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Toward Developing a Patient-Reported Outcome Measure for Fatigue in Hemodialysis

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Fatigue is a component of health-related quality of life and is one of the most frequently cited burdens for patients undergoing maintenance hemodialysis.[1,2] Although the prevalence and implications of fatigue among patients treated with hemodialysis are being increasingly recognized by the nephrology community, there is no universally agreed upon psychometrically robust patient-reported outcome measure (PROM) to assess fatigue in these patients.[3–5] A recent assessment of the Multidimensional Fatigue Inventory 20, a 20-item scale designed to evaluate 5 components of fatigue (general, physical, mental, reduced motivation, and reduced activity), showed poor validity and reliability in hemodialysis.[6,7] Thus, assessing the presence and severity of fatigue-related symptoms in end-stage kidney disease (ESKD) remains challenging in the absence of valid, efficient, and meaningful instruments.[8]

The development of a fatigue-specific PROM in hemodialysis must begin with conducting and evaluating qualitative studies, which have the unique ability to capture and contextualize patients' symptoms and experiences. In this issue of *AJKD*, Jacobson et al[9] move toward the development of a PROM specific to fatigue by conducting a scoping literature review and providing a synthesis and analysis of existing qualitative studies that assessed perspectives of fatigue among dialysis patients who experienced fatigue. This work is notable and has a number of strengths. The authors summarize patient perspectives from 15 different countries, include diverse modes of patient interviews (in person, audiorecorded, and telephone), and construct a conceptual framework that illustrates the full meaning and impact of fatigue on the life of a patient maintained on hemodialysis who reports fatigue. The perception of fatigue is synthesized into a thematic framework that contains physical exhaustion, loss of sleep, restrictions in life participation, decreased stamina for exercise and sexual intimacy, loss of pleasure in daily activities, inability to provide for family, dependence on others, and perceptions of judgment from peers.

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This work from Jacobson et al is a formative step toward the development of a PROM to assess fatigue in hemodialysis patients. The authors acknowledge that their findings arise from perspectives of patients who reported fatigue and that marked heterogeneity of experiences of fatigue by individual patients exists across patient subgroups. Further advances will be needed to develop a PROM related to fatigue that captures the full spectrum of experiences while maintaining relevance to individual patients. Here, and as summarized in Table 1,[10–12] we outline remaining challenges and the need for further investigation.

Unraveling complex and dynamic relationships between fatigue that could be related to comorbid conditions, deconditioning, depression, and medications and fatigue that could be related to dialysis treatments is critical for developing targeted treatment strategies that will address fatigue. For instance, in a cross-sectional analysis of 571 hemodialysis patients, anemia (defined as hemoglobin < 9 g/dL) and erythropoietin resistance were associated with fatigue, and in a prospective cohort of 450 hemodialysis patients, alterations in thyrotropin levels were linked with fatigue.[13,14] In a longitudinal cohort of 917 incident hemodialysis patients, higher baseline levels of fatigue were associated with pain and poor sleep quality.[15]

Fatigue may also coexist with depressive symptoms. Clinical depression occurs in 25% to 30% of prevalent hemodialysis patients, and the presence and severity of these symptoms vary on a month-to-month basis.[16] Diurnal patterns of fatigue differ according to the severity of patients' depressive symptoms, as demonstrated in a prospective observational study of 51 hemodialysis patients.[17] Those with more severe depressive symptoms experienced fatigue throughout the day, whereas those whose symptoms were less severe experienced increases in fatigue mainly after a dialysis session was completed. Lack of exercise and deconditioning affect fatigue-related symptoms. Several studies, including 1 cross-sectional analysis and 15 randomized controlled trials, showed that hemodialysis patients with higher levels of physical activity reported lower levels of fatigue.[18,19] Finally, the pill burden faced by patients with ESKD may contribute to fatigue-related symptoms.

Patients' experiences of fatigue that are related to dialysis treatments may vary according to time of administration of the PROM instrument in relation to a dialysis session, as well as characteristics of the session itself. Patients treated with conventional thrice-weekly hemodialysis need an average of 4 to 5 hours to recover after dialysis, as was found using a single-item PROM of dialysis recovery time that has shown both validity and test-retest reliability.[20] In an analysis of 6,040 patients in the DOPPS, recovery time ranged from 2 to 12 hours after hemodialysis.[21] In both an intention-to-treat and perprotocol analysis from the FREEDOM Study, patients who switched from thrice-weekly hemodialysis to more frequent home hemodialysis reported a significant improvement in postdialysis recovery time (from >6 to ~1 hour) and depressive symptoms at 4 and 12 months.[22] Patient perceptions of fatigue and postdialysis recovery time have also been shown to be affected by changes in blood flow rate, ultrafiltration rate, extracellular fluid volume status, and dialysis vintage.[23–25] In an analysis of patients enrolled in the CHOICE Study, 27% reported worsened vitality/fatigue scores on the 36-Item Short Form Health Survey questionnaire 1 year after dialysis initiation.[26,27]

When an appropriate fatigue PROM is identified, the nephrology community will need to determine how to incorporate the instrument into a patient's ESKD care plan in a clinically useful and sustainable way. How frequently should fatigue be assessed in a dialysis patient? Measuring fatigue daily will be burdensome, but asking patients to report symptoms over longer periods may subject their answers to recall bias. When should the questionnaire be given in relationship to the dialysis session itself? How will the results of the questionnaire affect treatment decisions? It should be noted that certain patients, including some whose interviews were included in the review from Jacobson et al, remained skeptical that any therapy besides transplantation would alleviate fatigue. However, if measured in the context of an individual patient's comorbid conditions, laboratory studies, and overall clinical status, a fatigue-specific PROM could trigger interventions that meaningfully improve patients' symptom burdens. Changes in the dialysis prescription or switching to more frequent hemodialysis or to peritoneal dialysis are options that hold promise.[28] Additionally, according to a recent systematic review and meta-analysis, administration of erythropoiesis-stimulating agents may improve fatigue in hemodialysis patients, particularly among those with a baseline hemoglobin level < 10 g/dL.[29] The KDIGO guideline for anemia in chronic kidney disease recommends that for some patients, increasing hemoglobin levels to higher targets than usual may result in improvement in various measures of health-related quality of life, which include fatigue.[30] Treatment of depression can result in a decrease in patients' self-reported frequency of depressive symptoms and scores on corresponding scales, which often include perceptions of fatigue.[31] An ongoing trial of a 4 to 6-week cognitive behavioral therapy intervention to treat depressive symptoms in hemodialysis patients plans to test for improvements in fatigue.[32]

It is important to note that results of the studies reviewed by Jacobson et al should be interpreted cautiously. Symptoms of fatigue in the included studies were captured using various instruments, measured during different times in relation to a patient's dialysis session, and ascertained among patients reporting fatigue who had a wide range of comorbid conditions. Jacobson et al appropriately emphasize that fatigue is being prioritized by patients and increasingly recognized by nephrologists as an important outcome measure. Now, formative research needs to be done to define, individualize, and validate a measure of fatigue in hemodialysis patients that takes into account relevant comorbid conditions, dialysis prescriptions, and medications while capturing the unique experiences of each individual patient. Only then can targeted personalized interventions be developed to meaningfully improve patient experiences of fatigue in hemodialysis.

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Table 1.

Challenges in Developing and Implementing an Individualized PROM for Fatigue in Hemodialysis Patients and Recommendations for Resolution

Challenge	Recommendation
Imprecise definition of fatigue; various factors influence fatigue	Use of questions and clinical and/or laboratory assessments that help distinguish symptoms of fatigue related to comorbid conditions from those related to dialysis treatments
Heterogeneity of patient experiences of fatigue across dialysis treatment regimens	Development of fatigue PROMs that are specific for different dialysis treatment regimens
Difficulty for patients in interpreting the term “fatigue”	Creation of materials tailored to a 7th- or 8th-grade literacy level, using resources such as the CMS Toolkit for Making Writing Clear and Effective[10,11]
Within- and between-individual variation in experiences of fatigue over time	Repeated assessments of fatigue PROM that are consistent in relation to the dialysis treatment regimen
Difficulties with sustained uptake, repeated assessments, and implementation in an incenter hemodialysis unit	Use of computer adaptive testing for a fatigue PROM during a dialysis session[12]
Need to develop an action plan after fatigue-specific PROM collection	Multidisciplinary assessment and treatment approach: • Change in dialysis prescription (shorter duration, increased frequency, decreased fluid removal, etc) • Change in dialysis modality (switch to peritoneal dialysis, more frequent hemodialysis) • Trial of exercise regimen • ESA dosing to appropriate hemoglobin target • Antidepressant and/or cognitive behavioral therapy

Abbreviations: CMS, Centers for Medicare & Medicaid Services; ESA, erythropoiesis-stimulating agent; PROM, patient-reported outcome measure.