

Health related quality of life and the CKD patient: challenges for the nephrology community

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The compromised health-related quality of life (HRQOL) of patients with chronic kidney disease is now well documented. The recent mandate by the Center for Medicare Services in the United States that all dialysis units monitor HRQOL as a condition of coverage has focused attention on the importance of these measures. The challenge for the nephrology care team is understanding how to interpret and utilize the information obtained from these HRQOL measurements. Can HRQOL of these patients be improved? The present review addresses this issue by commenting on strategies that have been used to improve the HRQOL of chronic kidney disease patients. A systematic approach is suggested for nephrology care providers to attempt to evaluate and improve the HRQOL of CKD patients.

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The compromised health-related quality of life (HRQOL) of patients with end-stage renal disease (ESRD) is now well documented.^{1–7} Numerous studies and reviews have addressed this subject, using a variety of tools and instruments to assess the degree of impairment.^{1–7} The reliability, validity, and reproducibility of many of these tools have now been established. The importance of systematically evaluating this impairment is underscored by the association of various HRQOL measures with morbidity and mortality of ESRD patients.^{1–5} In addition, as Fukuhara *et al.*⁷ have suggested, nephrologists must look not only at biological outcomes but also at the patient's perceptions of their quality of life to properly assess patient status. Thus, the use of measuring HRQOL as a primary outcome of various interventions in ESRD treatment regimens is increasingly being accepted. In fact, it is now mandated in the United States by the Center for Medicare Services that dialysis facilities perform routine measurements of HRQOL preferentially using the Kidney Disease Quality of Life-36 (KDQOL-36) questionnaire; additional instruments may be used.⁸ These measurements are to be done at regular intervals, defined as within 4 months of the initiation of treatment, and then at least annually or more often if indicated by a significant life changing event. But, what is the clinician to do with this information and how will it be used? How will the measurement of HRQOL assist the clinician to manage the patient and modify and improve treatment? The mandate from the Center for Medicare Services indicates that 'to address the psychosocial needs ... each patient's plans of care ... must include interventions individualized to meet the patient's psychosocial needs and aimed at optimizing the patient's adjustment to kidney failure and its treatment.'⁸

Quality of life has been defined by the World Health Organization as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. Health-related quality of life can be defined as the extent to which one's usual or expected physical, social, or emotional well-being (quality of life) is affected by a medical condition and/or its treatment. HRQOL includes physical, social, psychological, and therapy-related components, as summarized in Figure 1.

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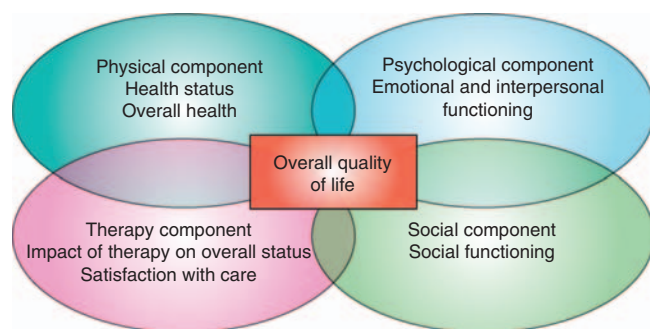


Figure 1 | Domains encompassed in health-related quality of life assessments.

ASSESSMENT OF HRQOL

Instruments used to assess HRQOL involve both subjective and objective measures. Subjective assessments involve patient-reported outcomes, which can be defined as measurements of any aspect of a patient's health status that comes directly from the patient, without the interpretation of the response by a health care provider. The importance of patient perceptions of their own physical and mental functioning has been emphasized. Thus, the recommended HRQOL assessments in the United States involve a patient-reported outcome. The value of patient reports as opposed to clinician assessments is underscored by the well-documented discrepancies between ESRD patient and health care provider assessments of problems and difficulties.⁹ As a result, several investigators have emphasized the significance of patient assessments, suggesting that the patient himself is the expert when it comes to assessing his/her own quality of life.¹⁰ These researchers have stressed eliciting from the patient domains and concerns that may be unique to their own experience—not simply relying on generic categories included in standardized HRQOL instruments.¹⁰ This is particularly important, as it permits the formulation of effective treatment strategies for the individual patient. On the other hand, the medical team may need to include objective assessments of patient status to evaluate the impact of health on quality of life and formulate clinical intervention strategies. For example, physical functioning can be assessed by patient reporting or documented by a variety of objective measures, such as 6 min walking test or treadmill exercise testing.¹¹ Moreover, depressive symptoms can be assessed by a variety of self-reporting instruments such as the Beck Depression Inventory, Patient Health Questionnaire-9, and so on. However, establishing a diagnosis of clinical depression according to standard Diagnostic and Statistical Manual of Mental Disorders 4 criteria involves a direct patient, structured interview using an objective, and evidence-based scoring system.² This objective evaluation of depression by a trained interviewer is essential to formulate an effective treatment plan and to evaluate the impact of interventions.²

The HRQOL areas of difficulty most frequently cited for chronic kidney disease patients include cognitive dysfunction, depression, anxiety, pain, sleep disturbance, reduced

physical functioning, sexual dysfunction, reduced social interaction, reduced global perception of general health or overall quality of life, and a variety of other symptoms commonly noted in ESRD patients, such as muscle weakness, restless legs, post-dialysis fatigue, and so on. In fact, it is noteworthy that these domains are now being carefully tracked in a prospective study in the United States of incident dialysis patients, as noted in a recent study design outlined by Kutner *et al.*¹² Importantly, several of these domains have been associated with increased morbidity and mortality. For example, dialysis patients who report a reduced general perception of health have a nearly threefold higher risk of hospitalization or death.⁵ Hemodialysis (HD) patients and peritoneal dialysis (PD) patients with increased depressive symptomatology have a nearly twofold increase in mortality rates and a twofold higher peritonitis rate, respectively, than patients who report a lower incidence of symptoms.^{13,14} In addition, HD patients who meet standard psychiatric criteria for clinical depression, based on a structured interview, have a twofold greater chance of death or hospitalization than patients who are not clinically depressed.² Studies using generic HRQOL instruments, such as the SF-36, have indicated that reduced scores in HD patients are associated with significantly higher hospitalization rates and mortality. For example, reduced physical component summary scores (<25) on the SF-36 Health Survey have been associated with nearly twofold greater chance of death and a 60% greater chance of hospitalization than patients (after corrections for a variety of standard variables) with scores >46 in studies involving several thousand HD patients in the Dialysis Outcomes and Practice Patterns Study.¹

INTERVENTIONS TO IMPROVE HRQOL

A major challenge for the medical team is how to clinically use data obtained from measurements of HRQOL. This will be a particular issue for nephrologists in the United States, as they are now mandated to routinely assess HRQOL, as noted above. Little guidance is provided by the literature, as few studies have documented interventions that result in significant improvements in HRQOL scores; some important clinical trials have in fact shown that major modifications in treatment regimens do not impact on HRQOL measurements. For example, data from the Adequacy of Peritoneal Dialysis in Mexico study indicated that improving small molecule clearances in a large cohort of chronic PD patients did not result in an improvement in HRQOL scores, when using the Kidney Disease Quality of Life Short Form as the assessment tool.¹⁵ The HEMO trial also suggested no or minimally significant changes in HRQOL measures by increasing the eKT/V urea of HD patients from 1.05 to 1.45 or by using high flux membranes, when using the Index of Well-Being and the Kidney Disease Quality of Life-Long Form questionnaires.¹⁶ Moreover, cross-sectional and prospective studies comparing PD and conventional, 3 times per week HD patients have not shown consistent effects attributable to the dialysis regimen.^{17,18} The most striking

difference seems to be in the satisfaction with therapy and the impact of therapy on the lives of patients, with PD patients generally reporting better satisfaction and a less negative impact of the therapy than the conventional HD patients.^{17,19,20}

What interventions, then, have been shown to positively impact on ESRD patients' HRQOL measurements? A few studies, some preliminary, have suggested that treatment of anemia, exercise programs, treatment of depression, and selected modifications in the dialysis treatment regimen have resulted in improved HRQOL assessments. Treatment of sleep disturbances and pain may also have a positive effect. In addition, counseling in response to individual patient issues and cognitive behavioral therapy can be helpful. Finally, there are lessons to be learned from health psychology.

The relationship between anemia and HRQOL has been the subject of extensive study. The interpretation of these studies has been complicated by the recent United States Food and Drug Administration hearing concerning erythropoietic-stimulating agents and CKD patients. This hearing suggested that hemoglobin levels over 12 g% may be associated with increased morbidity and mortality, and that the HRQOL benefits of these drugs have not been established, as the studies investigating this relationship were not satisfactorily done.²¹ However, two recent articles re-examined this issue and both came to similar conclusions.^{22,23} A detailed review by Leaf and Goldfarb²² concluded that erythropoietin therapy resulted in significant improvements in various HRQOL domains. In studies using the SF-36 Health Survey domains, the most dramatic improvements were noted in physical symptoms, vitality, energy, and performance. Smaller improvements were noted in social functioning and mental health, and little, if any, improvement in emotional health or pain. The maximal increase in HRQOL per change in hemoglobin level occurred in the range of 10–12 g%. These findings were virtually identical to the results reported in a large cross-sectional analysis studying the relationship between hemoglobin levels and HRQOL in 1200 CKD patients not on dialysis.²³ Additional domains showing possible improvements with erythropoietin therapy include sleep, cognitive functioning, and sexual functioning.²²

There has been considerable interest in the impact of modifications of the dialysis regimen on a variety of outcomes of ESRD patients maintained on HD.^{24–34} These regimens include short daily HD done at home or in-center, and nocturnal HD done three or more times per week at home or in-center. Several studies have suggested improvements in selected medical outcomes with these regimens, including improved blood pressure control and need for anti-hypertensive medications, reduced phosphate levels, and lower ultrafiltration rates.

The impact of these newer regimens on HRQOL has generated much interest.^{24–34} Studies examining the impact of more frequent HD on HRQOL have been somewhat

difficult to interpret because a wide variety of instruments have been used, the findings have not been consistent, the patients have in general not been randomized, and the number of patients studied has been small. However, in general, the findings suggest that selected domains are impacted by more frequent HD.^{24–34} These include sleep, depressive symptoms, global quality of life assessment, patient satisfaction, general health perception, cognitive dysfunction, and other selected domains that may not be well covered in standard HRQOL instruments.^{29,33} Importantly, some investigators have suggested that to fully evaluate the impact of more frequent HD, it is important to listen to what individual patients report, as the impact that the change in therapy is having on their lives may not be captured by standardized HRQOL instruments.^{29,33} The positive impact of the newer treatment regimens on patient-reported outcomes needs to be balanced by the burden of the therapy—in terms of the impact on both the patient as well as the caregiver.

Various HRQOL measures have been included as primary and secondary end points in recent trials evaluating these new regimens. For example, in the National Institutes of Health sponsored Frequent Hemodialysis Network Trial comparing conventional HD to 6 times per week in-center HD and 5–6 times per week nocturnal home HD, one of the two primary outcomes is a composite of the physical health composite score of the SF-36 and mortality; three of the nine secondary outcomes involve HRQOL measures (Beck Depression Inventory, Trailmaking B test, and the physical composite score).²⁴ The Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements (FREEDOM) Study is designed to evaluate 500 patients with 6 times per week short daily HD using the NxStage dialysis machine (NxStage Medical, Lawrence, MA, USA).²⁵ Mortality, hospitalizations, and costs will be compared with 5000 matched patients in the USRDS database. HRQOL domains being monitored in the 500 NxStage patients include the SF-36, Beck Depression Inventory, global assessment of quality of life and physical intimacy, time to recovery after a dialysis session, and symptoms of sleep difficulties and restless legs.

One of the most dramatic changes in patient-reported outcomes with more frequent HD is the time to recover after a dialysis session (that is, How long does it take to resume usual activities after completion of a dialysis treatment?).²⁶ Lindsay *et al.*²⁶ have reported dramatic decreases in the time to recovery for patients treated with more frequent dialysis. Thus, patients maintained on conventional 3 times per week HD report an average recovery time of about 6 h, whereas patients converted to more frequent short daily or nocturnal HD report less than 1 h recovery time. This change strongly correlates with improvements in various HRQOL domains. These associations include the physical and mental component scores as well as seven of the eight domains of the SF-36 Health Survey, five domains of the Health Utility Index, and the majority of the subscales on a dialysis stress questionnaire.²⁶

A recently reported randomized trial from Alberta of five or six times per week nocturnal HD compared with conventional HD examined a variety of HRQOL outcome measures.^{27,28} These included the European Quality of Life –5D Index Score (a measure of overall quality of life), the European Quality of Life visual analog scale (global health perception), and four domains from the Kidney Disease Quality of Life (burden of kidney disease, effects of kidney disease, and sleep and kidney disease-related symptoms and problems). After 6 months of therapy, there were not significant changes in the European –5D Index Score or visual analog scale, but a significant improvement in the effects of kidney disease (8.6 point increase) and burden of kidney disease (9.8 point increase). In addition, there were non-significant improvements in all domains of the SF-36, including the physical component score and mental component score.

Preliminary data from the FREEDOM study have also suggested an improvement in a variety of HRQOL domains. A 4-month interim analysis of 78 patients (planned in the initial study design) has indicated a significant decrease in Beck Depression Inventory scores (12.6 to 8.3), increases in physical and mental components scores from the SF-36 Health Survey, and dramatic reductions in time to recovery after a dialysis session from 568 to 65 min.³⁰ The improvement in Beck Depression Inventory scores and time to recovery was sustained at 12 months after initiation of 6 times per week home HD.³¹

Another domain associated with impaired HRQOL that has been reported to improve with more frequent HD is sleep difficulties.^{34,35} Sleep disturbances are common in ESRD patients; in a Dialysis Outcomes Practice Patterns Study examining over 11,000 HD patients, 49% were judged to experience poor sleep quality using a self-reported sleep questionnaire.³⁵ Impaired sleep quality was associated with significantly lower physical and mental component scores, after standard corrections for various co-morbidities.³⁵ Treating the sleep disturbances of ESRD patients has proven to be challenging and is an area that requires further study. Thus, the reports of the impact of more frequent, nocturnal HD on sleep apnea are of interest.³⁴ Converting patients from conventional 3 times per week HD to nocturnal HD 6 or 7 times per weeks resulted in a reduction in the frequency of apnea and hypopnea from 25 ± 25 to 8 ± 8 episodes per hour of sleep ($P = 0.03$).³⁴

Cognitive dysfunction is commonly noted in ESRD patients. The management of this difficult problem generally consists of optimizing medical and psychosocial care. The potential positive impact of nocturnal HD on cognitive function is, therefore, of considerable interest. A recent report examining just 12 patients suggested that nocturnal HD may be associated with improved general cognitive efficiency as measured by tests focusing on psychomotor efficiency and attention, and working memory.³⁶

Depression is a major problem for CKD patients.^{2-4,37-39} Depression is well documented to be the most common

psychological problem of dialysis patients; between 25 and 30% of ESRD patients have a diagnosis of clinical depression.^{2,37} The presence of depressive symptoms is associated with increased morbidity and mortality, as discussed above, and has been associated, not surprisingly, with reduced HRQOL scores.^{4,37} Few studies have systematically studied the treatment of depression in CKD patients.^{2,37,38} It is important to recognize that before the treatment of depression is planned, a diagnosis of clinical depression needs to be established by direct patient interviews.^{2,37-39} The use of questionnaires, such as the Beck Depression Inventory, indicates the presence of depressive symptoms. But, the diagnosis of clinical depression requires a structured interview using standard psychiatric criteria.^{2,39} Once the diagnosis is established, then treatment can be considered. Various treatment regimens for depression of chronic kidney disease patients have been described.³⁷⁻⁴² Anti-depressant medications have been used and have been reported to result in significant improvement in depressive symptomatology.^{37,38} However, it is challenging to establish an effective pharmacological treatment program of ESRD patients for a variety of reasons. Patients are often unwilling to complete the evaluation for depression, are reluctant to take additional medications, and may not complete a course of therapy.^{37,38} Non-pharmacological treatment of depression, using psychotherapy, exercise therapy, and cognitive behavioral therapy have met with some success in small series.³⁹⁻⁴² Of particular note is a recent randomized trial of cognitive behavioral therapy, presented in abstract form, in which 85 dialysis patients with clinical depression diagnosed by interview were randomized to standard care or standard care with cognitive behavioral therapy with a psychologist.⁴⁰ There was an 80% compliance with the treatment regimen, and after 3 months of treatment, there was a significant difference in the Beck Depression scores between the treatment and control groups (14.1 ± 8.7 vs 21.2 ± 9.1 , respectively, $P < 0.01$).⁴⁰ Of particular note, there was a significant improvement in several domains on the KDQOL-SF, including burden of kidney disease, overall health, social interaction, sleep, and mental component score.⁴⁰ This preliminary study, therefore, suggests that psychological interventions, such as cognitive behavioral therapy, counseling, stress reduction, and so on, can be useful in reducing depressive symptoms and improving HRQOL, as is well documented in other disease states.

Structured exercise programs may also have a beneficial effect on HRQOL in chronic kidney disease patients.^{11,41-42} The reduced physical functioning of patients can in part be ameliorated with exercise programs which in turn can result in an improvement of various HRQOL parameters.^{11,41-42} For example, in one recent study, a 12-week program of 90 min/day, 3 times per week exercise in a cohort of HD patients resulted in a significant reduction in depression scores ($P < 0.001$) and improvement in the physical and mental component scores of the SF-36 Health Survey ($P = 0.002$ and $P = 0.004$, respectively).⁴¹ In another recent

study, 35 HD patients were randomized to a 10-month intradialytic exercise training program or standard care.⁴² There was a dramatic increase in exercise capacity in the study group (nearly 25% increase in their aerobic capacity and exercise time) associated with a 40% reduction in Beck Depression Inventory scores and increase in Life Satisfaction Index and physical component score (40.5–44.5).⁴²

Studies have also noted an association between sexual dysfunction and a variety of other quality of life parameters, such as various mental and physical components of the SF-36 and depression scores.^{43–48} These studies raise the question of whether specifically addressing the sexual dysfunction of patients could have a positive impact on their quality of life measures.^{43–48} For example, recent studies have shown that in men with mild-to-moderate depressive illness, an improvement in erectile dysfunction is associated with significant improvement in not only depressive symptoms but quality of life assessments as well.⁴³ Thus, systematic evaluations of sexual difficulties of chronic kidney disease patients and strategies to address these difficulties need to be incorporated into evaluations of HRQOL of patients with chronic kidney disease.^{44–48}

The psychosocial impact of pain for chronic kidney disease patients is another area that needs further exploration.^{49,50} Chronic pain is a common complaint for patients with ESRD. The pain is often moderate or severe, and significantly impacts virtually every aspect of HRQOL.^{49,50} Unfortunately, there has been limited clinical research in this area. Pain in ESRD patients is often undertreated, in part because of the reluctance of nephrologists to prescribe narcotics to patients with kidney disease. The challenges of developing safe and effective treatment regimens for the often complex ESRD patient has recently been reviewed.⁴⁹

Stress for patients with kidney disease may be burdensome. There are a variety of stressors that impact on the life of a dialysis patient.⁵¹ These stressors may include the impact of the illness on overall functioning, dietary issues, loss of supportive structures and relationships, loss of employment, financial difficulties, time constraints, mood fluctuations, functional limitations, and fear of disability and death. Adaptive coping mechanisms are needed to deal with these complex changes in patients' lives. In the absence of adequate coping strategies, these stressors can aggravate the patients' perception of their quality of life. It is important, therefore, for the nephrology team to be aware of these areas of difficulty and explore coping mechanisms with the patient.

Anxiety is also commonly noted in ESRD patients; 27% of urban HD patients have a major anxiety disorder.⁵² The presence of an anxiety disorder is associated with a significantly lower overall perceived quality of life ($P < 0.05$).⁵² Evaluating and understanding anxiety in the ESRD patient may open therapeutic avenues to explore, which may positively impact on HRQOL.

Social support has been shown to correlate with a variety of HRQOL domains, including depressive symptoms, perception of illness effects, satisfaction with life, and overall

quality of life of ESRD patients.^{53,54} Marital and family discord are commonly observed in ESRD patients and may negatively impact on HRQOL.^{45,55,56} Active community support, including spiritual involvement, has been associated with improved HRQOL assessments.^{57,58} However, as pointed out by Cohen *et al.*,⁵⁴ few studies have examined the impact of social support interventions in ESRD patients and these studies have been limited by small sample size, lack of appropriate controls, and a retrospective analysis.

The impact on the caregivers who provide support for patients with CKD and ESRD is an area that has received surprising little attention.^{59,60} Of note is a recent systematic literature review that noted only three articles that describe interventions for caregivers of CKD patients; all assess the effect of educational material given to the caregiver and describe an improvement of knowledge with no report of other outcomes.⁵⁴ Importantly, lessons from other chronic diseases have suggested that exploring ways of supporting caregivers can have beneficial effects on the outcomes for both the patient and the caregiver.^{59,60}

CONCLUSION

In summary, there is an increasing interest in assessing HRQOL in patients with chronic kidney disease. Importantly, it is now mandated in the United States that HRQOL measurements be done routinely on all ESRD patients. The interpretation and use of the information obtained from these HRQOL assessments pose certain challenges for the nephrology care team. The focus clearly needs to be on developing strategies to improve the compromised HRQOL of the patient with chronic kidney disease. To address this properly requires that careful assessments be done in a variety of domains (outlined in Table 1) and that the interventions use the resources of the entire patient care team (physicians, nurses, social workers, dieticians, psychologists, technicians, physical rehabilitation therapists, family, community resources, religious organizations, and so on). It will be important to document that interventions can positively

Table 1 | Strategies to improve health-related quality of life of the chronic kidney disease patient

1. Assessment of patient symptom burden using patient reported measures: formulation of treatment options
2. Optimization of medical therapy
3. Review social support systems
4. Management of anemia: maintenance of hemoglobin levels in 11–12 range
5. Treatment of depression: medication, counseling, and/or other strategies
6. Modifications in dialysis treatment regimen: more frequent hemodialysis
7. Physical functioning: utilization of exercise programs
8. Assessment and treatment of sleep disturbances
9. Assessment and treatment of pain
10. Assessment and treatment of stress and anxiety
11. Assessment and treatment of sexual dysfunction
12. Assessment of cognitive dysfunction with appropriate support
13. Caregiver assessment and support

impact on the HRQOL, as they have in other health care arenas. Enlisting patient cooperation in participating in these investigations and interventions will require careful attention and thought; this may well prove to be difficult and require creative ways of engaging the patient. In addition, identifying the financial resources to provide appropriate interventions will require strategic planning. Certainly, if the interventions translate into improved medical outcomes and reduced hospitalizations, then funding to support these programs should not be difficult to arrange. Thus, carefully tracking the impact of these interventions on not only HRQOL but also medical outcomes, hospitalizations, and the global cost of care is essential.

DISCLOSURE

Dr Finkelstein is on the scientific advisory board of NxStage Medical.

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