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Longitudinal Changes in Health-Related Quality of Life in Primary Glomerular Disease: Results From the CureGN Study

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Introduction: Prior cross-sectional studies suggest that health-related quality of life (HRQOL) worsens with more severe glomerular disease. This longitudinal analysis was conducted to assess changes in HRQOL with changing disease status.

Methods: Cure Glomerulonephropathy (CureGN) is a cohort of patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, IgA vasculitis, or IgA nephropathy. HRQOL was assessed at enrollment and follow-up visits 1 to 3 times annually for up to 5 years with the Patient-Reported Outcomes Measurement Information System (PROMIS). Global health, anxiety, and fatigue domains were measured in all; mobility was measured in children; and sleep-related impairment was measured in adults. Linear mixed effects models were used to evaluate HRQOL responsiveness to changes in disease status.

Results: A total of 469 children and 1146 adults with PROMIS scores were included in the analysis. HRQOL improved over time in nearly all domains, though group-level changes were modest. Edema was most consistently associated with worse HRQOL across domains among children and adults. A greater number of symptoms also predicted worse HRQOL in all domains. Sex, age, obesity, and serum albumin were associated with some HRQOL domains. The estimated glomerular filtration rate (eGFR) was only associated with fatigue and adult physical health; proteinuria was not associated with any HRQOL domain in adjusted models.

Conclusion: HRQOL measures were responsive to changes in disease activity, as indicated by edema. HRQOL over time was not predicted by laboratory-based markers of disease. Patient-reported edema and number of symptoms were the strongest predictors of HRQOL, highlighting the importance of the patient experience in glomerular disease. HRQOL outcomes inform understanding of the patient experience for children and adults with glomerular diseases.

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IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and minimal change disease (MCD) are primary glomerular diseases that have severe and lasting impacts on affected individuals. In both children and adults, these diseases frequently cause chronic kidney disease and can lead to end-stage kidney disease.[1] Traditional laboratory measures of kidney function and related disorders (e.g., serum creatinine or proteinuria) are important for clinical management but fail to fully capture the patient experience. Understanding the substantial and far-reaching impact of the experience of glomerular diseases is essential to improving HRQOL.

Patient-reported outcomes (PROs), including HRQOL, are increasingly recognized as a priority by agencies such as the National Institutes of Health and the Food and Drug Administration.[2,3] PRO assessment is essential for incorporating patient perspectives into clinical decision making and research, while providing a more complete and meaningful understanding of the experience of glomerular diseases.

Glomerular diseases (IgAN, FSGS, MN, and MCD) frequently cause nephrotic syndrome leading to edema, hyperlipidemia, and complications such as venous thromboembolic disease.[4,5] Management of these glomerular diseases includes immunosuppressive therapy (IST), which is associated with additional risks and side effects. Patients with nephrotic syndrome have been reported to experience poor HRQOL, on par with dialysis patients.[6,7] However, there have been few studies describing HRQOL in this population, especially adults. Further, these studies have mostly reported only cross-sectional HRQOL without longitudinal follow-up.

The Cure Glomerulonephropathy (CureGN) study is a multicenter longitudinal cohort study following children and adults with IgAN, FSGS, MN, and MCD. The objectives of the current study are (1) to describe longitudinal patterns of HRQOL in patients with these primary glomerular diseases and (2) to evaluate how disease activity affects HRQOL over time.

METHODS

Patients

The CureGN study recruits children and adults with a diagnostic kidney biopsy within the last 5 years showing MCD, FSGS, MN, or IgAN (including IgA vasculitis [IgAV]) from 67 sites across the United States, as well as 2 sites in Canada, 1 in Italy, and 1 in Poland (https://curegn.org). Approximately 600 patients each of MCD, FSGS, and MN and 650 patients with IgAN or IgAV will be enrolled. Patients are ineligible if they have end-stage kidney disease or any of the following before first kidney biopsy: solid organ or bone marrow transplant, active HIV infection, hepatitis B or C infection, diabetes mellitus, systemic lupus erythematosus, or active malignancy. Each participating site obtained approval from an institutional review board, and all patients and/or legal guardians of children gave informed consent and, where age appropriate, informed assent prior to enrollment in the study.[8]

In the current study, we present longitudinal data from all enrolled patients in CureGN with PRO data available at enrollment and follow-up up to September 5, 2018. Study details, including data collected, frequency of collection, and relationship to diagnostic biopsy have been reported previously by Mariani et al.[8] Data from the September 5, 2018 CureGN Standard Analysis File were used for this analysis.

HRQOL Data

HRQOL was assessed at enrollment and follow-up using measures selected from PROMIS.[9] Each PROMIS measure generates a T score (mean = 50, SD = 10; normed to the calibration population) where a higher score indicates higher levels of the trait being measured (i.e., higher mobility score = better mobility; higher anxiety score = worse anxiety). We considered a minimally important difference (MID) in outcomes an absolute change of 3 units, which is likely a conservative estimate based on available literature.[10] Each question uses a common time frame of "…the past 7 days," and responses use a 5-item Likert-type scale from "never" to "almost always" for the majority of domains. PROMIS was administered as a paper form using a fixed number of items. These items were chosen *a priori* during the design of the CureGN study by a working group of clinician investigators, with the aim of measuring domains broadly relevant to patients with glomerular disease while balancing the time burden on study participants. Questionnaires were available in French, Spanish, Italian, and Polish. PROMIS domains have been validated in Spanish,[11] and translations for other languages were by native speakers to ensure that the intent of the question remained the same.

Pediatric domains included global assessment of health (7-item short form), mobility (4-item custom form), fatigue (10-item short form), and anxiety (single item custom form). Adult domains included: global assessment of physical health (5-item short form), global assessment of mental health (5-item short form), sleep-related impairments (single-item custom form), fatigue (7-item custom form), and anxiety (single-item custom form).

For fatigue and anxiety, pediatric and adult measures were combined for pooled analyses. Pediatric scores were converted to adult scales using linking parameters. For both domains, average linking parameters of disabilities and special health care needs

cohorts were used, and child scores were converted to the adult scale.[12,13] The remaining age-specific domains (child global health, child mobility, adult physical and mental health, and adult sleep impairments) were analyzed in age-specific strata. A total of 7 PRO measures were analyzed.

Statistical Analysis

Categorical variables were described using frequencies and percentages, and continuous variables using medians and interquartile ranges. To facilitate comparison and understanding, PROMIS domains were transformed so that higher scores indicate better HRQOL. The analysis sample was limited to patients with PRO assessments at baseline and at least 1 follow-up visit.

Linear mixed effects models with subject-specific slopes and intercepts were used to test for a significant temporal change in each score over time. These models were repeated by domain with domain score as the outcome and time, in units of days since baseline, as the sole predictor. Functional form was explored by testing polynomial terms for time (e.g., time^2, time^3). Longitudinal predictors of HRQOL were also assessed using linear mixed effects models. A list of putative predictors was generated including variables that were thought to potentially affect HRQOL based on clinical expertise and review of literature. The following time-fixed and time-varying covariates were tested for main effects on HRQOL: age, sex, race, disease duration, socioeconomic status (SES; measured by ≥college education in adults and ≥maternal college education in children), diagnosis, any edema, number of symptoms (patient-reported), health care utilization (hospitalizations/emergency department visits in the past 4 months), obesity status (BMI >30 in adults; BMI >95th percentile in children), short stature (measured by height <2.5th percentile in children and height <152 cm in adult females or <164 cm in adult males), number of comorbidities, log urine protein–creatinine ratio, eGFR (measured by modified CKiD formula in children and CKD-EPI in adults),[14,15] serum albumin, hemoglobin, IST exposure, steroid dose in the past 30 days, steroid response pattern (responsive, relapsing, resistant, or not treated), number of medications, and patient-reported medication adherence. Interaction terms were used to test for differences in changes in HRQOL over time in the following baseline covariates: age at enrollment, sex, race, disease duration at enrollment, SES, and diagnosis.

Each covariate was tested as an unadjusted predictor of each HRQOL domain. Any unadjusted association with HRQOL at P <0.20 entered a multivariable backward selection model. Variables were removed in order of descending P value until all remaining variables were statistically significant at p <0.05. Components of significant interactions were retained to ensure all models were hierarchically formulated. Multivariable models were adjusted for time. There were no imputations for missing data.

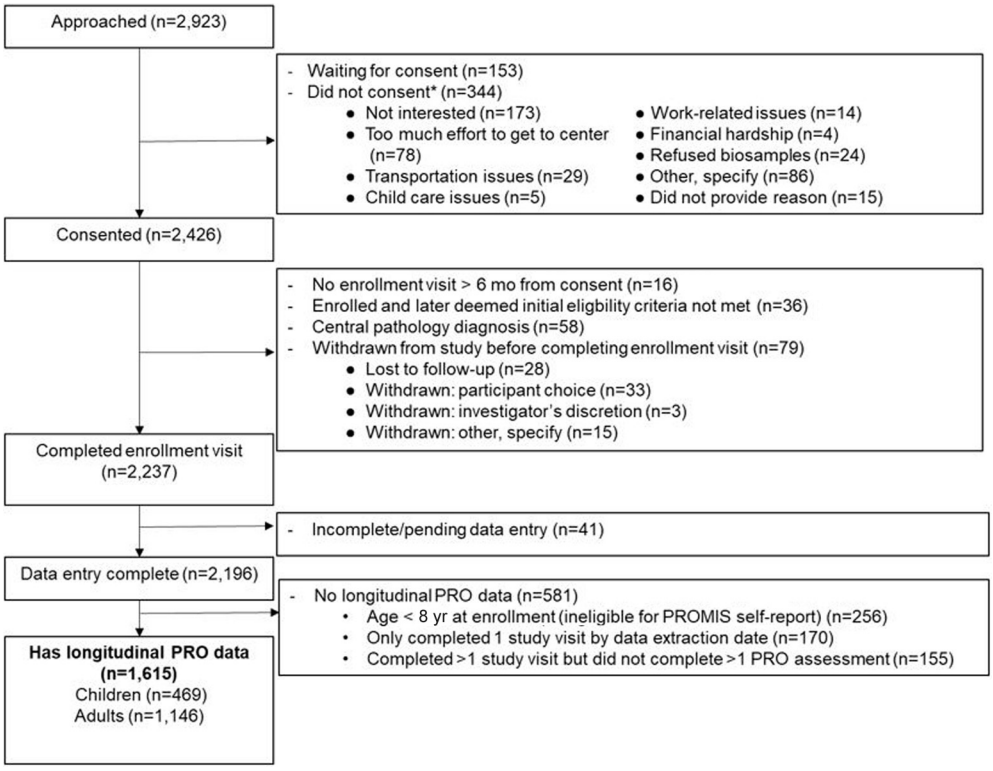

Figure 1. CONSORT flow diagram of included patients. Data as of September 5, 2018. *Could provide more than 1 reason. PRO, patient-reported outcomes.

Sensitivity analyses examined the relationship in between-visit changes in edema status and between-visit changes in HRQOL using linear mixed effects models with the outcome of change in HRQOL score since last visit and the predictor of change in edema status coded categorically as resolution of edema (edema to no edema), persistence of edema (edema to edema), onset of edema (no edema to edema), and no edema (no edema to no edema).

RESULTS

A STROBE flow diagram of included patients from CureGN is displayed in Figure 1. These analyses are based on 469 children (1795 observations) and 1146 adults (4764 observations) with longitudinal HRQOL data. Characteristics of included versus excluded patients ≥8 years of age (i.e., eligible for PROMIS self-report) are compared in Table S1. CureGN patients without longitudinal HRQOL data were more likely to be older, less likely to be Hispanic, and more likely to have IgA. The characteristics of included patients are shown in Table 1 stratified by age. At enrollment, the majority of patients had more than 1 year of follow-up since diagnosis (median of 14 months in children; 17 months in adults). Samples were well represented by diagnosis. Most frequent diagnoses among children were MCD (32%) and FSGS (24%), and among adults were MN (29%) and IgAN (28%). Children were less likely than adults to present with edema at enrollment (34% of children vs. 60% of adults); they also presented with lower urine protein–creatinine ratio (median 0.5 vs. 1.6 g/g) and higher eGFR (median 97 vs. 70 ml/min per 1.73 m^2).

HRQOL Changes Over Time

Results of tests for temporal changes in HRQOL domains over time are presented in Figure 2. All domains were associated with a significant improvement over time, with the exception of mental health in adults. No models show significant relationships with time squared or cubed, and hence only linear effects are shown. Among children, the largest improvement over time was fatigue (mean = +1.6 points/yr) and the smallest was anxiety (mean = +0.5 points/yr). Among adults, the greatest improvement was seen in fatigue (+1.0 point/yr).

Table 1. Descriptive characteristics of included patients with baseline and at least 1 follow-up HRQOL assessment

Characteristic	Overall (*N* = 1615 patients; *N* = 6559 observations)	Children (*n* = 469 patients; *n* = 1795 observations)	Adults (*n* = 1146 patients; *n* = 4764 observations)
Age at enrollment, median (IQR)	34 (16–52)	13 (10–15)	45 (32–58)
Female, n (%)	708 (44)	203 (43)	505 (44)
Race, n (%)			
Black/African American	260 (16)	91 (19)	169 (15)
White/Caucasian	1089 (67)	304 (65)	785 (68)
Other	266 (16)	74 (16)	192 (17)
Hispanic ethnicity, n (%)	196 (12)	49 (10)	147 (13)
Duration of disease at enrollment, median (IQR)	16 (5–40)	15 (4–43)	16 (5–39)
Months of follow-up, median (IQR)	16 (7–27)	14 (6–25)	17 (8–28)
Number of PROMIS assessments, median (IQR)	4 (2–5)	3 (2–5)	4 (2–5)
Diagnosis, n (%)			
MCD	306 (19)	150 (32)	156 (14)
FSGS	399 (25)	113 (24)	286 (25)
MN	363 (22)	28 (6)	335 (29)
IgAV	122 (8)	71 (15)	51 (4)
IgAN	425 (26)	107 (23)	318 (28)
Edema at enrollment, n (%)	843 (52)	161 (34)	682 (60)
UP-C at enrollment (g/g), median (IQR)	1.2 (0.3–3.7)	0.5 (0.1–1.9)	1.6 (0.4–4.2)
<0.3, n (%)	363 (22)	173 (37)	190 (17)
0.3–0.9, n (%)	268 (17)	90 (19)	178 (16)
1.0–3.5, n (%)	361 (22)	73 (16)	288 (25)
≥3.5, n (%)	350 (22)	74 (16)	276 (24)
Missing, n (%)	273 (17)	59 (13)	214 (19)
eGFR at enrollment (ml/min per 1.73 m^2), median (IQR)	80 (50–104)	97 (82–115)	70 (43–97)
≥90, n (%)	601 (37)	275 (59)	326 (28)
60–89, n (%)	401 (25)	118 (25)	283 (25)
30–59, n (%)	346 (21)	27 (6)	319 (28)
<30, n (%)	144 (9)	12 (3)	132 (12)
Missing, n (%)	123 (8)	37 (8)	86 (8)

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerular sclerosis; IgAN, IgA nephropathy; IgAV, IgA vasculitis; IQR, interquartile range; MCD, minimal change disease; MN, membranous nephropathy; PROMIS, Patient-Reported Outcomes Measurement Information System; UP-C, urine protein–creatinine ratio.

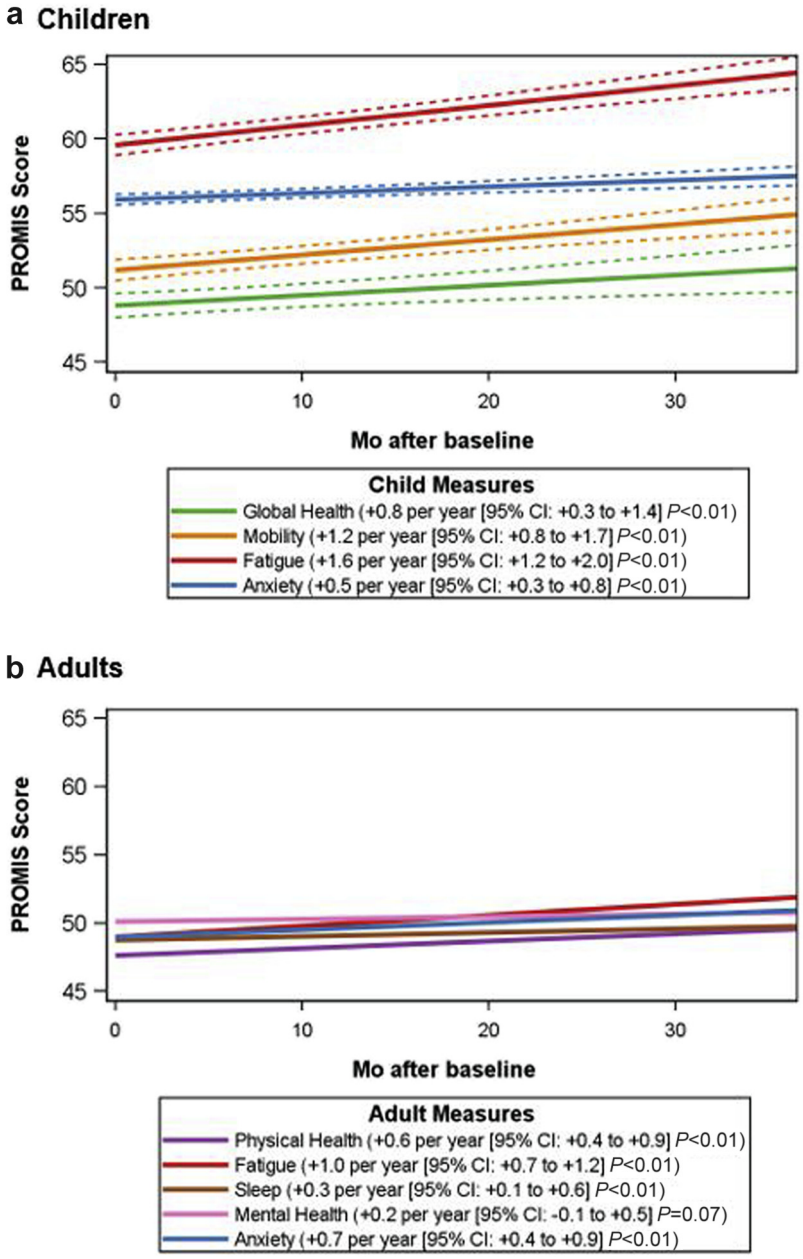

Figure 2. Change in health-related quality of life (HRQOL) over time: results of linear mixed effects models by measure. Fatigue and anxiety are linked to be on the same scale for children and adults. (a) *95% confidence intervals are shown as dashed lines. (b) Due to the overlapping estimates, confidence intervals were suppressed to aid visualization. Patient-Reported Outcomes Measurement Information System (PROMIS) scores were rescored so that higher numbers reflect better HRQOL.

Among children, 36% reported that their illness had an effect on their education: 2% had left school, 3% had repeated a grade, 6% had changed schools, and 30% reported impaired attendance. Of those reporting missing school, participants reported missing a median of 1 (IQR = 0.5–2.5) day per month. Among adults, 11% had reported missing work or school, a median of 1 day per month (IQR = 0.5–3.5 days).

Predictors of HRQOL Over Time

Results of unadjusted analyses are summarized in Table S2. Sex, SES, edema, symptom burden, number of comorbidities, health care utilization, weight, proteinuria, serum albumin, and number of medications were significant unadjusted predictors of each of the HRQOL measures.

Final models for the combined child and adult measures (fatigue and anxiety) are presented in Table 2. Younger age, female sex, presence of edema, and more symptoms were significant predictors of both fatigue and anxiety. Higher SES, higher eGFR, and greater medication adherence were associated with less fatigue. Obesity and greater number of medications were associated with worse fatigue.

Results of final models for the pediatric-specific domains (global health and mobility) are displayed in

Table 2. Final adjusted multivariable linear mixed effects models of child and adult combined measures (*N*=1615 patients; *N*=6559 observations)

Measure	β (95% CI)	*P*
Child + adult: fatigue		
Age (per yr)	−0.12 (−0.15, −0.09)	<0.001
Male vs. female	2.80 (1.74, 3.85)	<0.001
SES (college education vs. none)	1.79 (0.73, 2.85)	0.001
Edema (any vs. none)	−2.93 (−3.59, −2.28)	<0.001
Number of symptoms (per symptom)	−0.87 (−1.09, −0.66)	<0.001
Weight		0.002
Underweight	0.58 (−1.84, 3.00)	0.64
Overweight	−1.17 (−2.10, −0.23)	0.01
Obese	−2.04 (−3.09, −0.99)	<0.001
Normal	Ref	
eGFR (per 30 ml/min per 1.73 m^2)	0.52 (0.13, 0.91)	0.01
Number of medications (per medication)	−0.26 (−0.38, −0.14)	<0.001
Exposed to CTX	−2.59 (−4.91, −0.27)	0.03
Time (per year)	1.01 (0.65, 1.37)	<0.001
Child + adult: anxiety		
Age (per yr)	−0.10 (−0.12, −0.09)	<0.001
Male vs. female	2.00 (1.40, 2.61)	<0.001
Edema (any vs. none)	−1.71 (−2.11, −1.32)	<0.001
Number of symptoms (per symptom)	−0.40 (−0.53, −0.28)	<0.001
Time (per yr)	0.36 (0.16, 0.57)	<0.001

CI, confidence interval; CTX, Cytoxan (cyclophosphamide); eGFR, estimated glomerular filtration rate; Ref, referent; SES, socioeconomic status.
For each domain, scores have been transformed so higher scores indicate better health-related quality of life.

Table 3. Edema, greater number of symptoms, obesity, and lower serum albumin were significant predictors of worse global health and mobility. Female sex and greater number of comorbidities predicted worse global health, and more medications predicted worse mobility.

Adult-specific final models are shown in Table 4. Edema, greater number of symptoms, and greater number of comorbidities were significant negative predictors of all 3 adult measures. Diagnosis was associated with sleep and mental health but not physical health; HRQOL scores were best in IgAV, followed by MN, IgAN, FSGS, and MCD. Higher serum albumin and fewer medications were associated with better physical and mental health.

Changes in Disease Activity and HRQOL

We characterized disease activity primarily by edema status, though proteinuria and albumin were also evaluated as markers of disease activity. The multivariable models demonstrate that edema is consistently associated with worse HRQOL. That is, patient visits with edema have worse scores than those without edema. Results of sensitivity analyses of visit-to-visit changes in scores in response to changes in edema are shown in Figure 3. Change in edema status was a significant predictor of changes in all HRQOL domains. For example, a child having resolution of edema, on average, experienced a 3.6-point improvement in mobility, whereas a child with onset of edema had an average 1.9-point decrease in mobility. Children whose edema status remained the same showed either no change or a minor improvement in mobility: 0.4-point increase associated with persistent edema; 0.6-point increase with no edema. As a reference, a minimally important difference of 3.0 has been reported in children.[10] Changes greater than 3 points are shown in Table S3. For example, among those with resolution of edema, 44% had a ≥3-point improvement in fatigue, 18% had a ≥3-point worsening, and the remaining 38% did not change by more than 3 points. This was modestly different from those with onset of edema for which 28% had a ≥3-point improvement in fatigue, 33% had a ≥3-point worsening, and the remaining 39% did not change by more than 3 points. These results show that children whose edema resolves between visits (mean 4 months apart) improve above the minimally important difference for mobility and fatigue. Similar trends were seen for adults, but changes showed smaller effect sizes.

DISCUSSION

CureGN is the largest study to date to evaluate HRQOL in patients with glomerular disease. By prospectively

Table 3. Final adjusted multivariable linear mixed effects models of child measures (*n* = 469 patients; *n* = 1795 observations)

Measure	β (95% CI)	*P*
Child: Global		
Age (per yr)	−0.44 (−0.69, −0.19)	<0.001
Male vs. female	2.11 (0.68, 3.55)	0.004
Edema (any vs. none)	−2.75 (−3.84, −1.66)	<0.001
Number of symptoms (per symptom)	−0.50 (−0.84, −0.16)	0.004
Number of comorbidities	−1.16 (−1.98, −0.34)	0.006
Weight		<0.001
Underweight	0.04 (−3.12, 3.24)	
Overweight	−0.78 (−2.17, 0.62)	
Obese	−4.00 (−5.46, −2.54)	
Normal	Ref	
Serum albumin (per g/dl)	1.37 (0.72, 2.03)	<0.001
Time (per yr)	0.37 (−0.37, 1.10)	0.33
Child: Mobility		
Edema (any vs. none)	−3.13 (−4.17, −2.09)	<0.001
Number of symptoms (per symptom)	−0.72 (−1.04, −0.39)	<0.001
Weight		0.002
Underweight	1.50 (−1.51, 4.51)	
Overweight	−0.58 (−1.85, 0.70)	
Obese	−2.37 (−3.66, −1.08)	
Normal	Ref	
Serum albumin (per g/dl)	1.43 (0.81, 2.05)	<0.001
Number of medications (per medication)	−0.27 (−0.46, −0.07)	0.008
Time (per yr)	0.43 (−0.19, 1.05)	0.17

CI, confidence interval; Ref, referent.
For each domain, scores have been transformed so higher scores indicate better health-related quality of life.

Table 4. Final adjusted multivariable linear mixed effects models of adult measures ($n = 1146$ patients; $n = 4764$ observations)

Measure	β (95% CI)	P
Adult: Physical health		
Male vs. female	1.81 (0.94, 2.67)	<0.001
SES (college education vs. none)	2.13 (1.25, 3.00)	<0.001
Edema (any vs. none)	−3.16 (−3.72, −2.59)	<0.001
Number of symptoms (per symptom)	−1.02 (−1.20, −0.84)	<0.001
Number of comorbidities	−0.98 (−1.35, −0.61)	<0.001
Weight		<0.001
Underweight	−0.02 (−3.02, 3.04)	
Overweight	−0.89 (−1.69, −0.09)	
Obese	−2.55 (−3.46, −1.64)	
Normal	Ref	
eGFR (per 30 ml/min per 1.73 m^2)	0.89 (0.55, 1.24)	<0.001
Serum albumin (per g/dl)	0.94 (0.51, 1.37)	<0.001
Number of medications (per medication)	−0.27 (−0.36, −0.18)	<0.001
Exposed to steroids (yes vs. no)	−0.66 (−1.30, −0.01)	0.04
Time (per yr)	0.23 (−0.06, 0.52)	0.11
Adult: Sleep impairments		
Diagnosis		0.004
MCD	−1.58 (−3.57, 0.42)	
FSGS	−2.57 (−4.45, −0.69)	
MN	−0.78 (−2.64, 1.08)	
IgAN	−1.70 (−3.55, 0.16)	
IgAV	Ref	
Edema (any vs. none)	−2.05 (−2.52, −1.59)	<0.001
Number of symptoms (per symptom)	−0.59 (−0.75, −0.44)	<0.001
Number of comorbidities	−0.69 (−1.00, −0.39)	<0.001
Exposed to CTX (yes vs. no)	−2.62 (−4.20, −1.04)	0.001
Time since enrollment (per yr)	0.07 (−0.15, 0.29)	0.55
Adult: Mental health		
Diagnosis		<0.001
MCD	−5.00 (−8.95, −1.08)	
FSGS	−3.50 (−7.35, 0.34)	
MN	−1.30 (−5.18, 2.58)	
IgAN	−2.70 (−6.56, 1.15)	
IgAV	Ref	
Edema (any vs. none)	−1.28 (−2.13, −0.42)	0.003
Number of symptoms (per symptom)	−0.61 (−0.89, −0.32)	<0.001
Number of comorbidities	−1.44 (−1.97, −0.91)	<0.001
Serum albumin (per g/dl)	0.99 (0.34, 1.63)	0.003
Number of medications (per medication)	−0.27 (−0.41, −0.13)	<0.001
Medication adherence (yes vs. no)	1.38 (0.63, 2.13)	<0.001
Time (per yr)	0.63 (0.16, 1.09)	0.009

CI, confidence interval; CTX, Cytoxan (cyclophosphamide); eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerular sclerosis; IgAN, IgA nephropathy; IgAV, IgA vasculitis; MCD, minimal change disease; MN, membranous nephropathy; Ref, referent; SES, socioeconomic status.
For each domain, scores have been transformed so higher scores indicate better health-related quality of life. Other tested covariates that were tested but not significant in any of the final models included race, disease duration, socioeconomic status, diagnosis, ethnicity, hospitalizations, short stature, urine protein–creatinine ratio, hemoglobin, immunosuppression exposure, steroid dose in the past 30 days, and steroid response pattern.

collecting longitudinal data, this study details how HRQOL in this population changes over time. Disease activity and key PRO, particularly edema, have important associations with HRQOL. In CureGN, HRQOL improved in association with reductions in edema and number of symptoms.

HRQOL improved over time in nearly all domains, with the greatest improvement seen in fatigue. This was true for both children and adults. The influence of time in adjusted models was small and changes in disease activity were stronger predictors of HRQOL. Notably, edema was the strongest predictor of HRQOL scores and change in within-patient edema status from one visit to the next was associated with change in HRQOL across all domains. This is consistent with cross-sectional analyses suggesting edema as a strong predictor of HRQOL in this population.[16–18] Although not surprising given how profoundly edema can affect individuals with these diseases, these longitudinal results add to prior cross-sectional work by demonstrating that changes in edema for an individual patient over time are associated with change in HRQOL. Though proteinuria and serum albumin were associated with all HRQOL measures in unadjusted analyses, in the final multivariable model, proteinuria failed to be an independent predictor of HRQOL and albumin was significant in only 4 of 7 domains. The only domain in which no significant improvement occurred over time was adult mental health, but many improvements were relatively modest.

The number of symptoms was predictive of scores on all HRQOL measures, which reinforces the importance of patient experience—from a disease or its treatment—for HRQOL. The fact that both edema and number of symptoms were stronger predictors of HRQOL than laboratory markers is particularly meaningful. In clinical practice, these lab-based markers of disease activity—proteinuria, serum albumin, and eGFR—are often given more attention than the more patient-centered metrics of edema or symptom reporting. Our findings underscore the importance of these PROs as meaningful for individuals with primary glomerular disease—in practice as well as in research.

Other variables that were longitudinally associated with worse HRQOL in various domains included number of comorbidities, obesity, female sex, lower SES, and lower serum albumin. The relationship between HRQOL scores and variables such as sex, obesity, SES, and comorbidity has been reported previously in other settings.[19] For these primary glomerular diseases, we were interested in whether HRQOL was responsive to changes in disease activity, as measured by edema, proteinuria, serum albumin, and eGFR. In the final model, only eGFR was significant in predicting fatigue in adults and children and physical health in adults. Diagnosis was independently associated with 2 domains of HRQOL, sleep impairment and mental health, in adults. Specifically, HRQOL scores were best in IgAV, followed by MN, IgAN, FSGS, and MCD. There was no relationship between diagnosis and

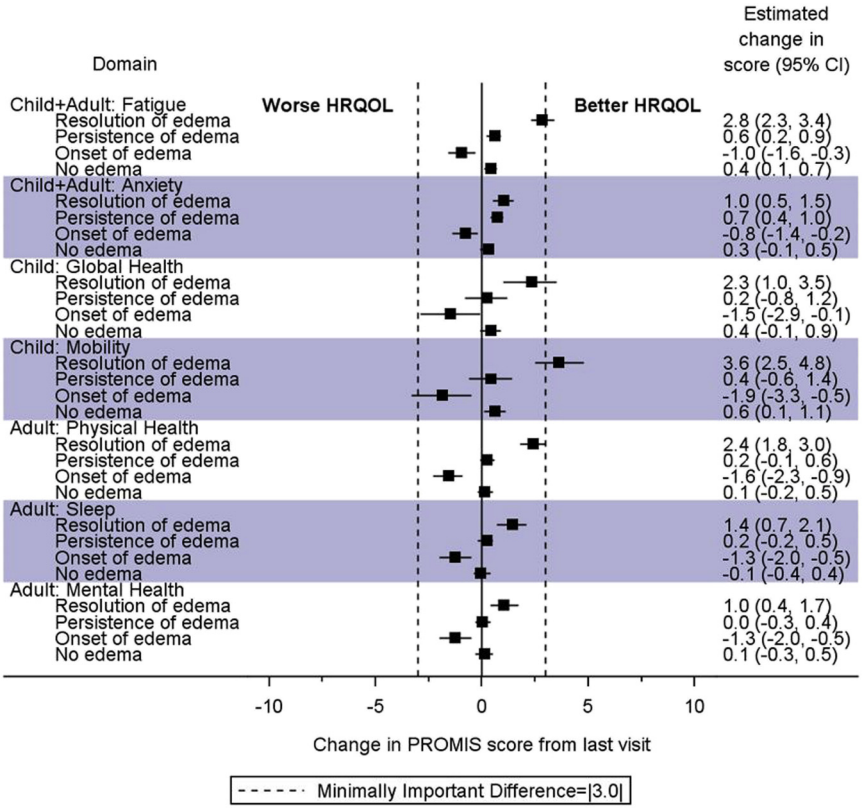

Figure 3. Linear mixed effects models of change in patient-reported outcomes since last visit by edema. CI, confidence interval; PROMIS, Patient-Reported Outcomes Measurement Information System.

HRQOL in children. The lack of association between diagnosis and HRQOL in most domains suggests that among these glomerular diseases, individual patient factors and clinical markers are more important determinants of HRQOL than the specific disease. IST was not retained in any of the final models as an independent predictor of HRQOL. This may be due at least in part to the opposing effects on HRQOL by IST. Though IST can have significant side effects that adversely affect HRQOL, it can also improve HRQOL through decreasing the symptoms and disease effects.

The effect sizes found in this study were relatively modest. Most of the statistically significant differences reported here were smaller than the PROMIS minimally important difference of |3.0|. It is important to note, however, that these differences are for the group, and it is likely that a substantial number of individuals achieved this level of change. Nonetheless, these attenuated findings at the group level are surprising because clinical experience and prior studies suggest primary glomerular diseases can have a profound impact on one's quality of life,[6,7] and we suspect that this may reflect limited sensitivity of the PRO measure used. Decreased responsiveness of the instrument may also explain the lack of association we found for some putative determinants of HRQOL, such as proteinuria, eGFR, diagnosis, and IST. Disease-specific PRO instruments are more responsive to disease status changes than generic instruments; however, no validated disease-specific PRO instruments existed for these glomerular diseases when data collection for CureGN began. A previous study of 127 children with nephrotic syndrome did not identify statistically significant trends between changes in disease activity and changes in PROMIS scores; however, changes did correlate with other self-reported global assessments of change.[20] Our study highlights the importance of measuring PROs but also shows that developing more responsive instruments for patients with glomerular disease is critical to the utility of PROs for patients, providers, and researchers alike.

This study was limited by lack of a validated PRO instrument, which should include input from the target population, generally elicited via qualitative methods.[21,22] The domains included in the CureGN PRO assessment were selected based on available data and knowledge of the diseases at the inception of this study, but no such data on patient experience in this population had been published. Research since that time has corroborated the importance of the domains included here,[23] but we suspect that not all the

domains important to the experience of these diseases are captured by our assessment. Another limitation of this study is that some domains are composed of a single item (anxiety in children and adults, sleep impairments in adults) and thus provide less precision. Choice of domains was informed by prior work in pediatric nephrotic syndrome, and little published data was available to guide choice of domains in adult nephrotic syndrome.[17,18] Additionally, it is possible that the temporal improvements seen in this cohort are attributable to enrollment in a clinical research study, which may limit generalization beyond CureGN participants. Alternatively, temporal improvements could be influenced by incomplete follow-up. Although we did not observe baseline differences in HRQOL among those with and without longitudinal HRQOL data, it is possible that participants who withdrew early, and were thus absent from this analysis, also had a decrease in HRQOL. Finally, although we controlled for disease activity and severity (edema, proteinuria, albumin, eGFR, hemoglobin, and health care utilization), disease severity may not be adequately reflected by these covariates.

In conclusion, HRQOL scores improved over time in both children and adults with primary glomerular diseases, with the greatest improvements in fatigue. Edema was the strongest longitudinal predictor of poorer HRQOL, highlighting the importance of addressing this symptom. Although this is the largest study of HRQOL in patients with glomerular diseases to date, the impact of these diseases on patient experience is likely to be incompletely captured here, and well-developed validated measures are needed. Direct input from patients in such scientific inquiry will greatly improve knowledge that meaningfully impacts clinical care.

APPENDIX

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Biomedical Research Institute at Harbor, University of California Los Angeles (UCLA); Charles Alpers, University of Washington; Raed Bou Matar, Cleveland Clinic; Elizabeth Brown, University of Texas (UT) Southwestern Medical Center; Daniel Cattran, University of Toronto; Michael Choi, Johns Hopkins; Katherine M. Dell, Case Western/Cleveland Clinic; Ram Dukkipati, Los Angeles Biomedical Research Institute at Harbor UCLA; Fernando C. Fervenza, Mayo Clinic; Alessia Fornoni, University of Miami; Crystal Gadegbeku, Temple University; Patrick Gipson, University of Michigan; Leah Hasely, University of Washington; Sangeeta Hingorani, Seattle Children's Hospital; Michelle A. Hladunewich, University of Toronto/Sunnybrook; Jonathan Hogan, University of Pennsylvania; J. Ashley Jefferson, University of Washington; Kenar Jhaveri, North Shore University Hospital; Duncan B. Johnstone, Temple University; Frederick Kaskel, Montefiore Medical Center; Amy Kogan, CHOP; Jeffrey Kopp, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Intramural Research Program; Kevin V. Lemley, Children's Hospital of Los Angeles; Laura Malaga- Dieguez, NYU; Kevin Meyers, Children's Hospital of Pennsylvania; Alicia Neu, Johns Hopkins; Michelle Marie O'Shaughnessy, Stanford; John F. O'Toole, Case Western/Cleveland Clinic; Rulan Parekh, University Health Network, Hospital for Sick Children; Heather Reich, University Health Network; Kimberly Reidy, Montefiore Medical Center; Helbert Rondon, UPMC; Kamalanathan K. Sambandam, UT Southwestern; John R. Sedor, Case Western/Cleveland Clinic; David T. Selewski, University of Michigan; Christine B. Sethna, Cohen Children's Medical Center-North Shore Long Island Jewish (LIJ) Health System; Jeffrey Schelling, Case Western; John C. Sperati, Johns Hopkins; Agnes Swiatecka-Urban, Children's Hospital of Pittsburgh; Howard Trachtman, NYU; Katherine R. Tuttle, Spokane Providence Medical Center; Joseph Weisstuch, New York University; Olga Zhdanova, New York University.
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Steering Committee Chair: Lisa M. Guay-Woodford, Children's National Health System CureGN. Principal Investigators are noted with an asterisk.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

STROBE Statement.

Table S1. Comparison of participants age ≥8 years old with and without longitudinal PRO data.

Table S2. Summary of results of unadjusted linear mixed effects models of all PRO measures.

Table S3. Change in PRO since last visit by edema.

REFERENCES

1. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis*. 2019;73:A7–A8.

2. US Department of Health and Human Services Food and Drug Administration guidance for industry on patient-reported outcome measures: use in medical product development to support labeling claims. *Federal Register*. 2009.
3. Selewski DT, Thompson A, Kovacs S, et al. Patient-reported outcomes in glomerular disease. *Clin J Am Soc Nephrol*. 2017;12:140–148.
4. Wang CS, Greenbaum LA. Nephrotic syndrome. *Pediatr Clin N Am*. 2019;66:73–85.
5. Agrawal S, Zaritsky JJ, Fornoni A, et al. Dyslipidaemia in nephrotic syndrome: mechanisms and treatment. *Nat Rev Nephrol*. 2018;14:57–70.
6. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life. *Kidney Int*. 2011;79:678–685.
7. Liborio AB, Santos JP, Minete NF, et al. Proteinuria is associated with quality of life and depression in adults with primary glomerulopathy and preserved renal function. *PLoS One*. 2012;7:e37763.
8. Mariani LH, Bomback AS, Canetta PA, et al. CureGN study rationale, design, and methods: establishing a large prospective observational study of glomerular disease. *Am J Kidney Dis*. 2019;73:218–229.
9. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care*. 2007;45:S3–S11.
10. Thissen D, Liu Y, Magnus B, et al. Estimating minimally important difference (MID) in PROMIS pediatric measures using the scale-judgment method. *Qual Life Res*. 2016;25:13–23.
11. Paz SH, Spritzer KL, Morales LS, et al. Evaluation of the Patient-Reported Outcomes Information System (PROMIS®) Spanish-language physical functioning items. *Qual Life Res*. 2013;22:1819–1830.
12. Tulsky DS, Kisala PA, Boulton AJ, et al. Determining a transitional scoring link between PROMIS(R) pediatric and adult physical health measures. *Qual Life Res*. 2019;5:1217–1229.
13. Reeve BB, Thissen D, DeWalt DA, et al. Linkage between the PROMIS(R) pediatric and adult emotional distress measures. *Qual Life Res*. 2016;25:823–833.
14. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol*. 2009;20:629–637.
15. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
16. Canetta PA, Troost JP, Murphy S, et al. Health-related quality of life in glomerular disease. *Kidney Int*. 2019;95:1209–1224.
17. Gipson DS, Selewski DT, Massengill SF, et al. Gaining the PROMIS perspective from children with nephrotic syndrome: a Midwest pediatric nephrology consortium study. *Health Qual Life Outcomes*. 2013;11:30.
18. Selewski DT, Troost JP, Massengill SF, et al. The impact of disease duration on quality of life in children with nephrotic syndrome: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol*. 2015;30:1467–1476.
19. Porter AC, Lash JP, Xie D, et al. Predictors and outcomes of health-related quality of life in adults with CKD. *Clin J Am Soc Nephrol*. 2016;11:1154–1162.
20. Selewski DT, Troost JP, Cummings D, et al. Responsiveness of the PROMIS(R) measures to changes in disease status among pediatric nephrotic syndrome patients: a Midwest pediatric nephrology consortium study. *Health Qual Life Outcomes*. 2017;15:166.
21. Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity—establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: part 1—eliciting concepts for a new PRO instrument. *Value Health*. 2011;14:967–977.
22. Rothman M, Burke L, Erickson P, et al. Use of existing patient-reported outcome (PRO) instruments and their modification: the ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. *Value Health*. 2009;12:1075–1083.
23. Mathias SD, Vallow S, Gipson DS, et al. Development of focal segmental glomerulosclerosis patient-reported outcome measures: Symptom Diary and Symptom Impact Questionnaire. *Am J Kidney Dis*. 2017;70:532–540.