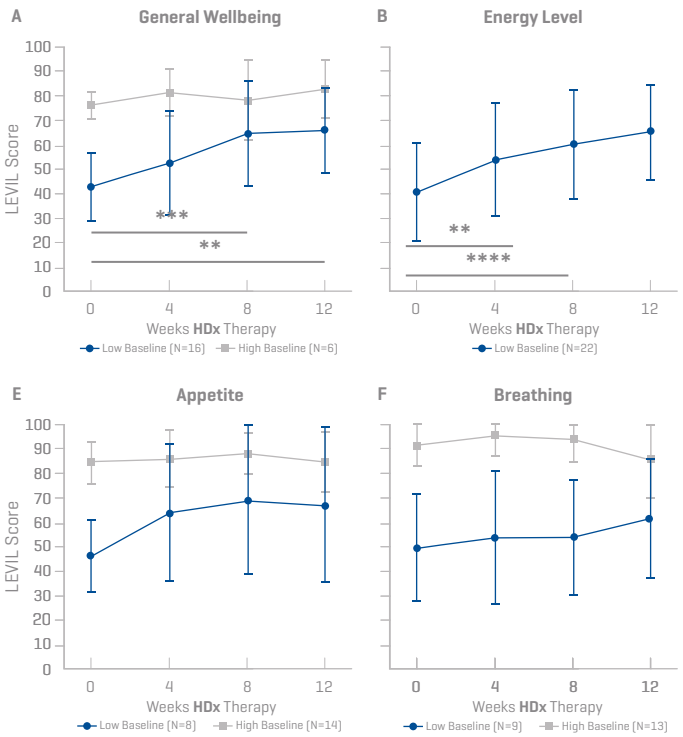
Note: Values are represented as mean ± standard deviation.

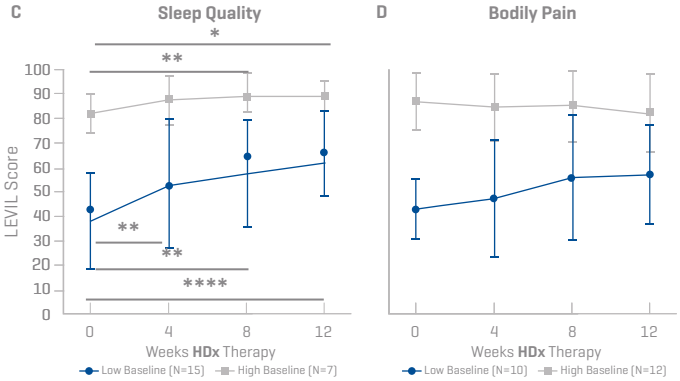
Domain-specific Subgroup Analysis

Both Table 1 and Figure 2 illustrate changes in individual domains over time:

- General well being improved significantly at 8 and 12 weeks ($P < 0.001$, $P = 0.002$, respectively) for those in the low HRQoL group at baseline and did not change among those with a high baseline score.
- Energy level was poor for all patients at baseline, but improved significantly at 8 and 12 weeks ($P = 0.001$, $P < 0.001$, respectively).
- Sleep quality improved significantly among those with low baseline scores at 4, 8, and 12 weeks ($P = 0.01$, $P = 0.002$, $P < 0.001$, respectively). Those with acceptable sleep quality at baseline reported additional benefit after 8 and 12 weeks of **HDx** therapy ($P = 0.001$, $P = 0.04$, respectively).
- Bodily pain, appetite, and difficulty breathing/shortness of breath were not significantly affected by **HDx** therapy over 12 weeks.

FIGURE 2. Subgroup analysis: domain specific analysis. (A) General well-being, (B) energy, (C) sleep, (D) pain, (E) appetite, and (F) breathing. Figure adapted from Penny, et al.

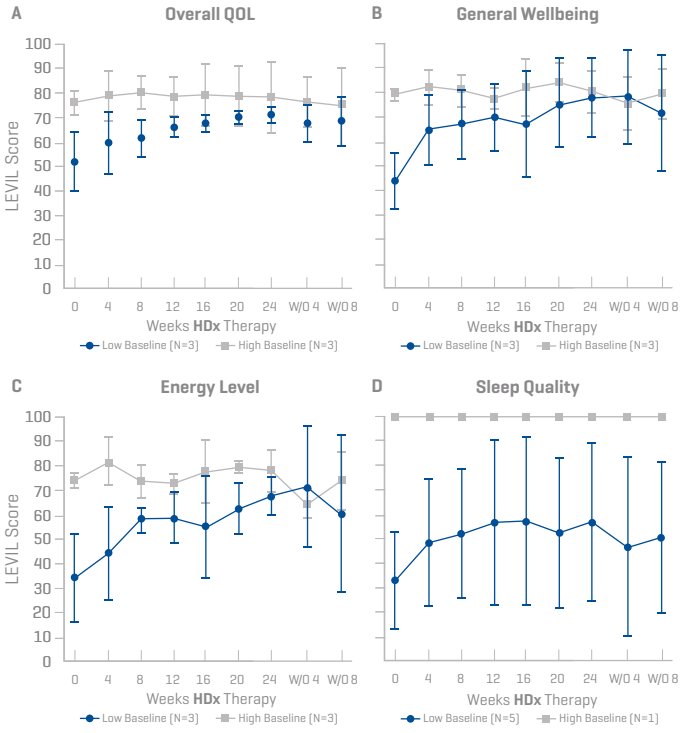




Extension Evaluation

The COVID-19 pandemic hindered data collection in all but 6 patients, so significance cannot be accurately assessed; Figure 3 is included simply to illustrate that these 6 patient profiles followed a profile consistent with that of the main study. Overall HRQoL, general well-being, and energy level seemed to follow different trends during the 8-week washout period.

FIGURE 3. Extension phase; 24 weeks of **HDx** therapy with 8 weeks of washout (W/O). (A) Overall and (B, C, D) domain-specific quality of life. Figure adapted from Penny, et al.



Study Limitations

Study limitations included small sample size in a single-center setting and nonrandomized unblinded design.

CONCLUSIONS

In this study, expanded hemodialysis using medium cut-off dialyzers over 12 weeks was shown to reduce symptom burden and improve overall HRQoL, particularly among those with poorer HRQoL at baseline. Specific findings include the following:

- Overall HRQoL improved significantly at 8 and 12 weeks among those with low HRQoL at baseline and did not change for those with higher baseline scores.
- Improvements in overall HRQoL seemed to be driven mainly by scores in the domains of general well being, energy level, and sleep quality, which all improved for the group with low scores in those domains at baseline. Interestingly, sleep quality improved with **HDx** therapy even for those with "acceptable" sleep quality at baseline.
- Laboratory values show no significant change in albumin levels for the total population nor for the subpopulations after 12 weeks of **HDx** therapy.
- B2M levels in serum were not significantly changed over 12 weeks, but the reduction ratio of B2M was significantly higher in **HDx** therapy versus high-flux HD .
- A significant reduction in serum levels of κ-FLC was noted in the overall population and the low HRQoL subpopulation but not the high HRQoL population. For L-FLC, the overall population showed a significant decrease over 12 weeks (P = 0.02) even though subpopulations did not reach statistical significance. Reduction ratios were consistently significantly higher for K-FLC and L-FLC in **HDx** therapy versus high flux HD in the total population and the subpopulations.

The **Theranova** dialyzer is indicated for patients with chronic kidney failure who are prescribed intermittent hemodialysis. It provides an expanded solute removal profile with increased removal of various middle molecules (up to 45 kDa) that may play a pathologic role in the uremic clinical syndrome. The **Theranova** dialyzer is not intended for hemofiltration or hemodiafiltration therapy. The total extracorporeal blood volume for the **Theranova** dialyzer and the set should represent less than 10% of the patient's blood volume. For single use only.

Rx only. For safe and proper use of these devices refer to the Instructions for Use.

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