Longitudinal Study of Renal Function in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To determine the prevalence of renal disease and the course of renal function over time in patients with systemic sclerosis (SSc).

Methods. We performed a multicenter, longitudinal study of 561 patients with SSc followed in the Canadian Scleroderma Research Group registry. Renal function was measured by the estimated creatinine clearance rate (eCcr) using the Cockcroft-Gault formula. Longitudinal changes in renal function were modeled using statistical analyses that adjusted for patient dropout.

Results. Among the study subjects, 112 (20%) had abnormal renal function with no history of scleroderma renal crisis (SRC) and 29 (5%) had a history of SRC at baseline. In models adjusting for patient dropout, we found that patients with abnormal baseline renal function experienced the same annual decline in eCcr as patients with normal baseline renal function (–0.89% per year, 95% CI –2.02%, 0.26%), which is similar to that observed in the general population. Patients with a history of SRC also showed the same rate of decline, although starting from a lower baseline.

Conclusion. Renal dysfunction is common in SSc, even among those without a history of SRC. It is generally mild and renal function declines at a rate similar to the general population. These data are of considerable prognostic value for clinicians caring for patients with SSc. (J Rheumatol First Release Aug 1 2012; doi:10.3899/jrheum.111417)

Key Indexing Terms:
SYSTEMIC SCLEROSIS RENAL FUNCTION LONGITUDINAL STUDIES

Systemic sclerosis (SSc) is a rare, chronic autoimmune rheumatic disorder of uncertain etiology. It is characterized by diffuse vasculopathy and widespread fibrosis of the skin and internal organs. Several forms of renal disease are recognized in SSc. The most dramatic of these is scleroderma renal crisis (SRC), which usually manifests as malignant hypertension and progressive renal failure. SRC is uncommon but is associated with high rates of morbidity, including temporary and permanent dialysis, and mortality[1]. Other than SRC, renal disease in SSc has been reported to be common and to result from a variety of causes, including both scleroderma-related causes (concomitant heart, lung, and gastrointestinal disease) and other nonscleroderma causes [including hypertension, infection, and drugs such as nonsteroidal antiinflammatory drugs (NSAID), penicillamine, and angiotensin-converting enzyme (ACE) inhibitors][2,3]. Few studies have assessed renal function in SSc longitudinally and therefore little is known about the progression of renal disease in patients with SSc. Yet longitudinal analysis of renal function in SSc could provide important new prognostic information as well as identify potential relationships between renal dysfunction and specific demographic and disease-related characteristics.

A major potential confounding factor in longitudinal analysis of cohort data is patient dropout[4]. This occurs when a patient can no longer participate in a study because of disease-related reasons such as deteriorating health, or death. This in turn can make the remaining cohort appear healthier over time simply because sicker patients are more likely to withdraw. Statistical approaches to handle patient dropout exist and should ideally be implemented when studying a debilitating and fatal disease such as SSc. We recently demonstrated the importance of accounting for patient dropout in longitudinal data analysis of patients with SSc. We showed that the magnitude of the functional decline (measured with the Health Assessment Questionnaire) experienced by patients with SSc over time would have been significantly underestimated if the analysis had failed to account for patient dropout[5].

The purpose of our study was thus to determine the

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prevalence of renal disease and the course of renal function over time in patients with SSc, while accounting for patient dropout.

MATERIALS AND METHODS

Design. We conducted a longitudinal study of a large, multicenter cohort of patients with SSc.

Study subjects. The study subjects consisted of patients enrolled in the Canadian Scleroderma Research Group (CSRG) registry. Patients in this registry are recruited from 15 sites across Canada. They must have a diagnosis of SSc confirmed by a rheumatologist, be ≥ 18 years of age, fluent in English or French, and likely to be compliant with study procedures and visits. Patients recruited into the registry undergo an annual medical evaluation with standardized reporting of history, physical evaluation, and laboratory investigations, including serum creatinine. For this study, patients with baseline visits between August 2004 and September 2009 were included.

Study groups and outcome measure. Patients were separated into 3 groups: those with normal renal function, those with abnormal renal function, and those with a history of SRC at their baseline registry visit. Renal function was estimated using the Cockcroft-Gault formula [a surrogate of glomerular filtration rate (GFR)]:

estimated creatinine clearance (eCcr, ml/min) = [140 – age (yrs) × weight (kg) × 1.23 if male or 1.04 if female/serum creatinine (μmol/l)]

Normal renal function was defined as eCcr > 60 ml/min and abnormal was defined as values below that cutoff. There is no gold standard to define SRC. Thus, for the purposes of our study, a report of SRC confirmed by a study physician was used to define that condition.

Covariates. Demographic information, including age and sex, and comorbidities (including diabetes mellitus and hypertension) were self-reported by the patients. Disease duration was recorded by the study physician and determined from the onset of the first non-Raynaud's disease manifestation. Skin involvement was assessed using the modified Rodnan skin score, a widely used clinical assessment in which the examining rheumatologist records the degree of skin thickening ranging from 0 (no involvement) to 3 (severe thickening) in 17 areas (total score range 0–51). Patients are classified into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) subsets, based on the definitions of Leroy, *et al*[6]. Medications currently taken by the study subjects, including ACE inhibitors, angiotensin receptor blockers (ARB), nonsteroidal antiinflammatory drugs, D-penicillamine, and cyclosporine, were recorded by the study physician.

Study visits. Patients in the registry are assessed at baseline and annually thereafter. For a variety of reasons, including disease-related reasons or death, patients may sporadically fail to return for their yearly visit on their scheduled visit date, may miss a yearly visit entirely, or may drop out of the registry. One possible reason for missed visits in our cohort could have been poor renal function. In this case, patients with more severe renal dysfunction could have been more likely to miss a visit than patients with normal renal function. Thus, followup visits were numbered 2, 3, 4, 5, and 6 as long as they fell within 6 months of the scheduled visit date, and visits that did not occur according to schedule were recorded as missed visits. In our study, visit numbers generally correspond to the annual visits. Indeed, visits were on average 358.26 and 359.75 days apart, respectively, for the complete and available case analyses.

Statistical analysis. Descriptive statistics were used to describe the study cohort. Linear mixed models were used to identify correlates of renal function, i.e., eCcr. The covariates included in the models were disease subset (lcSSc and dcSSc) at baseline, baseline eCcr, ethnicity, a history of scleroderma renal crisis (SRC; represented as a binary variable comparing yes to no), and the longitudinal time-dependent covariate represented by visit number. Age, sex, and weight were not included in the models given that they are accounted for in the Cockcroft-Gault formula for eCcr. A logarithmic transformation of eCcr was used to improve model interpretability.

We began by performing a complete case analysis in which our sample included all patients with complete baseline data and no missing followup visits (n = 410, 71.4% of available patients). We fit models that allowed both intercepts and slopes to vary by patient. Visit number was included as a covariate in the analysis to model the longitudinal aspect of the disease and to look for trends in time. We also fit models that included an interaction between visit number and baseline eCcr and visit number and history of SRC, to test for a dependence of the trajectory on these 2 baseline covariates. The final models were selected using the Bayesian information criterion (BIC). To assess the effect of possible patient dropout, we then performed an available case analysis by fitting the above models to all eligible patients. All models were fit using the lme4 package in R statistical computing.

Finally, we used the general estimating equation package in R to fit inverse probability weighted generalized estimating equation models to the data to examine the robustness of our conclusions to 2 key assumptions: (1) normality of the residuals, and (2) data that are missing at random.

Ethical considerations. Ethics committee approval for the CSRG Registry data collection protocol was obtained at McGill University (Montreal, Canada) and at all participating study sites. All subjects provided written informed consent to participate in the registry.

RESULTS

Our study included 561 subjects. Mean (SD) age was 55.5 (12.0) years, 87.9% of subjects were women, 59.7% had lcSSc, 40.3% had dcSSc, and mean disease duration was 10.9 (8.8) years. The baseline characteristics of the 401 patients without any missing visits (complete cases) were similar to those of the whole cohort (available cases). The median followup time for patients included in the complete and available case analyses was 761 days [interquartile range (IQR) 406–1191] and 756 days (IQR 399–1127), respectively.

At baseline, 420 patients (74.9%) had normal renal function (eCcr > 60 ml/min), 112 (20.0%) had abnormal renal function and no history of SRC (eCcr < 60 ml/min), while 29 (5.2%) had a history of SRC (Table 1). Those with abnormal renal function at baseline differed from those with normal renal function in the following respects: they were older, more likely to be female, more likely to have limited disease, and more likely to have longer disease duration. Those with a history of SRC at baseline differed from those with normal renal function in the following respects: they were more likely to be male, to have diffuse disease, and to have shorter disease duration. Aside from these differences, patients with abnormal renal function at baseline also differed significantly from those with normal renal function in the following respects: they were more likely to have hypertension and to be currently exposed to ACE inhibitors and ARB (Table 2). In addition, they were almost twice as likely to have diabetes mellitus and 6 times as likely to have been exposed to D-penicillamine.

Two patients with normal renal function at baseline (0.01%) and 1 patient with abnormal renal function at baseline (0.01%) developed SRC during followup. The small sample size precluded the precise estimation of a 95% CI around this difference.

Table 1. Baseline characteristics of study subjects.

	Normal Renal Function at Baseline	Abnormal Renal Function at Baseline	Scleroderma Renal Crisis
Complete case analysis (only patients without missing visits; n = 401)			
n (%)	295 (73.57)	83 (20.70)	23 (5.74)
Mean age (SD), yrs	53.37 (10.64)	64.77 (8.63)	55.22 (9.69)
Female, n (%)	258 (87.46)	79 (95.18)	20 (86.96)
Black, n (%)	4 (1.36)	0 (0)	0 (0)
Limited disease, n (%)	181 (61.36)	58 (69.88)	9 (39.13)
Mean weight, kg (SD)	71.32 (16.14)	58.02 (10.76)	70.93 (20.00)
Mean weight change, kg/year (SD)	0.41 (3.67)	–0.25 (2.78)	–0.56 (3.15)
Mean creatinine, μmol/l (SD)	72.38 (15.91)	103.01 (50.24)	177.74 (114.50)
Mean creatinine clearance, ml/min	93.34 (29.57)	47.54 (9.72)	46.15 (28.15)
Disease duration, yrs (SD)	9.76 (7.68)	14.35 (10.96)	8.40 (6.19)
Whole cohort (all available cases: n = 561)			
n (%)	420 (74.87)	112 (19.89)	29 (5.15)
Mean age (SD), yrs	52.84 (11.31)	65.70 (9.49)	54.72 (9.24)
Female, n (%)	364 (86.67)	107 (95.54)	22 (75.86)
Black, n (%)	5 (1.19)	1 (0.89)	0 (0)
Limited disease, n (%)	245 (58.33)	73 (65.18)	10 (34.48)
Mean weight, kg (SD)	71.50 (16.21)	57.88 (11.13)	69.35 (18.48)
Mean weight change, kg/year (SD)	0.58 (4.26)	–0.10 (2.85)	–0.67 (3.06)
Mean creatinine, μmol/l (SD)	72.04 (15.38)	110.10 (95.39)	179.7 (113.50)
Mean creatinine clearance, ml/min	94.78 (28.77)	46.46 (10.80)	45.75 (26.57)
Disease duration, yrs (SD)	10.31 (8.22)	13.96 (10.67)	8.00 (6.34)

Table 2. Non-disease-related differences between patients with normal and abnormal renal function at baseline.

	Patients with Normal Renal Function at Baseline	Patients with Abnormal Renal Function at Baseline	p
Diabetes mellitus, %	3.39	6.02	0.44
Hypertension, %	22.71	43.37	0.00
Congestive heart failure, %	2.37	9.64	0.01
Overlap with systemic lupus erythematosus, %	1.36	2.41	1.00
Nephrotoxic medications			
ACE inhibitors, %	12.20	22.89	0.01
Angiotension receptor blockers, %	8.14	13.25	0.05
Nonsteroidal antiinflammtory drugs, %	19.32	20.48	0.23
D-penicillamine, %	1.02	6.02	0.58
Cyclosporine, %	0.00	0.00	1.00
Corticosteroids, %	15.93	14.46	0.33
Drugs for heart failure, %	2.03	10.84	0.01
Anti-arrythmics, %	1.69	7.23	0.04
Prostacyclins, %			
Flolan, %	0.68	0.00	—
Trepostinil (UT-15), %	0.68	0.00	—
Iloprost, %	0.68	0.00	—

ACE: angiotensin-converting enzyme.

In the complete case analysis, the linear mixed model that fit the data best (according to the BIC) allowed for random intercepts and slopes for each patient, but no interaction of time with either baseline eCcr measurement or with history of SRC. It estimated that the median eCcr fell slightly at each study visit by 0.64% (95% CI: –2.00%, 0.73%) of the previous visit (Table 3). The BIC selected the same linear mixed model for the available case data (Table 4). This model, which adjusted for patient dropout, estimated a median decline in eCcr of 0.89% per visit (95% CI: –2.02%, 0.26%). Again, we found no strong statistical evidence of an interaction between the rate of decline and baseline eCcr or history of SRC.

We confirmed our results by fitting inverse-probability-of-missingness weighted generalized estimating equations. This different statistical approach showed no differ-

Table 3. Linear regression model (in terms of relative change) to identify correlates of renal function (eCcr)-complete case analysis (n = 401). All data are percentages.

	Estimated Median Change in eCcr, Adjusting for Other Variables (95% CI)	p
Visit number (year)	–0.64 (–2.00, 0.73)	0.36
Per 10% decrease in baseline eCcr	–6.86 (–7.41, –6.31)	< 0.0001
Black compared to white	–12.85 (–32.44, 12.41)	0.38
Diffuse compared to limited disease	4.00 (–1.36, 9.65)	0.15
History of SRC (yes vs no)	–17.4 (–26.60, –7.03)	0.001

eCcr: estimated creatinine clearance rate; SRC: scleroderma renal crisis.

Table 4. Linear regression model (percentage change) to identify correlates of renal function (eCcr)-available case analysis (n = 561). All data are percentages.

	Estimated Median Change in eCcr, Adjusting for Other Variables (95% CI)	p
Visit number (year)	–0.89 (–2.02, 0.26)	0.13
Per 10% decrease in baseline eCcr	–8.38 (–8.83, –7.91)	< 0.0001
Black compared to limited disease	–8.82 (–25.94, 12.26)	0.38
Diffuse compared to limited disease	4.51 (0.37, 8.81)	0.03
History of SRC (yes vs no)	–8.97 (–17.29, 0.20)	0.05

eCcr: estimated creatinine clearance rate; SRC: scleroderma renal crisis.

ence in estimates, statistical significance, or conclusions (data not shown).

DISCUSSION

In this large, longitudinal, multicenter cohort study, we found that abnormal renal function in the absence of prior SRC was common in SSc (about 20% of patients), but renal function declined only slightly over time, by about 0.89% per year. This is roughly equivalent to a decline of 0.8 ml/min per year in someone with a creatinine clearance of 90 ml/min and 0.45 ml/min per year in someone with a creatinine clearance of 50 ml/min. In the general population, renal function has been reported to decline slowly after the age of 30 (by about 0.6–1.1 ml/min/1.73m^2 per year)[7]. The magnitude of renal change found in our study is thus in the same range and suggests that it is unlikely to be of any additional clinical significance.

In addition, our data showed that having abnormal renal function at baseline was not associated with a large risk of developing SRC. In fact, we found that only 1 patient with abnormal baseline renal function and 2 patients with normal renal function at baseline went on to develop SRC during followup.

We also explored the possibility of causes of renal abnormalities other than scleroderma itself among our patients. Both hypertension and diabetes were more common among patients with abnormal baseline renal function than among those with normal renal function at baseline. In addition, patients with abnormal renal function were more likely than those with normal renal function to be taking ACE inhibitors, ARB, or penicillamine. Of note, NSAID use was less frequent among patients with abnormal renal function than in patients with normal renal function, possibly because of their known negative effect on kidney function. These data support the hypothesis that SSc patients with abnormal renal function may have renal abnormalities for reasons other than scleroderma.

Pathologic abnormalities, in particular changes suggestive of severe hypertension even in the absence of systemic hypertension, are common in SSc. In a study of 58 patients with SSc and 58 non-SSc controls[8], 58% of the cases and only 9% of the controls ($p < 0.001$) had evidence of fibrinoid necrosis in afferent arterioles or glomeruli, hyperplasia of interlobular arteries, thickening of basement membrane, or wire-looping on autopsy. Only half of the patients with SSc were known to have been hypertensive. Abnormalities in renal physiology have also been reported to be common in SSc. In a study of 57 patients[9], renal plasma flow was abnormally low in 69% of patients, plasma renin activity was abnormally elevated in about 45% of patients, and creatinine clearance was abnormally low in 16% of patients.

Clinical abnormalities in renal function have also been reported to be common. In a study of 675 patients with diffuse cutaneous SSc (dcSSc) from the University of Pittsburgh cohort[2], 16% of patients had elevated serum creatinine in the absence of SRC at some point in the course of followup. The causes of these abnormalities included both scleroderma-related causes (concomitant heart, lung, and gastrointestinal disease) and other nonscleroderma causes (including infection and drugs such as antiinflammatories, diuretics, penicillamine, and ACE inhibitors). None of these patients, followed for a mean of 10 years after the onset of SSc, progressed to endstage renal disease. Similarly, in another single-center study from Sweden (n = 475)[10], abnormal GFR was reported to affect 48 patients (10%). Fifteen of these patients were followed for > 4 years, and 11/15 had stable renal function over time. Of the 4 who progressed, 2 had endstage pulmonary arterial hypertension and 2 had biopsy-proven proliferative glomerulonephritis.

Our findings are highly consistent with published reports of renal dysfunction in SSc, both in terms of baseline frequency and evolution over time. We believe that our findings add considerably to the literature in several respects. First, ours is a multicentered study with the largest sample of subjects including patients with lcSSc and dcSSc. Including patients with lcSSc is of particular importance because our data suggest that they are more likely to have abnormal renal function than those with diffuse disease. Second, using advanced statistical modeling, we demonstrated that the rate of decline in renal function is mild, even

after accounting for potential confounding due to patient dropout. Indeed, previous studies reporting on "stable" courses of renal function in patients with SSc could have been misleading by failing to capture sicker patients who may have dropped out of the studies. Without adjusting for survivor bias, it is possible that only healthier patients with better renal function remain in the cohort, thereby underestimating changes in renal function over time. In the Swedish paper[10], only 15 of the 48 patients with abnormal renal function were followed over time. Patient dropout was not reported in the study from the University of Pittsburgh[2]. In our study, the steeper decline in the available case analysis, compared to the complete case analysis, was consistent with the hypothesis that patient dropout in longitudinal studies may lead to an underestimation of effect. However, in our study, the magnitude of the difference was not clinically significant.

Of note, in a recent study of 28 patients with SSc who had normal renal function, of which 9 had normal and 19 had abnormal renal functional reserve at baseline, creatinine clearance decreased by 2.6% in those with normal compared to 15.4% in those with abnormal renal functional reserve over 5 years[11]. The magnitude of the decline reported among those with normal renal functional reserve was in the same range as that reported here. The accelerated rate of decline among those with abnormal renal functional reserve at baseline was greater. We did not have any measure of renal functional reserve and could therefore not identify a subset of patients with normal renal function in that way. Further studies will be needed to confirm this intriguing finding.

This study is not without limitations. Misclassification may have resulted from the fact that the history of SRC was based on physician report and was not validated against a formal definition[12]. Thus some patients with unrecognized or aborted SRC may have been included among those labeled as having abnormal renal function in the absence of SRC, and some labeled as having SRC may have been misdiagnosed. Secondly, we did not have detailed data on some relevant causes of renal disease among those with abnormal renal function (e.g., renal artery stenosis, concomitant glomerulonephritis). On the other hand, we had data on some of the most important comorbidities, such as hypertension and diabetes, and concomitant medications (Table 2), and believe that other causes are likely relatively rare. Thirdly, the CSRG cohort is a multisite observational research cohort. Laboratory tests, and in particular serum creatinine, are measured in routine clinical laboratories and the data is collected for study purposes. The data used in our study spanned the years during which isotope dilution mass spectrometry (IDMS)-calibrated methods were adopted by clinical laboratories to measure serum creatinine. These methods result in values that are about 6% lower. Since some serum creatinine measurements used in this study were performed prior to the adoption of IDMS-traceable methods by clinical laboratories, we may have underestimated renal function and changes over time in our cohort. Finally, we acknowledge that our followup period remains fairly short and recognize this as a specific limitation of the study. In particular, we note that in some of our analyses, there was evidence that patients with abnormal baseline renal function had steeper trajectories of decline than patients with normal baseline renal function (data not shown). However, these models had inferior BIC values and the CI for the interaction terms were quite wide. Although our overall sample size was large, we would have required a longer followup time (i.e., more annual visits) per patient to estimate more precisely the dependence of trajectory on baseline renal function.

The best measure of renal function in SSc has yet to be validated[13]. Measures that have been used to date include direct measurement of GFR using EDTA[14], which is expensive and often not feasible, and indirect measures such as serum creatinine[2], which may be poorly sensitive in SSc[15]. Renal function in SSc has also been estimated using other indirect measures, in particular the Modification of Diet in Renal Disease (MDRD) formula, which uses serum creatinine and adjusts for age, sex, and race, and the Cockcroft-Gault formula, which adjusts for age, sex, and weight[15]. We did not have direct assessments of GFR, but ran all of our analyses using the 3 easily available indirect measures of renal function, namely serum creatinine, estimated GFR calculated using the MDRD, and eCcr calculated using the Cockcroft-Gault formula, concurrently. We found that renal function seemed to improve slightly with time with both serum creatinine and the MDRD formula (data not shown), whereas it deteriorated slightly over time with the Cockcroft-Gault formula, as presented herein. We concluded that renal function measured with the Cockcroft-Gault formula seemed to have the greatest face and content validity in our sample, because changes over time were in the same direction as the expected decline seen in the general population. Weight loss, which is common among some patients with SSc, likely accounted for the observed differences between changes in renal function over time using the Cockcroft-Gault formula compared to either serum creatinine or the non-weight-based MDRD formula. Thus we chose to present our results using the eCcr calculated with the Cockcroft-Gault formula. However, further work will be needed to validate measures of renal function in SSc.

This large, multicenter, longitudinal study of renal function in patients with SSc, accounting for patient dropout, provides robust data demonstrating that abnormal renal function in the absence of SRC occurs in about one-fifth of patients. However, it is generally mild and renal function declines at the same rate as expected in the general population. These data are of considerable prognostic value for clinicians caring for patients with SSc.

APPENDIX

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