The Relationship Between Renal Activity and Quality of Life in Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To evaluate the relationship between renal activity and quality of life (QOL) in patients with systemic lupus erythematosus (SLE).

Methods. Three hundred eighty-six patients completed annual Medical Outcomes Study Short Form-36 questionnaires and physicians completed the SLE Disease Activity Index and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. Concurrent association between renal activity and QOL was evaluated through regression models that adjusted for demographics and nonrenal disease activity and nonrenal damage. To characterize the longitudinal relationship between change in renal activity and change in QOL, all renal activity and QOL data over the entire study were used to estimate a linear trend within each individual patient through hierarchical modeling.

Results. In the regression model that assessed the association between renal activity and QOL, on average, each additional renal activity item fulfilled was associated with a 2.04-unit (95% CI 0.88, 3.24) decrease in the physical function subscale, a 5.28-unit (95% CI 2.76, 7.76) decrease in the role-physical subscale, a 2.24-unit (95% CI 0.72, 3.80) decrease in the social function subscale, and a 1.16-unit (95% CI 0.60, 1.72) decrease in the physical component summary score. In the hierarchical model, no association was observed between changes in renal activity and QOL.

Conclusion. Patients with SLE and active renal disease concurrently experience a slightly poorer QOL than those without renal disease, especially in the physical domains. Because the confidence intervals were wide, we could not accurately estimate whether a longitudinal change in renal activity was associated with a change in QOL. (First Release April 15 2009; J Rheumatol 2009; 36:947–52; doi:10.3899 /jrheum.080822)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS   QUALITY OF LIFE
RENAL ACTIVITY   HIERARCHICAL MODELING

With the significantly improved survival of patients with systemic lupus erythematosus (SLE), due, in part, to earlier diagnosis and advances in the treatment of the disease and its comorbidities, quality of life (QOL) is an increasingly important consideration when caring for patients with SLE[1].

Although numerous studies have shown that QOL in SLE is significantly poorer than in the general population[1]

and in some other chronic diseases[2,3], studies examining the variables influencing QOL are somewhat contradictory[1-21]. In cross-sectional studies, psychosocial and behavioral variables, such as patients' attitudes toward their disease, fatigue, and pain, are reported to compromise QOL[5-9,15-17]. In contrast, studies assessing the relationship between SLE disease activity and damage and QOL are equivocal, some[5,9,11,17-21] showing no relationship, while others report

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worsening QOL with increasing disease activity[4,6-8,12-14,22]. Further, in longitudinal studies, QOL seems to be stable over time in most patients and is not influenced by disease-specific and socioeconomic variables[1,10].

It is possible that QOL is influenced more by specific aspects of the disease than by overall disease activity. Although renal involvement occurs in up to 30% of SLE patients during the course of their disease[23] and is associated with increased morbidity and mortality, few studies have evaluated the QOL experienced by SLE patients with renal involvement[16,24-26]. We have previously shown that irreversible renal damage does not influence QOL[27]. Our aim was to evaluate the concurrent relationship between level of renal activity and QOL in SLE as well as the relationship between changes in renal activity and changes in specific QOL domains.

MATERIALS AND METHODS

Patients. Consecutive patients presenting to the McGill University Health Centre Lupus Clinic and fulfilling the American College of Rheumatology (ACR) revised criteria for SLE[28] are invited to complete annual questionnaires and the physician completes annual measures of disease activity and damage. Participants were enrolled from 1995 to August 1, 2007. The study was approved by the Institutional Review Board of the McGill University Health Centre.

Study instruments. QOL was determined using the standard version (4-week recall) of the Medical Outcomes Study SF-36 (SF-36)[29]. The SF-36 is a generic self-administered questionnaire that measures QOL in 8 areas of perceived health: physical function — limitations in physical activities because of health problems; role-physical — limitations in usual role activities because of physical health problems; bodily pain — influence of pain on daily activities; vitality — energy level and fatigue; role-emotional — limitations in usual role activities because of emotional problems; mental health — psychological distress and well-being; social function — limitations in social activities because of physical or emotional problems; and general health — subjective perception of health status. Scores range from 0 to 100, higher scores reflecting a more favorable QOL. The SF-36 subscales can be summarized into the physical component summary (PCS) and the mental component summary (MCS) scores, derived using the original US algorithm.

Disease activity was assessed using the SLE Disease Activity Index (SLEDAI)[30]. This instrument is a "weighted" index of disease activity in 9 organ systems: 8 points for each item characterizing involvement of the central nervous and vascular systems; 4 for items describing renal and musculoskeletal involvement; 2 for items describing serosal, dermal, and immunologic involvement; and 1 for items describing constitutional and hematologic involvement. The maximum theoretical score is 105, but in practice, few patients have scores exceeding 45.

Patients were considered to have renal activity if they fulfilled any of the following SLEDAI items that specifically characterize renal activity: (1) presence of heme-granular or red blood cell casts; (2) > 5 red blood cells per high power field; or (3) urine protein > 500 mg/day. Each item was scored according to the SLEDAI weight attributed to that item (i.e., 4 points per item) and the patient's level of renal activity was expressed as the sum of these 3 renal SLEDAI items. Pyuria was not included in the definition of renal activity since it is possible that in some cases, urinary tract infections were not definitively excluded as the cause of the pyuria. Nonrenal activity was determined by all the other SLEDAI items (excluding pyuria) and scored accordingly.

Cumulative disease damage was calculated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI)[31]. Damage is assessed in 12 organ systems: ocular (range of score for this item 0–2), neuropsychiatric (0–6), renal (0–3), pulmonary (0–5), cardiovascular (0–6), peripheral vascular (0–5), gastrointestinal (0–6), musculoskeletal (0–7), skin (0–3), gonadal (0–1), endocrine (0–1), and malignancy (0–2). Damage over time either remains stable or increases monotonically, theoretically to a maximum total score of 47. Each item is required to be present for at least 6 months (with a few exceptions) to be scored as cumulative damage.

Patients were considered to have renal damage if they fulfilled any of the following SLICC/ACR-DI items that specifically characterize renal damage: (1) estimated or measured glomerular filtration rate < 50%; (2) 24-hour proteinuria ≥ 3.5 g; or (3) endstage renal disease (regardless of dialysis or transplantation). Nonrenal damage was determined by all the other SLICC/ACR-DI items and scored accordingly.

Statistical analyses. Demographics, disease characteristics, and QOL are presented using means, medians, standard deviations, interquartile ranges, and proportions, as appropriate.

To estimate the relationship between level of renal activity and QOL, 2 different analyses were performed. (1) The concurrent association between the renal SLEDAI score (at time t) and each QOL outcome (at time t) was assessed through multivariate regression models, adjusting for the following potential confounders (all measured at time t): age, sex, ethnicity (Caucasian vs non-Caucasian), marital status (married vs unmarried), education (continuous variable), disease duration (defined as the time from the diagnosis of SLE until the study visit), nonrenal SLEDAI, and nonrenal SLICC/ACR-DI. Model selection was based on Bayes factor as approximated by the Bayesian information criteria. We used the Bayesian information criteria algorithm in order to explore the most plausible predictive models, and to select among these a model that included as many predictors as possible that were either significantly associated with the outcome and/or confounding the association between the outcome and our main predictor of interest (i.e., renal SLEDAI). (2) To characterize the longitudinal relationship between change in renal activity and change in QOL, all renal activity and SF-36 subscale and PCS and MCS scores over the entire course of the study were used to estimate the linear trend across time within each individual patient. This was done through 2-level hierarchical modeling, an approach that allows the borrowing of strength across patients while still allowing for individual within-patient variations. A Gibbs sampler algorithm, as implemented in WinBUGS 1.4 software[32], was used to estimate the model parameters, with 95% credible intervals (CrI). In contrast to the first analysis, where the concurrent association between renal activity and QOL at each point in time is examined, in this analysis, there is only one observation per patient for each of renal activity and QOL measures, expressed as estimated average yearly change (i.e., a slope over time) in renal activity and QOL over the observation window. Potential covariates included study entry values of age, sex, ethnicity, marital status, education, disease duration, renal and nonrenal SLEDAI, nonrenal SLICC/ACR-DI, and the outcome variable. As in the first analysis, the best predictive model was selected using the Bayesian information criteria.

A sensitivity analysis was conducted to address the possibility that hematuria may represent a urinary tract infection and not renal activity, by considering hematuria as indicative of activity only if occurring in the absence of pyuria or in the presence of heme-granular or red blood cell casts.

RESULTS

Three hundred eighty-six patients (354 women, 71.5% Caucasian), with a mean age of 40.6 years (SD 14.5) and mean disease duration 8.1 years (SD 8.8, range 0–42.7 yrs), were evaluated (Table 1). Of the 386 participants, 322 had ≥ 2 visits with renal activity and QOL data.

The patients were followed for an average of 5.4 years (SD 4.5, range 0–14.5), with an average of 4.8 annual visits

Table 1. Demographic, clinical, and quality of life characteristics at study entry and throughout observation interval.

Variables	At Study Entry	Average During Observation Interval
Demographic		
Age, yrs, mean (SD)	40.6 (14.5)	
Male, %	8.3	
Caucasian, %	71.5	
Married, %	48.4	
Education, yrs, mean (SD)	13.0 (3.1)	
Disease duration, yrs, mean (SD)	8.1 (8.8)	
Clinical		
Renal activity, %	10.4	51*
Renal SLEDAI, mean (SD)	1.8 (3.4)	1.4 (2.2)
Median (IQR)	0 (0, 4)	0 (0, 4)
Nonrenal SLEDAI, mean (SD)	4.9 (4.6)	3.9 (2.9)
Median (IQR)	4 (2, 7)	3 (0, 6)
Total SLEDAI, mean (SD)	6.7 (6.7)	5.3 (4.1)
Median (IQR)	4 (2, 9)	4 (2, 8)
Renal SLICC/ACR-DI, mean (SD)	0.1 (0.4)	0.2 (0.5)
Median (IQR)	0 (0, 0)	0 (0, 0)
Nonrenal SLICC/ACR-DI, mean (SD)	1.0 (1.5)	1.4 (1.7)
Median (IQR)	0 (0, 2)	1 (0, 2)
Total SLICC/ACR-DI, mean (SD)	1.1 (1.6)	1.5 (1.9)
Median (IQR)	1 (0, 2)	1 (0, 3)
Slope of change in renal SLEDAI (95% CI)	NA	–0.06 (–0.07, –0.05)
SF-36		
Physical function, mean (SD)	67.4 (26.3)	70.6 (23.7)
Role-physical, mean (SD)	44.2 (43.2)	52.4 (35.8)
Bodily pain, mean (SD)	58.3 (26.8)	61.7 (22.1)
Vitality, mean (SD)	47.2 (22.5)	49.6 (19.2)
Role-emotional, mean (SD)	63.8 (42.6)	67.0 (33.4)
Mental health, mean (SD)	65.3 (20.6)	67.5 (33.4)
Social function, mean (SD)	66.5 (27.4)	70.4 (21.4)
General health, mean (SD)	51.4 (23.1)	52.5 (21.0)
Physical component summary, mean (SD)	40.2 (11.6)	41.8 (10.3)
Mental component summary, mean (SD)	45.3 (20.6)	46.4 (9.7)
Slope of change in physical component summary (95% CI)	NA	0.36 (0.32, 0.40)
Slope of change in mental component summary (95% CI)	NA	0.36 (0.32, 0.40)

SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; NA: not applicable.
* Refers to percentage of patients with at least one non-zero renal activity score over the course of study.

per patient (range 1–17). At baseline, 10.4% of the patients had renal activity. Over the study period, 51% of the patients had at least one non-zero renal activity score. Over the entire study interval, the average total SLEDAI was 5.3 (SD 4.1); the average of the renal and nonrenal SLEDAI items was 1.4 (SD 2.2) and 3.9 (SD 2.9), respectively. The average PCS and MCS score was 41.8 (SD 10.3) and 46.4 (SD 9.7), respectively (Table 1).

In the multiple regression models that examined the concurrent associations between renal activity and QOL, and which were adjusted for age, sex, ethnicity, marital status, education, disease duration, nonrenal disease activity, and nonrenal disease damage, on average, each additional renal activity item fulfilled was associated with a 2.04-unit (95% CI 0.88, 3.24) decrease in the physical function subscale, a

5.28-unit (95% CI 2.76, 7.76) decrease in the role-physical subscale, a 2.24-unit (95% CI 0.72, 3.80) decrease in the social function subscale, and a 1.16-unit (95% CI 0.60, 1.72) decrease in the PCS score. The other SF-36 subscales and the MCS score did not differ between patients with and those without renal activity (Table 2).

In the hierarchical model that examined the association between changes in renal activity and changes in QOL, each additional renal activity item fulfilled was associated with a 6.68-unit (95% CrI –6.24, 19.56) decrease in the physical function subscale and a 2.56-unit (95% CrI –1.40, 6.52) decrease in the PCS. No other associations between renal activity and the other QOL outcomes were observed, but wide confidence intervals preclude definitive conclusions for many of the QOL subscales (Table 2).

Table 2. Regression models for the concurrent and longitudinal association between renal activity and quality of life (QOL).

QOL Outcomes	Multiple Regression Model* Coefficient[†] (95% CI)	Hierarchical Model** Coefficient[††] (95% CrI)
Physical function	–2.04 (–3.24, –0.88)	–6.68 (–19.56, 6.24)
Role physical	–5.28 (–7.76, –2.76)	–3.08 (–18.64, 12.44)
Bodily pain	–1.08 (–2.52, 0.32)	–1.08 (–8.76, 6.64)
Vitality	–0.96 (–2.20, 0.24)	1.2 (–7.96, 10.36)
Role emotional	–1.20 (–3.68, 1.32)	–3.6 (–18.92, 11.72)
Mental health	–0.52 (–1.56, 0.56)	–0.76 (–7.52, 4.6)
Social function	–2.24 (–3.80, –0.72)	–5.44 (–18.04, 7.16)
General health	–0.76 (–1.88, 0.36)	–3.84 (–12.44, 4.76)
Physical component summary	–1.16 (–1.72, –0.60)	–2.56 (–6.52, 1.40)
Mental component summary	–0.16 (–0.80, 0.52)	–0.4 (–4.68, 3.92)

CI: confidence interval; CrI: credible interval. * This regression model examines the concurrent association between renal activity and each QOL outcome, adjusting for the potential confounders of age, sex, ethnicity (Caucasian vs non-Caucasian), marital status (married vs unmarried), education (continuous variable), disease duration, nonrenal SLEDAI, and nonrenal SLICC/ACR-DI. The nonrenal SLEDAI and SLICC/ACR-DI scores were measured at Time t and the other covariates at study entry only. ** This hierarchical model examines the longitudinal association between change in renal activity and change in each QOL outcome, adjusting for the potential confounders of age sex, ethnicity (Caucasian vs non-Caucasian), marital status (married vs unmarried), education (continuous variable), disease duration, renal and nonrenal SLEDAI, nonrenal SLICC/ACR-DI, and the outcome variable, all measured at study entry only. [†] Coefficient expresses the association between the renal activity score and the specified QOL outcome. [††] Coefficient expresses the association between the longitudinal change in renal activity and change in the specified QOL outcome.

The results for the concurrent association between renal activity and QOL were unchanged when only hematuria occurring in the absence of pyuria or in the presence of heme-granular or red blood cell casts was considered reflective of renal activity.

DISCUSSION

Several studies have shown little association between overall disease activity and QOL in SLE[1,4,5,9,11,17-20]. It has been suggested that the perception of QOL may be modulated more by sociodemographic (age, education) and behavioral (coping with illness) characteristics than by overall disease activity[5-9,15-17]. However, the influence of specific SLE manifestations on QOL was not assessed in most of these studies. Renal involvement is still associated with increased morbidity in SLE, and responses to induction treatment vary. Renal relapses are frequent, and patients now routinely receive longstanding maintenance therapy with immunosuppressive drugs[23]. We therefore analyzed specifically the influence of active renal disease on QOL. We have shown previously that irreversible renal damage is not associated with change in QOL[27]. In the multiple regression model that examined the concurrent association between renal activity and QOL, we observed that patients with active renal disease experience a poorer QOL than those without renal disease, especially in the physical domains. Each additional renal activity item fulfilled was associated with a 2.04-unit (95% CI 0.88, 3.24) decrease in the physical function subscale, a 5.28-unit (95% CI 2.76, 7.76) decrease in the

role-physical subscale, a 2.24-unit (95% CI 0.72, 3.80) decrease in the social function subscale, and a 1.16-unit (95% CI 0.60, 1.72) decrease in the PCS score. It has been suggested that minimum clinically important differences, which should reflect a degree of change perceptible to patients, require changes of 5 to 10 points in the individual domains of the SF-36 and 2.5 to 5 points for the PCS and MCS scores[10,33]. Hence, most of the changes we observed did not quite attain clinically meaningful differences.

Our study has some limitations. Disease activity and QOL are assessed only at the time of the patient's annual research visit. Given the potential fluctuations in the disease course, our data may not reflect the patient's full experience with SLE throughout the entire year. Further, patients who are unwell may be unwilling to attend a long research visit. Therefore, our results could have underestimated the effect of renal activity on QOL. Further, the SF-36, a generic instrument for characterizing QOL, may not identify SLE-specific manifestations that may compromise QOL[10]. However, the SF-36 allows comparison of QOL between different diseases and it alone has been used in almost all studies analyzing QOL in SLE[1,4-7,9-11,13-17,20-22]. In most studies, as in our own, the SF-36 was completed annually[1,10,11]. In one previous short-term study where the SF-36 was administered monthly, an association between disease activity and QOL was observed[14].

Similar to our findings, others have also shown that the physical domains were more frequently affected than the mental domains in patients with SLE[1,24,34,35]. In one study,

SLE patients with impaired renal function reported better mental well-being, but poorer physical functioning and general health, than SLE patients with preserved renal function[24]. One possible explanation is that patients with worse medical conditions may experience better mental than physical well-being due to various forms of social support (emotional, instrumental, self-esteem, and companionship)[7,17,35]. Existing studies examining QOL in patients with renal involvement[16,24-26] are small, short-term, and do not include a comparator group without renal dysfunction.

In contrast to these few other studies that examined the concurrent association between renal activity and QOL[16,24-26], we also evaluated the association between change in renal activity and change in QOL. However, wide confidence intervals precluded definitive conclusions. A larger sample size or a more comprehensive indicator of renal activity may have allowed more precise estimates. Although sequential renal biopsies may better characterize renal activity than the renal components of the SLEDAI, a renal biopsy is usually only performed when there is a reasonable clinical suspicion of renal activity because it carries substantial risk. Further, we acknowledge it is possible that a persistent low level of proteinuria, which is scored as renal activity on the SLEDAI, does not necessarily reflect renal activity. This limitation in the SLEDAI was recognized by the SELENA (Safety of Estrogens in Lupus Erythematosus: National Assessment) trial investigators[36,37]. In an attempt to better identify renal activity, the SLEDAI proteinuria item was modified to require "new onset or recent increase in proteinuria of > 500 mg per 24 hours" instead of presence of this level of proteinuria. Unfortunately, this SLEDAI modification was introduced only relatively recently and therefore, disease activity in our cohort was evaluated using the older instrument.

Kuriya, et al[1] have conducted the only other research that examined the relationship between disease activity and QOL over time in SLE. It differs from our study in that it did not specifically assess renal activity. Further, Kuriya, et al[1] included only those patients with at least 6 evaluations and used linear regression to estimate a slope for the change in QOL for each patient. However, by using hierarchical modeling, an approach that allows borrowing of strength across patients while still allowing for individual within-patient variations, we were able to include patients with only 2 observations. Further, the hierarchical modeling accounts for the variance in the estimation of the slopes.

In this longitudinal study, we observed that the majority of patients had relatively low disease activity and a stable QOL. As indicated in Table 1, the average slope of change in renal activity over the observation interval was –0.06 (95% CI –0.07, –0.05) and the average slope of change in the physical and mental component summary scores was 0.36 (95% CI 0.32, 0.40). Our findings are consistent with previous longitudinal assessments, which, although sparse,

have shown that QOL is relatively stable over time in SLE patients with longstanding disease[1,10]. In our study, the average disease duration of 8.1 years combined with relatively low disease activity over the study period could have contributed to the stable QOL.

We observed that SLE patients with active renal disease concurrently experience a poorer QOL than those without renal disease, especially in the physical domains. Because the confidence intervals were wide, we could not determine whether a longitudinal change in renal activity was associated with a change in QOL. Disease-specific QOL instruments that better characterize the unique manifestations of SLE than the generic measures may be more likely to fluctuate in accord with specific features of SLE activity.

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