Health-Related Quality of Life and Hemoglobin Levels in Chronic Kidney Disease Patients

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Background: The relationship between quality of life (QofL) and anemia has been the subject of recent debates; it has been suggested that the QofL changes associated with the treatment of anemia of chronic kidney disease (CKD) or ESRD patients should not be used in making decisions to treat anemia in CKD patients.

Design, setting, participants, & measurements: This study examines the relationship between Kidney Disease Quality of Life (KDQofL) questionnaire domains and hemoglobin (Hgb) levels in 1200 patients with stage 3, 4, and 5 CKD followed in seven centers. QofL measures were compared in a stepwise fashion for hemoglobin levels of <11, 11 to <12, 12 to <13, and ≥13. ANOVA was used to examine the relationship between QofL scores and Hgb level, age, CKD stage, and albumin level; a history of diabetes, congestive heart failure, or myocardial infarction; use of erythropoetic-stimulating agents (ESA); and the interaction of hemoglobin level and ESA.

Results: The results demonstrate that with increasing Hgb levels there is a statistically significant increase in all four physical domains, the energy/vitality domain, and the physical composite score of the SF-36, and the general health score on the kidney disease component of the questionnaire. The most dramatic improvements in these various domains occurred between the <11 and the 11 to 12 group.

Conclusions: Higher Hgb levels are associated with improved QofL domains of the KDQofL questionnaire. These findings have implications for the care of CKD patients in terms of the initiation of and the Hgb target of ESA therapy.

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The reasons for using erythropoetic-stimulating agents (ESA) in patients with chronic kidney disease (CKD) have recently been called into question (1–4). Findings in patients with CKD have prompted the U.S. Food and Drug Administration (FDA) in the United States to suggest that increases in hemoglobin levels to values over 12 g% may be associated with increased morbidity and mortality and that the benefits of these drugs have not been well documented (4). Although many nephrologists feel that the ESA improve the quality of life of patients with CKD, the FDA has indicated that the studies supporting this impression have not been satisfactory and have discounted these studies in providing guidelines for the use of ESA in CKD patients. In fact, the FDA is in the process of preparing a document reviewing guidelines for the use of patient-reported outcome instruments to assess health-related quality of life. The FDA advisory of November 8, 2007 states that for patients with CKD "quality of life claims in the previous labeling were removed, with the exception of improved exercise tolerance and functional ability for chronic renal failure patients." This recommendation was based on the lack of controlled studies demonstrating an improvement in health-related quality of life measures. For example, the recent CHOIR study by Singh *et al.* examining various health-related quality of life measures in CKD patients randomized to target hemoglobin (Hgb) levels of 11.3 and 13.5 demonstrated no difference in QOL between the higher and lower target groups; however, previous randomized trials did demonstrate an improvement in physical function in CKD patients randomized to higher Hgb levels (5).

The purpose of this study is to examine the relationship between anemia severity and health-related quality of life in a cross-sectional study of a cohort of CKD patients (stages 3 to 5). The patients were enrolled in the CRIOS study (CKD RenalSoft Informatics Observational Study). The Kidney Disease Quality of Life questionnaire was completed by 1186 patients and the data were correlated with Hgb levels at the time of the completion of the questionnaire.

Materials and Methods

CRIOS is a prospective observational cohort study designed to identify trends in practice patterns and outcomes in CKD patients. From January 2003 to December 2006, 2295 patients were enrolled from seven North American sites that included academic medical centers, private nephrologists offices, and hospital-based programs in the United States and Canada. Programs were selected to participate in the study if they had an organized CKD patient care program and had established a

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structured CKD patient education program. After local research ethics board approval was obtained, subjects signed informed consent to allow collection of clinical and laboratory data to be entered into the software application. Participating centers in the United States were Brigham and Women's Hospital, Boston, Massachusetts; Metabolism Associates, New Haven, Connecticut; Mid-Atlantic Nephrology Associates, Baltimore, Maryland; Nephrology Associates, Birmingham, Alabama; and in Canada the centers were Humber River Regional Hospital, Toronto, Ontario; Royal Victoria Hospital, Montreal, Quebec; and Queen Elizabeth Health Science Centre, Halifax, Nova Scotia.

In its entirety, the CRIOS study was designed to collect data on clinical care practices and selection of patients for specific renal replacement therapy; and access planning, placement, quality of life, and the effect of patient educational intervention. The data were entered into a software program (RenalSoft, Baxter Healthcare Corporation), a clinical management tool in which patient information was de-identified of specific patient information and forwarded to a data repository on a monthly basis.

Patients with CKD were continually enrolled throughout the duration of the study. Subjects in each site were identified and approached for study entry by the principal and/or coinvestigators. Inclusion criteria included: (1) GFR <60 ml/min/1.73 m^2 on the basis of estimated GFR using the Modification of Diet in Renal Disease formula (CKD stages 3 to 5, not on dialysis), (2) age 18 and older, and (3) ability to read and communicate in English or French. Subjects were followed at regular intervals as dictated by their stage of kidney disease and the standard of care in the outpatient clinic setting in which they were enrolled. Patients remained in the program until they began renal replacement therapy, died, or transferred care to another program. Patient-specific information regarding demographics, health care delivery, prescriptions, pre-educational assessment, renal replacement therapy choices, access planning, and access placement information were collected at baseline and on an ongoing basis at time of physician or educator interaction. Demographic data that were obtained included age, sex, and race; presence or absence of a history of diabetes, congestive heart failure, or myocardial infarction; and use of ESA.

All patients who agreed to participate in the study and were medically stable were asked to complete the Kidney Disease Quality of Life Short Form Questionnaire (KDQofL-SF), a self-administered survey of consisting of 79 items. This questionnaire, which measures a variety of health-related quality of life domains, has been widely used in the assessment of patients with kidney disease (1,5–9). The questionnaire includes 36 generic items (the SF-36) and an additional 43 kidney-disease-specific questions. The domains measured by the SF-36 include physical domains [physical functioning, role limitations due to physical health (role-physical), general health perceptions, pain] and mental domains [energy/fatigue (vitality), social functioning, emotional well being (mental health), role limitations due to emotional problems]. The domains targeted specifically for patients with kidney disease (on the basis of the 43 kidney-disease-specific questions) include work status,

Table 1. Basic demographics by CKD stage

Parameter	CKD Stage			
	All	III	IV	V
Age				
N	1186	369	592	225
mean	65.6	64.6	67.2	63.2
SEM	0.4	0.7	0.5	1.0
range	19 to 87	19 to 86	19 to 87	23 to 87
Gender				
male (%)	58.0	63.7	56.8	52.0
female (%)	42.0	36.3	43.2	48.0
Race				
Asian/Indian/Filipino (%)	2.3	1.6	2.2	3.6
Black (%)	10.4	14.4	8.4	8.9
Pacific islander (%)	0.1	0.0	0.2	0.0
White (%)	72.8	70.5	75.5	69.3
other/multiracial (%)	1.7	1.4	1.5	2.7
missing (%)	12.8	12.2	12.2	15.6
Diabetes				
diabetic (%)	45.7	45.5	46.8	43.1
nondiabetic (%)	54.3	54.5	53.2	56.9
Primary renal disease				
diabetes	28.8	26.6	29.4	30.7
glomerulonephritis/vasculitis/autoimmune diseases	12.3	12.7	11.0	15.1
interstitial nephritis/pyelonephritis	3.3	3.8	3.4	2.2
hypertension/large vessel/renal vascular disease	27.1	30.4	26.2	24.0
neoplasms/tumors	1.4	1.1	1.0	3.1
cystic/hereditary/congenital diseases	8.0	6.8	7.6	11.1
miscellaneous conditions	18.0	18.2	20.1	12.4
missing	0.7	0.3	0.8	0.9

quality of social interactions, burden of kidney disease, social support, cognitive function, sexual function, sleep, effects of kidney disease (overall health), and symptoms/problem list. The scores are aggregated and transformed linearly to a 0- to 100-possible range, with higher scores indicating better status. The physical and mental domains from the SF-36 questions are summarized in physical and mental component summary scores, which are standardized to the general U.S. population (mean ± SD score of 50 ± 10) (10).

Of the 2295 patients enrolled in the CRIOS study, 1186 completed KDQofL-SF questionnaires. Hgb levels, creatinine values, and demographic data taken within 60 d of completion of the KDQofL-SF questionnaire were used in this analysis. If patients did not have laboratory data within this period, they were excluded from the analysis. If a patient did not answer a specific item on the questionnaire, then that patient's data were not used in the analysis for that specific question or score. When comparing the patients completing the KDQofL-SF to those not completing the questionnaire, the patients completing the KDQofL-SF assessment had similar diagnoses, had a similar incidence of diabetes, a similar percent utilization of ESA, were slightly older (mean age of 64.8 *versus* 61.1), and included a higher percent of men (54.6% *versus* 45.4%).

Preliminary analyses demonstrated a relationship between Hgb levels and various domains of the KDQofL-SF. We then decided to control for those parameters that we thought might have an effect on these relationships; only those parameters were chosen for which we had results in the majority of patients. ANOVA was used to determine if the scores from various domains in the KDQofL-SF were then related to these demographic and comorbidity data obtained at the time of KDQofL-SF assessment. The dependent factors in the analyses were the scores from the various domains in the KDQofL-SF. The independent factors in the analyses were Hgb level, age, CKD stage, and albumin level; presence or absence of a history of diabetes, congestive heart failure, or myocardial infarction; use of supplemental iron (oral or intravenous); use of ESA; and the interaction of Hgb level and ESA. There was one analysis performed for each domain. All of the covariates were included in each analysis.

Results

The basic demographic data of the 1186 patients included in this study are shown in Table 1. Significant representation of all three stages of CKD was present in the cohort. The demographic profile of the study population is very similar to the profile of patients initiating dialysis in North America with respect to age and diabetes prevalence. The mean ± age of the patients was 65.6 ± 13.8 yr. Forty six percent of the patients had diabetes, 12% had a history of congestive heart failure, and 13% had a history of a myocardial infarction; these percentages were similar in all three CKD stages.

Mean estimated GFR for all patients was 25.6 and was progressively lower as CKD stage advanced from 3 to 5, as expected (Table 2). Mean Hgb levels were 12.8 in stage 3 patients, 12.0 in stage 4 patients, and 11.4 in stage 5 patients ($P = 0.023$). Serum creatinine, blood urea nitrogen, and phosphorus levels were higher in stage 5 than stages 3 and 4 ($P = <0.0001$, <0.0001, and 0.0007, respectively). Serum calcium and albumin levels were not different in the three CKD stages.

Twenty-four percent of stage 3 patients, 43% of stage 4 patients, and 69% of stage 5 patients were receiving ESA. Seventy-one percent of patients with Hgb <11, 48% of patients with Hgb 11 to 12, 37% of patients with Hgb 12 to 13, and 21% of patients with Hgb levels >13 were receiving ESA. Fifty-five percent of patients receiving ESA were given epogen and 45% were given darbepoetin. Of those receiving epogen, 60% received weekly dosing and 40% received dosing less than once a week. Of those receiving darbepoetin, 80% received doses at intervals of 2 wk or less.

Table 2. Biochemical profile by chronic kidney disease (CKD) stage

Parameter	CKD Stage			
	All	III	IV	V
GFR				
N	1186	369	592	225
mean	25.6	39.4	22.4	11.2
SEM	0.3	0.4	0.2	0.2
BUN				
N	1136	375	584	177
mean	47.6	31.6	51.0	70.2
SEM	0.6	0.5	0.8	1.7
Creatinine				
N	1186	385	602	190
mean	2.8	1.8	2.8	5.1
SEM	0.0	0.0	0.0	0.1
Calcium				
N	1169	390	589	190
mean	9.2	9.4	9.2	9.1
SEM	0.0	0.0	0.0	0.1
Phosphate				
N	1132	360	582	190
mean	4.0	3.6	4.0	4.9
SEM	0.0	0.0	0.0	0.1
Albumin				
N	1155	388	582	185
mean	37.9	39.0	37.5	37.0
SEM	0.1	0.2	0.2-22.0	0.3
Hematocrit				
N	1169	377	595	197
mean	36.3	38.1	35.9	34.3
SEM	0.1	0.2	0.2	0.4
Hemoglobin				
N	1167	373	597	197
mean	12.2	12.8	12.0	11.4
SEM	0.1	0.1	0.1	0.1

The relationships between the Hgb levels and various domains on the KDQofL-SF are summarized in Table 3. Hgb levels were grouped into four categories (<11 g%, 11 to <12 g%, 12 to <13 g %, and ≥13 g%; the numbers of patients in each of the Hgb categories were approximately the same, varying between 211 and 284. Of the 229 patients with Hgb levels <11, only 63 had levels <10 g%; the quality of life measures in the patients <10 g % and 10 to 11 g% were not significantly different, so the group was analyzed as one entity.

As Hgb levels increased from <11 to ≥13, there were significant improvements in a variety of quality of life domains when only

Table 3. Kidney Disease Quality of Life Short Form Questionnaire scores in CKD patients and hemoglobin (Hgb) levels (unadjusted)

Instrument/Parameter	Hgb				*P*
	<11	11 to <12	12 to <13	≥13	
N	229	223	221	284	N/A
KDQOL					
kidney disease component summary	72.2	74.4	74.0	77.3	0.0006
symptom problem	77.4	78.7	78.8	83.9	<0.0001
effects kidney disease	80.6	81.4	81.8	86.6	0.0003
burden kidney disease	67.3	74.1	72.0	75.1	0.0069
work status	40.7	42.5	45.6	52.0	0.0017
cognitive function	83.9	83.5	83.2	85.2	0.6008
quality social interaction	80.2	83.5	80.7	81.0	0.1730
sexual function	82.3	85.4	78.3	85.7	0.2464
sleep	63.3	64.8	62.8	67.4	0.0559
social support	83.1	82.8	83.6	83.3	0.9873
SF-36					
mental component summary	48.9	50.1	50.3	50.5	0.3924
physical component summary	37.1	40.0	38.3	42.5	<0.0001
physical functioning	49.8	56.5	51.9	64.3	<0.0001
role—physical	40.1	51.6	47.5	61.7	<0.0001
pain	66.1	70.7	64.0	71.8	0.0041
general health	43.5	46.2	46.8	52.9	<0.0001
emotional well being	71.8	75.7	74.7	75.8	0.0869
role—emotional	67.6	72.6	69.9	78.6	0.0118
social function	70.0	76.3	73.9	79.1	0.0013
energy/fatigue	43.6	48.2	48.7	52.4	0.0005

KDQofL, Kidney Disease Quality of Life questionnaire; SF-36, short form of the KDQofL that includes 36 generic items.

Hgb level was accounted for in the analysis (Table 3). This was true for all domains of the SF-36 (except emotional well being, $P = 0.08$) as well as the physical component summary (PCS) score [$P < 0.001$]; the mental component summary (MCS) score increased slightly but the difference was not statistically significant ($P = 0.39$). Four of the KDQofL domains showed significant increases (symptom problem, effects of kidney disease, burden of kidney disease, and work status); the Kidney Disease Component Summary score also significantly increased ($P = 0.0006$).

In Table 4, the association between Hgb levels and quality of life measures was adjusted for a variety of variables using an ANOVA. The first column in this table (Hgb) addresses the association of Hgb levels with quality of life measures adjusting for age, gender, race, stage of CKD, and albumin level; a history of the use of ESA and iron (oral and intravenous); and the presence or absence of diabetes, congestive heart failure, or myocardial infarction. A significant association remained between Hgb levels and all four physical components of the SF-36 [physical functioning ($P = 0.003$), role physical ($P = 0.002$), pain ($P = 0.015$), and general health ($P = 0.049$)] as well as the PCS score ($P = 0.008$). The most dramatic improvements in these quality of life domains occurred between the <11 and the 11 to 12 group. For example, the physical function score increased from 51.2 in the <11 group to 56.9 in the 11 to 12 group; the >13 group had a score of 60.7. Of the mental domains, energy/fatigue ($P = 0.024$) remained significantly associated with Hgb levels. In terms of the KDQofL domains, only symptom problem ($P = 0.018$) remained with a significant association with Hgb levels; this score increased from 74.5 in the <11 group to 78.8 in the 11 to 12 group. For the other quality of life domains, as the Hgb increased from <11 to 11 to 12, it is noteworthy that all of the remaining domains on the SF-36 increased and six of the nine remaining KDQofL scores increased; the three KDQofL scores that did not increase declined by a score of 1 or less.

The Hgb-ESA interaction was then examined in the last column in Table 4 (Hgb-epo interaction). This interaction term tests if any change in quality of life measures across levels of Hgb is consistent for those subjects using ESA and those not using ESA. The findings indicate that there were no significant interactions between Hgb levels and the use of ESA, suggesting that the association between quality of life and Hgb levels was independent of ESA use. The type of ESA administered (epogen or darbepoetin) had no effect on the results.

Discussion

The use of ESA in the management of anemia of patients with CKD is being reexamined in view of recent publications relating increased morbidity and mortality in CKD patients treated

Table 4. Analysis of variance of KDQofL-SF scores and Hgb levels[a]

Instrument/Parameter	Hgb				*P*	
	<11	11-<12	12-<13	>13	Hgb	Hgb-Epoetin Interaction
KDQOL						
kidney disease component summary	73.8	74.9	73.3	75.1	0.503	0.407
symptom problem	78.6	79.2	78.3	82.7	0.018	0.802
effects kidney disease	82.6	82.0	80.8	84.4	0.217	0.896
burden kidney disease	70.9	75.2	70.1	69.7	0.097	0.604
work status	43.0	43.2	46.8	46.8	0.517	0.584
cognitive function	84.9	83.9	83.0	83.8	0.786	0.959
quality social interaction	80.8	83.6	79.9	79.9	0.074	0.587
sexual function	83.2	85.4	77.9	85.4	0.321	0.500
sleep	65.3	65.2	61.7	67.2	0.070	0.097
social support	83.7	83.1	82.8	83.5	0.980	0.842
SF-36						
mental component summary	49.7	50.5	50.0	49.5	0.820	0.979
physical component summary	37.4	39.9	38.5	41.0	0.008	0.333
physical functioning	51.2	56.9	53.1	60.7	0.003	0.920
role—physical	40.8	51.7	47.1	56.9	0.002	0.275
pain	67.4	71.4	63.7	70.8	0.015	0.694
general health	44.9	47.0	45.9	50.4	0.049	0.403
emotional well being	73.0	76.3	73.9	73.2	0.285	0.634
role—emotional	68.5	73.4	68.2	75.6	0.182	0.326
social function	71.7	76.9	72.8	76.2	0.152	0.434
energy/fatigue	43.4	48.8	49.0	50.1	0.024	0.213

[a]Adjusted for age, CKD stage, and albumin level; presence or absence of a history of diabetes, congestive heart failure, or myocardial infarction; the use of erythropoietin-stimulating agents (ESA) or supplemental iron (oral or intravenous); and the interaction of Hgb level and ESA.

with ESA who have higher Hgb levels (2,3). Furthermore, some recent studies have suggested that the higher Hgb levels in CKD patients achieved with ESA administration are not associated with an improved quality of life for these patients (2). In fact, the FDA has recently suggested that studies examining the quality of life of CKD patients treated with ESA have not been well done and therefore have suggested that labeling of the drug to indicate an improvement in quality of life is not warranted. These suggestions by the FDA are disturbing because many nephrologists feel that the use of ESA has significantly improved the quality of life of CKD patients (11–13). For example, several studies have reported an improvement in various quality of life domains in CKD patients treated with ESA (11–13). These studies have used a wide variety of quality of life instruments and thus comparisons between studies are often difficult. Furthermore, these studies were not randomized, controlled trials and therefore not felt to be acceptable for FDA labeling inclusion.

The study presented here examines the relationship between the various KDQofL domains and Hgb levels in a large cohort of CKD patients followed in seven centers in Canada and the United States. The data demonstrate a significant improvement in various quality of life domains associated with Hgb levels increasing from <11 to >13. These improvements persist in selected domains after correction for variety of factors (use of ESA, age, CKD stage, and albumin level; and the presence or absence of a history of diabetes, congestive heart failure, or myocardial infarction). These increases in scores on the SF-36 included the PCS score, all four physical domains on the SF-36, and the energy/fatigue (vitality) score of the mental domains; the symptom/problem domain increased on the KDQofL. The most dramatic changes occurred between the Hgb levels <11 and 11 to 12.

This study has some limitations; it is a nonrandomized, unselected cohort study involving seven selective centers. Only those patients completing the KDQofL-SF questionnaire with laboratory data within 60 d of completing the questionnaire were included (about half of the total study population). Only those covariates that were available were used in the statistical analyses; complete correction for a wider range of covariates was not possible. Whether the findings are generalizable to a broader range of centers and patients remains to be determined. Nevertheless, the findings in this study are consistent with previously reported investigations. For example, Lefebre *et al.* did a *post hoc* analysis of a multicenter, open-labeled study of ESA therapy and looked at ESA administration and quality of life in over 1000 CKD patients using the Kidney Disease Questionnaire (KDQ) and Linear Analog Scale Assessment (LASA) to measure quality of life (11). This analysis found a significant increase in all three domains of the LASA scale

(activity, energy, overall quality of life) with increasing Hgb levels, and in all six of the domains on the KDQ. The maximal incremental gain in quality of life for all scales occurred when the Hgb reached 11 to 12 g % (11). It is of interest that the findings in this study and in the Lefebre article support recent patient testimonials targeting Hgb levels over 11 g% (14).

The study by Singh *et al.*, examining the effect of targeting Hgb levels in CKD patients with baseline Hgb levels of 10.1 to 13.5 or 11.3, suggested that there were similar levels of improvement from baseline values in various quality of life domains in both groups with no additional improvement in the group with the Hgb level targeted to 13.5 (2). This study used the KDQ, LASA, and SF-36 to assess quality of life. It is noteworthy that the increase in Hgb levels from 10.1 to 11.3 in the lower targeted group resulted in an improvement in all LASA scores, the total KDQ score, and 5 of the 8 SF-36 scores (physical function, physical role, general health, energy/fatigue [vitality], and mental health). Our study found significant associations between Hgb level and SF-36 scores in four of these same domains.

In summary, this study of stage 3 to 5 CKD patients not on dialysis suggests a significant improvement in various quality of life domains as Hgb levels increase from <11 to 11 to 12 and higher, and these improvements persist in selected domains after correction for variety of factors including the use of ESA, and other comorbidities. These findings, added to previously reported studies in this patient population, suggest that there is a relationship between Hgb levels and various quality of life domains and that the greatest improvement in quality of life occurs with the increase in Hgb level to the 11 to 12 g% range. These findings have implications for the care of CKD patients in terms of the initiation of ESA therapy and the Hgb target of ESA therapy. The current approved FDA claims for the use of ESA do not reflect the quality of life changes observed in this study. Therefore, additional prospective studies should be done to systematically document the changes in health-related quality of life domains that occur with ESA use in CKD patients as Hgb levels are increased from <10 or 10 to 11 g/dl to higher levels. The potential implications of these studies for the care of CKD patients are critically important. What should the Hgb target be for CKD patients treated with ESA? At what Hgb level should ESA therapy be initiated? The effect of the answers to these questions for the health-related quality of life of CKD patients may well be substantial. Hopefully the final FDA report on the use of patient-reported outcomes to assess health-related quality of life will provide a useful framework for nephrologists to help answer these important questions.

Disclosures

None.

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