

Health-related Quality of Life in CKD Patients: Correlates and Evolution over Time

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Background and objectives: Very few large-scale studies have investigated the determinants of health-related quality of life (HRQOL) in chronic kidney disease (CKD) patients not on dialysis or the evolution of HRQOL over time.

Design and setting: A prospective evaluation was undertaken of HRQOL in a cohort of 1186 CKD patients cared for in nephrology clinics in North America. Baseline and follow-up HRQOL were evaluated using the validated Kidney Disease Quality Of Life instrument.

Results: Baseline measures of HRQOL were reduced in CKD patients in proportion to the severity grade of CKD. Physical functioning score declined progressively with more advanced stages of CKD and so did the score for role-physical. Female gender and the presence of diabetes and a history of cardiovascular co-morbidities were also associated with reduced HRQOL (physical composite score: male: 41.0 ± 10.2 ; female: 37.7 ± 10.8 ; $P < 0.0001$; diabetic: 37.3 ± 10.6 ; nondiabetic: 41.6 ± 10.2 ; $P < 0.0001$; history of congestive heart failure, yes: 35.4 ± 9.7 ; no: 40.3 ± 10.6 ; $P < 0.0001$; history of myocardial infarction, yes: 36.1 ± 10.0 ; no: 40.2 ± 10.6 ; $P < 0.0001$). Anemia and beta blocker usage were also associated with lower HRQOL scores. HRQOL measures declined over time in this population. The main correlates of change over time were age, albumin level and co-existent co-morbidities.

Conclusions: These observations highlight the profound impact CKD has on HRQOL and suggest potential areas that can be targeted for therapeutic intervention.

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Patients' perception of their well being and patient-reported outcomes (PROs) are becoming an integral part of evaluations of the human cost of chronic illnesses and the assessment of the impact of therapeutic interventions. Measures of health-related quality of life (HRQOL) have not only become popular investigative tools, but have been used in an effort to define and alter models of health care delivery. To date, there have been very few large-scale studies that have investigated the determinants of HRQOL in chronic kidney disease (CKD) patients not on dialysis, or the evolution of HRQOL over time using PROs. Most studies have tended to be small in size and cross-sectional (1–5). Larger studies have lacked a longitudinal component (6,7), and longitudinal studies have been modest in size (8) or used tools not developed for patients with kidney disease (9).

The quality of life of CKD patients is a frequently overlooked yet critical consideration when evaluating their overall medical care (10). The importance of measuring HRQOL has been un-

derscored by recent studies indicating an association between various HRQOL measures and mortality and hospitalization rates in dialysis patients (11–16). These studies have raised the question of whether addressing HRQOL problems in dialysis patients and patients with CKD can improve medical outcomes. Given the well documented, high mortality and hospitalization rate in CKD patients, understanding the HRQOL issues of CKD patients would seem to be an important area to explore (17).

Materials and Methods

Patients and Study Design

We conducted a prospective observational study, which profiled the care and characteristics of patients with CKD. After local Research Ethics Board approval was obtained, subjects signed informed consent to allow clinical and laboratory data to be collected. Eligibility for study entry included CKD stages III–V, and age greater than 18 yr. Subjects at each site were identified by investigators in a nonrandom fashion between January 2003 and December 2006. In addition to the clinical and laboratory data collected, HRQOL indicators were measured. Patients were recruited from seven centers in the United States and Canada, identified in the Acknowledgments section below.

HRQOL Questionnaire

Quality-of-life questionnaires were given to patients at baseline, and at approximately 6 mo intervals thereafter (a window of ± 2 mo) using

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the Kidney Disease Quality of Life (KDQOL) questionnaire, short form, version 1.3 (KDQOL-SF™), from the Rand Corporation. The completion of the self-completed KDQOL at baseline and during follow up was voluntary.

The KDQOL is a validated quality-of-life instrument that combines the generic SF-36 instrument with a kidney disease-specific instrument (17–19). Importantly, this instrument has been shown to be able to detect clinical changes over time in a large cohort of dialysis patients (20). The generic SF-36 instrument includes 36 items that measure eight dimensions or domains of functioning and well being on a 100-point scale (the higher the scale the better the patient's HRQOL). The eight domains are: (1) physical functioning; (2) role limitations caused by physical problems; (3) pain; (4) general health; (5) energy/fatigue; (6) emotional well being; (7) role limitations caused by emotional problems; and (8) social function. In addition to individual comparisons across all eight SF-36 domains, results from the SF-36 instrument were further summarized into a physical composite summary (PCS) score and a mental composite summary (MCS) score using the RAND scoring algorithm. The PCS aggregates items from physical functioning, role-physical, bodily pain, general health, vitality, and social functioning. The MCS aggregates items from role-emotional, mental health, and also includes elements of general health, vitality, and social functioning. In the general population, the mean for each summary scale is 50 points, with a SD of 10 points.

The disease-specific component of the KDQOL includes 44 questions, encompassing 43 kidney-disease targeted items and one overall health-rating question. Eleven domains, also on a 100-point scale, are measured with these questions, including (1) burden of kidney disease; (2) cognitive function; (3) dialysis staff encouragement; (4) effects of kidney disease; (5) patient satisfaction; (6) quality of social interaction; (7) sexual function; (8) sleep; (9) social support; (10) symptom problem; and (11) work status. The two questions relating to dialysis staff encouragement and patient satisfaction that are generally part of the

disease-specific component of the KDQOL were excluded as they were not pertinent to the population under evaluation. A kidney disease component summary (KDCS) score, also on a 100-point scale, was computed per Mapes *et al.* (13,21).

Statistical Methods

ANOVA was used to determine if there were differences in HRQOL baseline scores across the CKD stages. ANOVA was also used to determine if there was a relationship between various parameters and the baseline HRQOL scores. An analysis was run for each parameter and HRQOL scale combination. An ANOVA was used for each scale where all 10 parameters were included in the model. Regression was used to estimate the change in the HRQOL scores over time (change per year of follow-up).

Results

Patient Characteristics and Baseline HRQOL Findings

Two thousand twenty-five patients with CKD stages III-V were enrolled and 1186 patients completed a KDQOL questionnaire at baseline. Profiles of patients completing the baseline questionnaire were not different from those of the total population. The demographic and biochemical characteristics of patients with at least one KDQOL response are presented in Tables 1 and 2. Baseline measures of HRQOL overall and by various stages of CKD are presented in Table 3. Components of physical scores are consistently lower in these patients with CKD than the general population (6,19). Single and composite parameters tended to decline uniformly with the diminution of renal function (Figure 1). For the majority of the scores, the decline across the three stages of CKD exceeded what is considered the minimal clinically important difference on the scale

Table 1. Demographics of the patient population

Parameter	CKD Stage			
	All	III	IV	V
N	1186	369	592	225
Age (years, Mean ± SEM)	65.6 ± 0.4	64.6 ± 0.7	67.2 ± 0.5	63.2 ± 1.0
Male (%)	58.0	63.7	56.8	52.0
Race (%)				
White	72.8	70.5	75.5	69.3
Black	10.4	14.4	8.4	8.9
Asian/Indian/Filipino	2.3	1.6	2.2	3.6
Other/Multiracial	1.8	1.4	1.7	2.7
Missing	12.8	12.2	12.2	15.6
Diabetes (%)	45.7	45.5	46.8	43.1
Primary Renal Disease (%)				
Diabetes	28.8	26.6	29.4	30.7
Hypertension/ Vascular	27.1	30.4	26.2	24.0
Glomerulonephritis	12.3	12.7	11.0	15.1
Hereditary/Congenital	8.0	6.8	7.6	11.1
Interstitial Nephritis	3.3	3.8	3.4	2.2
Miscellaneous	19.4	19.3	21.1	15.5
Missing	0.7	0.3	0.8	0.9

Table 2. Biochemical profile of the patient population

Parameter	All	CKD Stage		
		III	IV	V
N	1186	369	592	225
GFR (ml/min)	25.6 ± 0.3	39.4 ± 0.4	22.4 ± 0.2	11.2 ± 0.2
BUN (mg/dl)	47.6 ± 0.6	31.6 ± 0.5	51.0 ± 0.8	70.2 ± 1.7
Creatinine (mg/dl)	2.8 ± 0.0	1.8 ± 0.0	2.8 ± 0.0	5.1 ± 0.1
Calcium (mg/dl)	9.2 ± 0.0	9.4 ± 0.0	9.2 ± 0.0	9.1 ± 0.1
Phosphate (mg/dl)	4.0 ± 0.0	3.6 ± 0.0	4.0 ± 0.0	4.9 ± 0.1
Albumin (g/L)	37.9 ± 0.1	39.0 ± 0.2	37.5 ± 0.2	37.0 ± 0.3
Hematocrit (%)	36.3 ± 0.1	38.1 ± 0.2	35.9 ± 0.2	34.3 ± 0.4
Hemoglobin (g/dl)	12.2 ± 0.1	12.8 ± 0.1	12.0 ± 0.1	11.4 ± 0.1

Values are Mean ± SD.

Table 3. Baseline measures of HRQOL for the total population and for patients in various CKD stages

	All patients	CKD III	CKD IV	CKD V	<i>P</i> value ^a
N	1186	369	592	225	
KDCS	74.6 ± 13.6	77.4 ± 12.8	74.4 ± 13.6	70.7 ± 14.0	<0.001
Symptom Problem	79.9 ± 15.5	82.2 ± 14.1	79.5 ± 15.9	77.0 ± 16.1	<0.001
Effects Kidney Disease	82.8 ± 17.6	86.8 ± 15.2	83.2 ± 16.8	75.7 ± 20.5	<0.001
Burden Kidney Disease	72.2 ± 26.5	79.7 ± 23.8	72.7 ± 26.0	59.6 ± 27.4	<0.001
Work Status	45.4 ± 35.6	48.9 ± 38.1	44.3 ± 33.8	42.8 ± 35.8	0.044
Cognitive Function	83.8 ± 18.4	84.8 ± 17.4	84.4 ± 18.2	80.6 ± 20.1	0.020
Quality Social Interaction	81.6 ± 16.8	82.2 ± 15.5	82.0 ± 17.0	79.6 ± 17.8	0.109
Sexual Function	82.7 ± 25.3	84.6 ± 22.2	81.4 ± 26.7	81.8 ± 28.3	0.413
Sleep	64.7 ± 20.9	67.5 ± 19.8	64.3 ± 21.1	61.6 ± 21.5	0.001
Social Support	83.3 ± 24.6	84.9 ± 22.5	83.0 ± 25.7	81.7 ± 24.6	0.136
MCS	49.8 ± 10.4	51.3 ± 9.0	49.8 ± 10.6	47.4 ± 11.5	<0.001
PCS	39.5 ± 10.6	40.4 ± 10.8	39.5 ± 10.5	37.9 ± 10.5	0.021
Physical Functioning	56.3 ± 28.7	59.9 ± 28.0	55.3 ± 28.5	53.1 ± 29.7	0.006
Role-Physical	50.0 ± 42.8	55.5 ± 42.8	50.2 ± 42.6	41.0 ± 42.2	<0.001
Pain	68.4 ± 27.7	69.4 ± 26.9	69.5 ± 27.9	64.1 ± 27.9	0.058
General Health	47.8 ± 21.3	52.5 ± 20.8	47.4 ± 21.8	41.5 ± 19.2	<0.001
Emotional Well-being	74.6 ± 19.5	77.1 ± 17.1	74.7 ± 19.8	70.8 ± 21.7	<0.001
Role Emotional	72.0 ± 40.3	77.5 ± 36.9	71.8 ± 40.8	63.8 ± 42.4	<0.001
Social Function	74.9 ± 26.8	78.9 ± 24.8	75.1 ± 27.0	68.2 ± 27.9	<0.001
Energy/Fatigue	48.1 ± 23.6	51.0 ± 22.0	47.7 ± 24.2	44.7 ± 23.6	0.003

Values are Mean ± SD.

^a*p*-value for trend across CKD stages

HRQOL, health-related quality of life; KDCS, kidney disease component summary; MCS, mental component summary; PCS, physical component summary.

(three to five units) (17). PCS declined progressively with more advanced stages of CKD (Table 3) and was lower than the score for the healthy population for all stages. The effects of CKD stage were significant for all four components of PCS, including physical functioning ($P < 0.005$), role physical ($P < 0.0001$), general health ($P < 0.0001$) and pain ($P < 0.05$). CKD stage had a pronounced effect on sleep scores ($P < 0.005$). Although a similar trend was observed for MCS (Table 3), only for stage V did it decrease below levels in the general population.

Correlates of Baseline HRQOL

Categorical Correlates

To establish the determinants of HRQOL in this population, we examined the impact of categorical parameters on HRQOL (Table 4). For continuous variables such as age, the mean of the population was considered as the boundary for categorical examination (65 yr). Clinically reasonable boundaries were chosen for albumin (35 g/L) and hematocrit (33%). For many of the scores discussed below, the observed differences between the

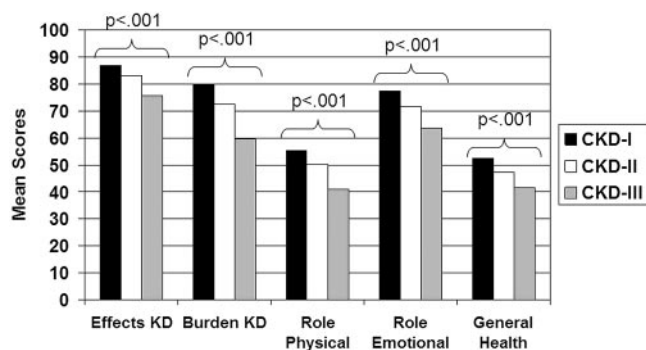


Figure 1. Examples of several domains of the health-related quality of life (HRQOL) showing progressive decline in scores with the more advanced stages of chronic kidney disease (CKD). Statistical significance values are for the trend across the three CKD stages.

categories approached or exceeded the minimal clinically significant differences for the instrument (17).

Effects of age. PCS was lower in older patients (>65 yr) (Table 4). Age impacted physical functioning ($P < 0.0001$) and general health ($P < 0.0001$), but had a marginal or no effect on role physical, pain or energy/fatigue. In contrast, MCS was higher in older patients (Table 4). This was driven predominantly by better emotional well being ($P < 0.0001$). Sleep was also better in older subjects ($P < 0.001$).

Effects of gender. Women had worse PCS (Table 4) and lower scores for physical functioning ($P < 0.0001$), role physical ($P < 0.001$), pain ($P < 0.0001$), general health ($P < 0.001$) and energy/fatigue ($P < 0.0001$). Similarly, women had lower MCS (Table 4) and lower scores for emotional well being ($P < 0.0001$), role emotional ($P < 0.0001$), social function ($P < 0.0001$), energy/fatigue ($P < 0.0001$) and sleep ($P < 0.01$).

Effects of co-morbidities. Diabetics, patients with a history of congestive heart failure (CHF), or a history of myocardial infarction (MI) had worse PCS compared with their respective counterparts (Table 4). This was also true for all components of the PCS examined individually, except for role physical in patients with a history of MI. These co-morbidities had no effect on MCS. Anemia severity (hematocrit <33%) had a modest effect on PCS (Table 4). Role physical was most significantly impacted by the degree of anemia ($P < 0.001$). MCS was modestly influenced by anemia severity (Table 4), predominantly in the social function metric ($P < 0.005$). Hypoalbuminemia (albumin <35 g/L) influenced PCS negatively (Table 4) by affecting physical functioning ($P < 0.02$), role physical ($P < 0.005$), general health ($P < 0.0001$) and energy/fatigue ($P < 0.001$). It also influenced MCS negatively by impacting emotional well being ($P < 0.05$), role emotional ($P < 0.005$), energy/fatigue ($P < 0.001$) and social function ($P < 0.005$). Hypoalbuminemia had no effect on sleep. Beta blockers usage was associated with reduced PCS (Table 4) and physical functioning ($P < 0.0001$). No significant changes were seen in the other components of PCS. Beta blockers usage was also associated with a reduced MCS, which was mainly due to

lower scores in role emotional ($P < 0.0001$). Sleep scores were lower in patients on beta blockers ($P < 0.01$).

Multiple Regression Analysis

Because the parameters examined above may be interrelated, we performed a multiple regression analysis on each of the HRQOL scales in which 10 parameters selected based on the results of categorical analysis in the preceding section were included. Age, plasma albumin, GFR and hematocrit were entered as continuous variables, all others necessarily categorical.

Table 5 shows the estimate (slope) of the relationship between the scores of the various domains of the KDQOL instrument and the parameters chosen (only significant slopes are shown). This analysis identifies the residual effect of a parameter (gender for example) when the effects of all the other listed parameters are considered. For the categorical parameters, being female resulted in a negative slope for 15 scores, implying that women had lower scores for these 15 domains due to their gender and not to any association between gender and any of the other examined parameters. The estimates (slopes) for the continuous variables relate a change in score for any increment in the continuous variable. A positive estimate (slope) with age, for example, means that for any increment in age there is an increase in score. A negative estimate (slope) indicates that for any increment in age there is a decrease in score.

It is clear from the table that some parameters have a more universal effect on the measures of HRQOL and others a more restricted effect. If we construct a descending hierarchy of importance based on the number of measures affected (out of a total of 17 scales analyzed in Table 5 excluding the composite scales KDSCS, PCS and MCS), the 10 parameters fall in the following order: gender (12 of 17), age (12 of 17), albumin (8 of 17), GFR (7 of 17), history of CHF (6 of 17), diabetes mellitus (5 of 17), history of MI (5 of 17), country of residence (5 of 17), use of beta blockers (4 of 17) and hematocrit (1 of 17).

Evolution and Correlates of HRQOL over Time

A minimum of one additional evaluation of HRQOL beyond the baseline determination was obtained in 649 patients. Repeat evaluations were obtained within one year in 594 subjects, within the second year in 450 subjects, within the third year in 188 subjects, and within the fourth year in 55 subjects. Subjects with repeat evaluations had baseline HRQOL scores similar to the overall population (data not shown). Changes in HRQOL over time were calculated as a rate of change in KDQOL score per year. A significant decline in HRQOL measures was evident in the composite scores (KDSCS, MCS and PCS) as well as in all the individual components with the exception of work status, cognitive function and sexual function (Table 6). As the latter parameter (sexual function) was not consistently completed by patients, the lack of statistical significance of the negative trend may have been due to informative censoring.

A limited number of factors were related to the evolution of HRQOL over time. A history of previous MI was the most commonly observed predictor of decline in HRQOL influencing role physical (slope [units per year] MI = -8.6 , no-MI = -1.37 , $P < 0.015$), general health (MI = -3.62 , no-MI = -0.61 ,

Table 4. Categorical factors and baseline HRQOL

Parameter		PCS				MCS			
		N	Mean	SD	p-value	N	Mean	SD	p-value
Age	≤65	460	41.4	10.9	<0.0001	460	48.4	10.5	<0.0001
	>65	590	38.3	10.1		590	51.3	9.9	
Gender	Male	616	41.0	10.2	<0.0001	616	51.2	9.6	<0.0001
	Female	434	37.7	10.8		434	48.4	11.0	
Diabetic	Non-Diabetic	573	41.6	10.2	<0.0001	573	50.3	9.9	0.3952
	Diabetic	477	37.3	10.6		477	49.7	10.7	
Hematocrit	≤33%	223	38.0	10.3	0.0072	223	48.7	10.9	0.0365
	>33%	626	40.2	10.7		626	50.4	10.2	
Albumin	≤35 g/L	126	38.0	10.4	0.0303	126	47.2	11.7	0.0036
	>35 g/L	481	40.3	10.7		481	50.3	10.4	
CHF	No CHF	912	40.3	10.6	<0.0001	912	50.2	10.1	0.2397
	CHF	138	35.4	9.7		138	49.1	11.6	
MI	No MI	903	40.2	10.6	<0.0001	903	49.9	10.2	0.3715
	MI	147	36.1	10.0		147	50.7	10.6	
BetaBlocker	No β Blockers	781	40.2	10.6	0.0053	781	50.4	10.3	0.0490
	β Blockers	269	38.1	10.3		269	49.0	10.1	

HRQOL, health-related quality of life; MCS, mental component summary; PCS, physical component summary.

$P < 0.02$), role emotional (MI = -8.9 , no-MI = -3.05 , $P < 0.03$), effects of kidney disease (MI = -3.67 , no-MI = -0.16 , $P < 0.002$) and PCS (MI = -1.89 , no-MI = -0.4 , $P < 0.05$). A history of congestive heart failure (CHF) was also a strong predictor of decline in HRQOL affecting the measures of effects of kidney disease (CHF = -3.35 , no-CHF = -0.52 , $P < 0.05$), the burden of kidney disease (CHF = -5.61 , no-CHF = -0.99 , $P < 0.05$) and general health (CHF = -4.53 , no-CHF = -0.77 , $P < 0.02$). An increase in hemoglobin during follow up had a salutary effect on HRQOL measures, specifically on PCS ($P < 0.05$), social function ($P < 0.03$) and energy/fatigue ($P < 0.005$). Interestingly, age younger than 65 yr was associated with greater decline in MCS (age $\leq 65 = -1.85$, age $> 65 = -0.33$, $P < 0.005$) and role emotional (age $\leq 65 = -6.7$, age $> 65 = -2.46$, $P < 0.005$). An albumin lower than 35 g/L was associated with a significant decline in sexual function (albumin ≤ 35 g/L = -8.48 , albumin > 35 g/L = -0.8 , $P < 0.05$).

Discussion

The present study explored prospectively HRQOL and its correlates in CKD patients. Our findings can be summarized as follows: HRQOL in patients with CKD is reduced by a magnitude that is considered clinically significant. HRQOL scores are significantly influenced by the severity grade of CKD, age, gender, diabetes and history of cardiovascular co-morbidities. Anemia and beta blocker usage are also associated with lower HRQOL scores. HRQOL measures decline over time in this population. The main correlates of change over time are age, co-morbidities and changes in hemoglobin.

It is of interest to compare the baseline HRQOL measures in this large population of CKD patients and the findings in CKD and dialysis patients reported by others. Figures 2 and 3 compare corresponding HRQOL summary scores and specific do-

mains in the present study and the large HD population in the Dialysis Outcomes and Practice Patterns Study (DOPPS) (13,21), the large PD population in ADEMEX (12) and the CKD population evaluated by Perlman *et al.* (6). PCS scores in our population (Figure 2) were more than one SD lower than the corresponding value in the general population. PCS in our study was higher than that observed by Perlman *et al.* (13), likely because of the more advanced CKD stage represented in their study. PCS scores in CKD V in our study were higher than those of HD patients in DOPPS (13,21), but similar to those of PD patients in ADEMEX (12). In the latter study, a large segment of the patients were new to dialysis, which may explain the similarity to our CKD V subjects (12). HRQOL scores decline with vintage on dialysis (12), likely explaining the lower values observed in DOPPS (13,21). MCS scores in our study (Figure 1) were not much different from the general population scores or those observed by Perlman *et al.* (6). Values in CKD V subjects were similar to those in ADEMEX (12). The individual scores for physical function, physical role and general health paralleled the findings in PCS (Figure 3).

A relationship between CKD stage and HRQOL has been reported in other studies (3,7,22). Rocco *et al.* (22) reported a positive correlation between the quality-of-well-being scale and GFR. Chow *et al.* in a large population study found a clear association between HRQOL and GFR level (7). It is curious that such a correlation was not observed in the study of Perlman *et al.*, which these authors ascribed to the narrow range of GFR in their study (6). In the ADEMEX study, however, an effect of GFR on HRQOL was still discernible despite the low GFR values in a PD population (12). The effect of CKD on HRQOL may modulate HRQOL response to nonrenal therapeutic interventions. CKD has been reported to reduce the

Table 5. Correlates of baseline HRQOL measures

	Age	Albumin	Diabetes	GFR	Gender	Country	Hct	CHF	MI	Beta Blocker
KDCS Symptom		0.324 ^b		0.153 ^b	-3.583 ^c			-3.327 ^a		
Problem	0.119 ^b	0.592 ^d			-4.287 ^d			-4.750 ^b		
Effects Kidney Disease	0.150 ^c	0.441 ^c		0.252 ^d						-3.550 ^a
Burden Kidney Disease	0.222 ^c			0.558 ^d						
Work Status	-0.449 ^d		-6.905 ^b		-7.099 ^b	6.766 ^a				
Cognitive Function		0.347 ^a			-3.118 ^a	-3.071 ^a		-3.996 ^a		
Quality Social Interaction	0.158 ^c					-2.735 ^a				
Sexual Function	-0.307 ^b									
Sleep	0.169 ^b		3.172 ^a	0.146 ^a	-3.527 ^a			-5.024 ^a		-5.257 ^b
Social Support	0.136 ^a					-3.890 ^a			5.360 ^a	
MCS	0.101 ^c	0.212 ^a		0.119 ^b	-2.791 ^b					-2.023 ^a
PCS	-0.155 ^d	0.248 ^b	-2.912 ^c		-2.639 ^c			-2.449 ^a	-2.814 ^b	
Physical Functioning	-0.521 ^d	1.111 ^d	-9.040 ^d		-9.919 ^d	-5.030 ^a		-7.789 ^b	-6.322 ^a	-4.415 ^a
Role-Physical	-0.435 ^d	0.882 ^c			-7.452 ^a		1.003 ^b	-12.521 ^c		
Pain					-11.612 ^d					
General Health	0.222 ^d		-6.030 ^d	0.240 ^c	-4.053 ^b				-6.183 ^b	
Emotional Well being	0.137 ^b			0.146 ^a	-7.755 ^d					
Role Emotional		1.103 ^c		0.386 ^b	-8.846 ^b			-7.999 ^a	11.911 ^b	-11.545 ^c
Social Function		1.039 ^d		0.219 ^a	-5.326 ^b	-5.871 ^b				
Energy/Fatigue		0.683 ^c	-3.263 ^a		-4.998 ^b				-5.169 ^a	

^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$; ^d $P < 0.0001$.

KDCS, kidney disease component summary; MCS, mental component summary; PCS, physical component summary

For categorical parameters (Diabetes, gender, country, CHF, MI and beta-blockers) a negative estimate (slope) indicates a lower score for the domain when the condition exists (female gender, presence of diabetes, CHF, and MI, use of beta-blockers and being US). For continuous variables (age, albumin, GFR and Hct), an increase in the parameter results in the indicated estimate (slope). A negative estimate (slope) for age, for example, means that as age increases the score for that domain declines. A positive estimate (slope) for GFR means that as GFR increases, the score for that domain increases.

improvement of HRQOL after coronary artery bypass graft (23).

In our analysis, gender emerged as a powerful predictor of low HRQOL scores in concordance with others (7,12,22). The fact that women suffer more from chronic illnesses is not unique to nephrology (24–32) and has not been adequately addressed in therapeutic approaches. The vulnerability of women to have lower scores was manifest in many domains and was of a magnitude judged to be clinically significant. These observations suggest that particular attention to the impact of CKD on HRQOL should be exercised by the managing nephrologist in female patients.

We observed a significant impact of co-morbidities on HRQOL and its evolution (Table 5). Patients with diabetes and CKD have significant impairment in their HRQOL due to the compounding of co-morbidities (2,7,12,33). A low albumin value had a negative impact on HRQOL consistent with find-

ings in the literature (6,12). Cardiovascular disease in the form of either a history of MI or CHF was also an independent predictor of low HRQOL and decline in HRQOL over time, also consistent with findings in patients with CKD (6,7) and the general population (25,27).

Sleep disturbances are increasingly the subject of evaluations in patients on dialysis (34–37), but are also present in patients with milder levels of CKD (4,38). We observed a profound effect of CKD stage on sleep scores. This effect was modulated by age, gender, co-morbidities and the use of beta blockers. Sleep disturbances affect other components of HRQOL such as cognitive function (34). It is therefore critical that inquiry into the symptoms of sleep disturbances be performed during a clinical encounter and remedial interventions (such as withdrawal of β -blockers if feasible) are undertaken. Increases in hemoglobin in response to ESA or iron therapy (39) are associated with improved HRQOL in patients with CKD (17,40). We

Table 6. Change in measures of HRQOL during follow up

Parameter	Change per Year		
	Estimate (slope)	SE	p-value
KDCS	-1.41	0.32	<0.0001
Symptom Problem	-1.08	0.36	0.0028
Effects Kidney Disease	-0.91	0.44	0.0368
Burden Kidney Disease	-1.57	0.65	0.0152
Work Status	-1.35	0.86	0.1149
Cognitive Function	-0.75	0.44	0.0910
Quality Social Interaction	-1.89	0.43	<0.0001
Sexual Function	-1.36	0.98	0.1664
Sleep	-1.47	0.50	0.0032
Social Support	-1.97	0.68	0.0039
MCS	-0.96	0.26	0.0002
PCS	-0.71	0.26	0.0063
Physical Functioning	-3.23	0.64	<0.0001
Role Physical	-2.81	1.12	0.0119
General Health	-1.30	0.49	0.0082
Emotional Well Being	-1.50	0.46	0.0012
Role Emotional	-4.28	1.04	<0.0001
Social Function	-1.72	0.67	0.0102

KDCS, kidney disease component summary; MCS, mental component summary; PCS, physical component summary.

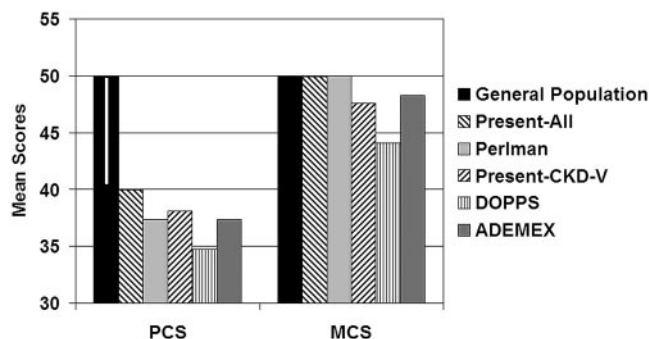


Figure 2. Physical composite summary (PCS) and mental composite summary (MCS) in the general population (6,18), patients in this study (all subjects and those in CKD stage V), in the Perlman *et al.* study (6) and patients in Dialysis Outcomes and Practice Patterns Study (DOPPS) (13,21) and ADEMEX (12). The white line in the general population bar represents one SD from the mean.

have observed a correlation between longitudinal improvements in HRQOL metrics and increases in hemoglobin.

The deterioration of HRQOL with time in patients with CKD has been observed in patients on dialysis (12,13,21) and with earlier stages of CKD (9,41). Our study has explored this phenomenon in greater detail and identified correlates of the progression. The degree (slope) of change observed in our study would suggest that decrements in HRQOL scores can cross the clinical significance threshold in a limited number of years of

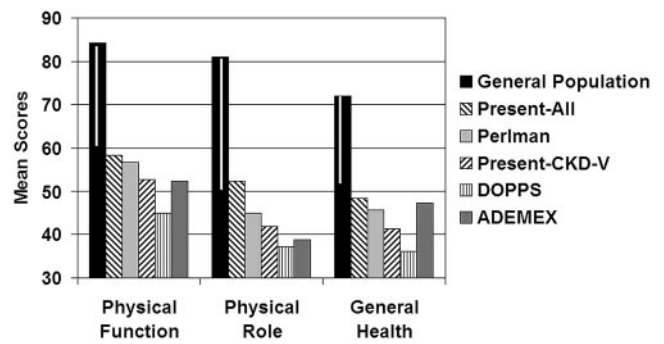


Figure 3. Three representative domains of HRQOL in the general population (6), patients in this study (all subjects and those in CKD stage V), in the Perlman *et al.* study (6) and patients in DOPPS (13,21) and ADEMEX (12). The white line in the general population bar represents one SD from the mean.

observation. This aspect of CKD has hitherto not factored in patient treatment plans and is particularly important since QOL measures have been associated with higher hospitalization and mortality rates in dialysis patients (12,13,16,21,42). For example, the presence of clinical depression (14) and reduced MCS and PCS scores have been associated with poorer outcomes in hemodialysis patients. Whether similar findings will be observed in CKD patients not on dialysis remains to be determined. Furthermore, selected HRQOL problems are potentially treatable. For example, treatment algorithms for depression in dialysis patients have been proposed (43,44) and sleep disturbances can be addressed.

One possible limitation of our study is the proportion of patients completing the HRQOL questionnaire. Completion of the questionnaire was voluntary. Factors affecting completion were not explored prospectively. We found no differences between the clinical or laboratory profiles of patients who completed the questionnaire and patients who did not complete the questionnaire. Furthermore, there was no difference in baseline KDQOL between patients who provided a follow up and those that did not. The differences in duration of follow up are due to the progressive recruitment of the subject and their duration of follow up within the study. These observations suggest that the findings of this study are not subject to selection bias. Generalizations of the findings to the CKD population at large, however, cannot ignore the potential presence of intangible factors. The concordance between our observations and those in the literature suggests that the risks in generalization are likely small.

The importance of HRQOL has been increasingly recognized by health care payers, health care providers, regulatory agencies and researchers, both within and outside the renal community. HRQOL scores have been associated with mortality and hospitalizations in ESRD patients and have been used to assess the effectiveness of ESRD therapies (12,13,21,42). But, despite the apparent need and potential benefits of HRQOL assessments in CKD patients, few studies have examined the utility of these assessments, in part perhaps because of practical limitations to implementation into the clinical arena. These

limitations can be addressed through the development of computer-adaptive testing (16,45). The routine use of HRQOL assessments in the care of patients with CKD represents an important opportunity for the nephrologist to better incorporate the values and concerns of the patient into their care (45). Whether integrating these assessments into direct patient care can result in an improvement in medical outcomes remains to be determined (43). Treatment of depression and sleep disorders holds particular promise in this regard (10,37,46).

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Disclosures

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