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Health-related quality of life outcomes in Chronic kidney disease

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Abstract

Purpose of Review—Patients with CKD endure compromised health-related quality of life (HRQOL). Although the link between HRQOL and increased mortality in ESRD patients is well-documented, less is known about the relationship between CKD and HRQOL. This article reviews the recent evidence on HRQOL, its correlates and proposed intervention strategies to improve HRQOL in CKD.

Recent findings—A growing body of literature indicates that various co-morbid conditions related to CKD play a substantial role in the impaired HRQOL in CKD. Hypertension, both a cause and complication of CKD, negatively affects HRQOL due to associated co-morbidities, side effects from anti-hypertensive medications and awareness of the diagnosis. Anemia has been associated with HRQOL, but concerns about the safety of erythropoietin-stimulating agents (ESA) have led to more conservative anemia treatment. Frailty, symptom burden and depression are also major contributory factors to HRQOL in CKD.

Summary—Certain determinants of HRQOL in CKD, namely anemia and depression are treatable. Early identification and correction may improve overall well-being of patients. Clinical trials are required to demonstrate whether treatment interventions benefit HRQOL in this high-risk population. Furthermore, whether integration of HRQOL assessment into routine clinical practice will improve HRQOL outcomes remains to be determined.

Keywords

Chronic kidney disease; quality of life; hypertension; anemia; frailty; symptom burden

Introduction

In recent years, there has been a growing interest in understanding the health-related quality of life (HRQOL) of patients with chronic kidney disease. It is now widely accepted that

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HRQOL is significantly compromised in patients with end-stage renal disease (ESRD) and HRQOL has been associated with increased mortality and morbidity [1**,2]. The importance of measuring HRQOL in ESRD patients is further highlighted by the adoption by the Center for Medicare Services of a mandatory requisite of routine measurement of HRQOL at all dialysis units [2,3]. While there is a growing understanding of HRQOL and its determinants in ESRD [4,5,6,7], little is known about the HRQOL in the CKD population.

HRQOL reflects the contribution of disease to the patients' sense of well-being and may serve as a valuable tool to assess the effectiveness of therapeutic interventions. In fact, the goals of treatment of CKD in developed nations have evolved over time from mere survival to achievement of a certain level of well-being [8]. Figure 1 demonstrates factors that have been described as contributors to HRQOL in CKD. There seems to be some inconsistency in what is considered a predictor or component of HRQOL. For instance, pain is measured as one of the aspects of HRQOL but is also associated with diminished HRQOL. The purpose of this article is to review the recent evidence on HRQOL and its correlates in various health states in pre-dialysis CKD patients and synthesize the related implications for optimizing care in this vulnerable population.

Chronic Kidney Disease and HRQOL

With only a handful of large-scale studies [1**], HRQOL in CKD patients not on renal replacement therapy remains relatively understudied. Mujais *et al.* [1**] observed that patients with CKD had significant impairment in HRQOL, with the most pronounced decrement being in physical function, as measured by the Kidney Disease Quality of Life (KDQOL) questionnaire. Women and older patients (>65 yr) had worse HRQOL scores, as did patients with diabetes, anemia and cardiovascular co-morbidities. Additionally, they noticed a progressive decline in HRQOL with worsening renal function (Figure 2). Furthermore, HRQOL was found to decline over time, with the main predictors of this decline being age, co-morbidities and changes in hemoglobin and albumin levels. Noteworthy is a study by Molsted *et al.* [9], the results of which were comparable to the study by Mujais and colleagues, except for a significant association between smoking and HRQOL reported in the former. The strength of these studies is that they used the KDQOL questionnaire, which assesses disease-specific HRQOL. However, the study by Mujais *et al.* [1**] was limited by loss of patients to follow-up and the one by Molsted *et al.* [9] suffered from non-responder bias and a small study population of patients with CKD (n=63).

There have been reviews of the evidence by Kutner citing favorable HRQOL outcomes with management of pre-ESRD care, anemia, sleep disorders, exercise programs and treatment of depression [10]. However, much of this evidence for exercise, sleep disorders and physical activity was synthesized from older adults in the general population or ESRD and whether these findings extrapolate to patients with CKD remains to be tested.

Hypertension and HRQOL

Hypertensive patients have been shown to experience a significant reduction in HRQOL compared to normotensive subjects [11,12*,13*,14*]. Hypertension is both a cause and a complication of CKD, and is a well established risk factor for CKD progression [15]. Furthermore, CKD and hypertension are independent risk factors for cardiovascular disease [15,16], the latter being recognized as a leading contributor to global burden of disease [17]. Li *et al.* [11] conducted a cross-sectional survey in the Chinese population and observed that awareness of the diagnosis and poorly controlled hypertension were associated with significantly impaired HRQOL. A more recent population-based study in China by Wang and colleagues [14*] reported marked deterioration of HRQOL in hypertensive individuals, while co-existing co-morbidities further worsened HRQOL scores. Two small clinic-based studies

in Brazil [12*,18] published results that were in accordance with the study by Wang and colleagues. In addition to the association between hypertension on decrements in HRQOL, a cross-sectional analysis of hypertensive Nigerian patients by Ogunlana *et al.* [19*] also identified symptom count and co-morbidity, particularly stroke and visual impairment, as major predictors of HRQOL. When assessing the impact of hypertension on HRQOL, the extent to which one should account for co-morbidity has been a challenge for investigators since one can reason that hypertension would alter HRQOL through end-organ damage such as stroke, cardiovascular disease, or CKD.

It is not surprising that these studies reported conflicting results in terms of impact of hypertension across the different aspects of HRQOL. For instance, most of the studies showed that hypertension negatively affected physical function [11,12*,13*,14*], Ogunlana and colleagues [19*] demonstrated a greater impact on the mental component score (MCS) and total quality of life score and Cavalcante *et al.* [18] reported differences in the emotional component and quality of sex life in a small, cross-sectional study. There are several possible reasons for the discrepant findings including differences in study populations, the use of varying HRQOL instruments, use of different anti-hypertensives with different side-effect profiles, disease severity and presence of co-morbidities. Since hypertension is a putatively asymptomatic condition, it has been presumed that the poor HRQOL among hypertensive individuals is attributable to complications or co-morbidities [12*,14*,19*], knowledge of the diagnosis or 'labeling' phenomenon [11,12*,13*,18,19*], and/or adverse effects from anti-hypertensive medications [11,12*,13*,18].

While the correlation between hypertension and HRQOL has been studied in patients with ESRD, there is a considerable gap in our understanding of HRQOL in hypertensive CKD [20]. The African American Study of Kidney Disease and Hypertension (AASK) was a trial of HRQOL exclusively among African Americans with hypertension and CKD [21]. The results of the study were consistent with the results in other populations, with the conclusion that hypertension substantially affected the physical dimensions of HRQOL relative to mental dimensions. Additionally, several clinical and demographic factors (employment status, education level, household income, body mass index, co-morbidity, duration of hypertension and number of anti-hypertensives prescribed, exercise status and male sex) were found to be independent predictors of HRQOL. The AASK study further demonstrated that there were no differences in the HRQOL for different levels of blood pressure control [20]. The impact of blood pressure level on HRQOL was also examined in a sub-study of the Hypertension Optimal Treatment (HOT) Study [22,23], which reported that lower levels of diastolic blood pressure were linked to better HRQOL as assessed by the Psychological General Well-Being index. However, more intense anti-hypertensive therapy was associated with a slight increase in subjective symptoms [23]. The seeming inconsistency in HRQOL findings between the AASK and HOT studies could be explained by longer follow-up, sicker patients and different HRQOL instruments used by the AASK study.

Considering the dramatically increasing prevalence of CKD, the risk of progression of CKD with hypertension [15] and the significant impact of the disease on HRQOL, improving HRQOL is emerging as one of the therapeutic goals in hypertensive individuals. However, there is a need for more studies in the CKD population to better understand the associations described. Of note, the planned NHLBI-SPRINT study of intensive blood pressure lowering will include participants with CKD Stage 3 [24].

Anemia and HRQOL

Anemia is highly prevalent in patients with CKD and is associated with adverse clinical outcomes [25] and diminished HRQOL [26,27,28,29,30**,31]. An extensive body of research

has established that treatment of anemia in CKD with erythropoietin-stimulating agents (ESAs) has a favorable impact on HRQOL [26,27,28,29,30**]. However, the large number of HRQOL assessment tools used, variability in data reporting and heterogeneity of patient populations in these studies make interpretation of the magnitude and nature of these improvements challenging. Studies using the Short Form 36 (SF-36) and Kidney Disease Questionnaire (KDQ) indices have shown greater impact on the physical domains, vitality, and performance [28,30**,32] whereas studies that employed the Sickness Impact Profile (SIP) scale revealed greater improvement in psychosocial dimensions of HRQOL [30**]. Additional domains not measured by commonly used instruments that have been shown to improve with ESAs include sleep [29,30**], cognitive functioning and sexual functioning [30**,32].

The use of ESAs has become a routine practice in CKD patients in an effort to correct anemia and improve HRQOL. Nonetheless, two simultaneously published trials [33*,34] raised concerns regarding the optimal hemoglobin target levels. Drueke *et al.* [33*], the CREATE investigators, reported significant increment in HRQOL with higher hemoglobin levels (Figure 3) whereas Singh *et al.* [34], the CHOIR investigators, reported no difference in the HRQOL between the low and high hemoglobin arms after EPO therapy. Additionally, normalization of hematocrit was shown to be associated with adverse cardiovascular outcomes in the CHOIR trial [34]. These trials were subject to extensive critique [35,36,37], which prompted a series of subsequent studies and systematic reviews that supported the ineffectiveness of normalization of hemoglobin, suggesting that maximal improvement in HRQOL occurred in the range of 10.0–12.0 g/dL, with blunting of the beneficial effects at higher levels [30**,38,39**].

In consideration of the conflicting results of these publications, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI) published revised guidelines for the management of anemia in CKD patients [40], which were further reviewed at the Kidney Disease: Improving Global Outcomes (KDIGO) international conference [41]. Members voiced a general consensus on maintaining target hemoglobin levels in the range of 11.0 to 12.0 g/dL [40] and acknowledged the potential for harm associated with levels higher than 13.0 g/dL [40,41].

Although the favorable effect of anemia correction on HRQOL is well recognized, the endeavor to identify optimal hemoglobin targets that limit the adverse outcomes in patients persists. Currently ongoing trials are expected to provide further clarification on this issue [40].

Frailty and CKD

There is a limited but growing literature examining the association between frailty and CKD. Frailty is an increasingly recognized biological syndrome that is related to, but distinct from aging, co-morbidity and disability [42]. It is characterized by diminished physiologic reserves, functional decline and increased vulnerability to acute stressors [43]. Fried *et al.* [44] proposed a well-validated screening tool, which defines frailty as the presence of ≥ 3 criteria: slow gait, unintentional weight loss, low physical activity, exhaustion and/or poor grip strength. A cross-sectional analysis by Shilpak *et al.* [45] found an independent association between CKD and frailty in community-dwelling elderly persons. Johansen *et al.* [46] reported a strong association between ESRD and frailty, even in younger age groups. Supporting evidence for these findings comes from a study by Wilhelm-Leen *et al.* [47**] which demonstrated that the prevalence of frailty was significantly higher in persons with CKD, and that this association was stronger in persons with more severe CKD. The biological mechanisms contributing to frailty in CKD are thought to involve a complex interplay of elevated inflammatory biomarkers, hormonal changes (declining levels of testosterone, vitamin D, growth hormone and thyroid abnormalities), malnutrition, anemia, sarcopenia and depression [43,48]. It is also notable that

studies investigating the impact of vitamin D replacement on HRQOL in vitamin D deficient CKD patients are currently ongoing [49]. However, the association between frailty and CKD in the study by Wilhelm-Leen and colleagues was present despite adjustment for these potential mediators [47**].

Frailty is an independent predictor of adverse health outcomes, including hospitalization, disability and mortality [44]. A study by Kanauchi *et al.* [50] identified a significantly lower HRQOL among frail clinic patients with cardiometabolic risk factors, than their non-frail counterparts. Masel *et al.* [51] further confirmed the association between frailty and impaired HRQOL in older Mexican Americans. Combining these results with the data reporting an association between CKD and impaired HRQOL [1**,2,8], it appears that frail individuals with CKD are highly susceptible to adverse health outcomes and poor HRQOL. This is supported by studies that found an independent association of frailty with mortality in patients with CKD [47**] and ESRD [46]. Additional evidence comes from the study by Kanauchi and colleagues [50], that found that patients with lower creatinine clearance had significantly lower scores on the World Health Organization Quality of Life-26 questionnaire.

The increasing prevalence of CKD in the older population [52] and the poor prognosis and impaired HRQOL associated with frailty warrant early identification of high-risk patients. Suggested management strategies to prevent further deterioration include exercise training and correction of malnutrition, anemia, depression and hormonal imbalances [48]. Growth hormone supplementation in elderly dialysis patients has been shown to improve muscle performance [48] and HRQOL [53], but whether this approach would be helpful in patients with non-dialysis dependent CKD remains to be established.

Symptom burden, Depression and HRQOL

The expanding awareness about objective parameters and their impact on HRQOL is complemented by few studies on subjective symptoms and their influence on HRQOL in CKD [10,54**,55]. The symptom burden that these patients struggle with include, fatigue [2,10,54**], cognitive difficulties [2,54**], sleep disturbances [1**,2,10,54**,56], sexual dysfunction [2,54**], pain [2,10,54**,56] and depression [2,10,54**], most of which are interlinked [1**,10]. While larger studies on pre-dialysis CKD patients are lacking, existing ones confirm the negative impact of these symptoms on HRQOL [2,55,56].

Abdel-Kader *et al.* demonstrated through two cross-sectional studies [54**,57**], that patients with advanced CKD (Stages 4–5) and ESRD report a comparable compromise in HRQOL, which may help to guide patients and providers on expectations following dialysis initiation. Furthermore, the study that addressed the symptom burden [54**] documented that both of these patient populations are afflicted with a similar symptom burden and have a similar prevalence of depression, whereas the other [57**] addressed individual factors affecting HRQOL and concluded that family and health were the most prominent patient-identified dimensions influencing HRQOL.

Although the detrimental role of symptoms on HRQOL in CKD is now better recognized, they are often under-treated despite availability of effective therapies for most symptoms and depression [10,55]. Symptoms including pain, sexual dysfunction, and depression have been shown to be effectively treated in the ESRD population. Whether interventions aimed at alleviating such bothersome symptoms translate into improved HRQOL in the ESRD and CKD populations is a matter of ongoing investigation.

Conclusion

CKD has a profound effect on HRQOL with the most prominent areas of difficulty being the physical domains. While the link between HRQOL and increased hospitalizations and mortality in ESRD is well characterized [1**], a parallel association in CKD patients remains unexplored. Further insights are needed into effective interventional strategies and their impact on HRQOL. Given the numerous factors contributing to HRQOL in CKD (Figure 1), whether intervention in a single aspect would translate into better HRQOL remains to be shown. With identification of CKD as a rising global health and economic burden[58], a better understanding of HRQOL issues would enable providers to deliver more patient-centered care and improve overall well-being of patients.

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Figure 1.
Factors contributing to health-related quality of life in chronic kidney disease (ORIGINAL)

Figure 2.

Examples of several domains of the health-related quality of life (HRQOL) showing the progressive decline in scores with the more advanced stages of chronic kidney disease (CKD). Statistical significant values are for the trend across the three CKD stages.

Figure 3.

Changes from baseline to Year 1 in Short Form Survey Instrument (SF-36) Health related Quality of Life Scores with erythropoietin treatment for anemic CKD patients in the CREATE Study [33*]. Group 1: Target hemoglobin range 13–15 g/dL. Group 2: Target hemoglobin range 10.5–11.5 g/dL. Positive changes indicate improvement in, and negative changes worsening of, the health related quality of life.