Is Vasculopathy Associated with Systemic Sclerosis More Severe in Men?

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ABSTRACT. ***Objective.*** To identify possible differences in morbidity and mortality between men and women with systemic sclerosis (SSc) by examining a homogeneous cohort at a single academic center.

Methods. Demographic, clinical, and outcome data for all 231 patients of Greek origin with SSc who were examined between 1995 and 2011 in our department (200 women) were recorded in consecutive 3-year intervals from disease onset; data were analyzed retrospectively.

Results. Factors comparable between sexes were age (yrs ± SD) at disease onset (46 ± 15 vs 46 ± 15), diffuse skin involvement (61.3% of men vs 46.4% of women), and anti-Scl-70 antibody positivity (66.6% of men vs 59.2% of women). Also comparable were prevalence of interstitial lung disease, upper or lower gastrointestinal (GI) tract involvement, and echocardiographic findings during the first, second, and third 3-year intervals from disease onset (2904 patient-yrs). In contrast, vasculopathy occurred earlier in men. During the first 3 years digital ulcers developed in 54% of men versus 31% of women ($p = 0.036$) and renal crisis developed in 17% of men versus 3% of women ($p = 0.006$). No significant differences regarding social history, smoking, medical history, or disease management were identified. After excluding non-SSc-related deaths, survival was worse in men ($p = 0.005$, Kaplan-Meier analysis) with significantly lower 6- and 12-year cumulative rates (77.2% and 53.8%, respectively, in men vs 97.3% and 89.2% in women).

Conclusion. Results derived from an unselected SSc population indicate that the disease is more severely expressed in men than in women, a finding that could be related to more rapid development of vasculopathy in men. Studies are warranted in other single-center cohorts to confirm these findings. (J Rheumatol First Release Nov 1 2012; doi:10.3899/jrheum.120667)

Key Indexing Terms:

SYSTEMIC SCLEROSIS | SEX | VASCULOPATHY
DIGITAL ULCERS | RENAL CRISIS | SURVIVAL

Systemic sclerosis (SSc) is an uncommon systemic autoimmune disorder, characterized by fibrosis of the skin and visceral organs, as well as by structural damage and dysfunction of the small vessels[1]. Disease expression is heterogeneous, in terms of both symptom severity and variability of clinical manifestations. The pathogenetic mechanisms underlying fibrosis and vasculopathy may differ and are not well understood, although certain genetic, environmental, and hormonal factors are involved[2,3]. Also identified as contributing factors are deregulation of cytokine expression, i.e., transforming growth factor-ß (TGF-ß), platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF); and aberrant proliferation of fibroblasts and the resultant excessive deposition of various extracellular matrix components, especially collagen type I and III, in skin and internal organs[4]. Depending on the severity of organ involvement, SSc may substantially affect functional capacity of patients[5] and reduce life expectancy[6].

Several studies have identified risk factors that determine poor prognosis in SSc[7,8,9] such as advanced age at disease onset, diffuse skin involvement, or presence of antitopoisomerase antibodies (Scl-70). Similarly to other autoimmune conditions, SSc has a pronounced female predominance, with a male-to-female ratio varying in different studies between 1:4 to 1:8[10]. However, the effect of sex on disease expression and survival remains unclear. Whether SSc is differently expressed in men and women has recently been readdressed, but data from relevant studies are controversial[11,12,13,14,15]. Clearly, the low prevalence of SSc, its heterogeneity, and the rarity of the disease among men make it difficult to identify differences in clinical expression between sexes. However, this controversy may also occur because those data from multiethnic cohorts include patients referred to tertiary care centers for severe disease. The men-to-women ratios are almost double (1:4–5) in those cohorts[16,17,18,19] compared to homogeneous ethnic cohorts[20,21,22,23,24], suggesting a bias associated with the underrepresentation of women with milder forms of SSc.

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The aim of our study was to detect possible sex-related differences in mortality and morbidity in a relatively large, homogeneous cohort comprising unselected patients with SSc who received standardized care in the setting of a single university hospital.

MATERIALS AND METHODS

For our study we retrospectively reviewed the charts of all patients with a diagnosis of SSc who fulfilled the American College of Rheumatology SSc classification criteria[25] and the LeRoy and Medsger criteria for the classification of limited (lcSSc) or diffuse (dcSSc) cutaneous SSc[26] and who had been examined at our department between January 1, 1995, and December 31, 2011. Using these criteria we excluded 4 patients with overlap syndromes or SSc *sine* scleroderma. After excluding 11 patients of non-Greek origin who were referred to us for severe disease, the medical records of 231 patients with SSc were retrospectively analyzed. Patients were classified as having either dcSSc, when skin thickening extended proximal to the elbows or the knees, or lcSSc, when skin thickening affected the face, the neck, and areas distal to the elbows and the knees[26]. Additional variables recorded included the following: sex; disease subtype; anti-Scl-70 and anticentromere antibody (ACA) positivity; duration of followup in years; and age at disease onset, defined as date of first symptom other than Raynaud phenomenon (RP).

To detect differences in disease progression over time and survival, clinical manifestations and medications for each patient were recorded in consecutive 3-year intervals from disease onset. Organ involvement was defined according to preestablished criteria. Digital ulcers were defined as denuded areas with loss of epithelialization on the digits of the hands or the feet. Musculoskeletal involvement was identified by the presence of myopathy, articular contractures, arthralgia, or arthritis. Involvement of the upper GI tract was recognized by clinical symptoms such as dysphagia or gastroesophageal reflux and was always confirmed by esophageal dilatation in chest computed tomography (CT) and/or endoscopy or esophageal manometry. Involvement of the lower GI tract was recognized by relevant clinical symptoms such as chronic or recurrent diarrhea or constipation that required therapy. Renal crisis was considered if rapidly progressive renal failure, with or without arterial hypertension, occurred that could not be attributed to other causes. Interstitial lung disease was defined by the presence of either fibrosis or ground-glass attenuation in a high-resolution CT scan of the lungs, in the absence of infection or left ventricular failure. Data of lung function tests (forced vital capacity, total lung capacity, and lung diffusing capacity for carbon monoxide) were also recorded. Arrhythmia was defined as the presence of rhythm disturbances in electrocardiography (more commonly premature ventricular contractions, flutter or paroxysmal supraventricular tachycardia, and transient atrial fibrillation), thereafter confirmed by 24-h Holter monitoring of cardiac rhythm[27]. Finally, using echocardiography, the value of 60% was considered a normal left ventricular ejection fraction (LVEF), whereas a value of 40 mm Hg was set as the limit above which pulmonary arterial systolic pressure (PASP) was considered elevated[28]. The presence of pulmonary arterial hypertension (PAH) was confirmed by right heart catheterization whenever feasible.

For patients who died during hospitalization, causes of death were recorded from the medical charts. For those who died in an outpatient setting, the cause of death was recorded as stated on the death certificate and was crosschecked with the families. In either case, we decided whether death could be attributed to SSc, based on clinical data.

Statistical analysis was performed using the IBM SPSS statistical package, version 20.0. The Pearson chi-squared test for qualitative variables and the 2-sample t-test for quantitative data were used for comparisons between female and male groups. Differences were considered significant for values of $p < 0.05$. Kaplan-Meier analysis and the Mantel-Cox test were used to estimate survival.

RESULTS

Demographic data and clinical features during disease progression. Overall, 231 patients of Greek origin with SSc were included in our study; the male-to-female ratio was 1:6.6. As shown in Table 1, the age at disease onset was comparable between sexes, whether defined as age at presentation of first symptom other than RP or as age at RP presentation (44.2 ± 15.3 yrs in men vs 43.1 ± 14.4 yrs in women). Ninety-three of 200 women (46.5%) compared to

Table 1. Organ involvement (percentage of patients completing followup periods) during disease progression and characteristics of 231 consecutive Greek patients with systemic sclerosis, stratified by sex (2904 patient-yrs).

Characteristic	Women, n = 200 at Baseline	Men, n = 31 at Baseline	p*
Age at onset, yrs, mean ± SD	45.9 ± 14.4	45.7 ± 14.8	0.93
Followup, yrs, mean ± SD	13.1 ± 10.2	9.2 ± 6.9	**0.046**
Anti-Scl-70 positivity, %	59.3	66.7	0.495
ACA positivity, %	22.8	9.5	0.167
Diffuse skin involvement, %	46.5	61.3	0.123
Pulmonary fibrosis, %			
1st–3rd year	40.7	45.5	0.676
4th–6th year	51.6	56.2	0.732
7th–9th year	60.7	75.0	0.435
Upper GI tract, %			
1st–3rd year	42.9	45.5	0.823
4th–6th year	52.4	37.5	0.274
7th–9th year	61.5	33.3	0.184
Lower GI tract, %			
1st–3rd year	12.9	13.0	0.982
4th–6th year	17.5	11.8	0.564
7th–9th year	24.1	14.3	0.562
Contractures, %			
1st–3rd year	10.8	33.3	**0.019**
4th–6th year	15.5	37.5	0.122
7th–9th year	31.1	66.7	0.206
LVEF ≤ 60% by ultrasound, %			
1st–3rd year	13.0	20.0	0.373
4th–6th year	15.2	16.7	0.875
7th–9th year	15.8	18.2	0.850
PASP ≥ 40 mm Hg by ultrasound, %			
1st–3rd year	12.6	18.2	0.495
4th–6th year	19.7	20.0	0.981
7th–9th year	34.1	33.3	0.971
Arrhythmia, %			
1st–3rd year	17.0	26.3	0.342
4th–6th year	23.7	18.2	0.685
7th–9th year	31.7	20.0	0.591
Digital ulcers, %			
1st–3rd year	31.5	54.2	**0.036**
4th–6th year	37.5	56.2	0.163
7th–9th year	58.5	50.0	0.651
Renal crisis, %			
1st–3rd year	2.9	17.4	**0.006**
4th–6th year	3.8	6.2	0.648
7th–9th year	2.1	0	0.718

Numbers in bold type are statistically significant. * By t-test for quantitative variables; by chi-squared for qualitative variables. ACA: anticentromere antibodies; GI: gastrointestinal; PASP: pulmonary arterial systolic pressure; LVEF: left ventricular ejection fraction.

19 of 31 men (61.5%) had the diffuse SSc subtype, but this difference did not reach statistical significance. Additionally, no significant differences in serologic markers were found between men and women; the prevalence of both antitopoisomerase (anti-Scl70) and ACA were comparable between sexes (66.7% in men vs 59.3% in women and 9.5% in men vs 22.8% in women, respectively).

During followup (2904 patient-yrs), the musculoskeletal symptoms did not differ significantly between sexes, with the exception of contractures that were more frequent in men during the early phase of the disease (p = 0.019 for the first 3-yr interval). As shown in Table 1, men tended to have pulmonary fibrosis more often than women (45.5% in men vs 40.7% in women, 56.2% vs 51.6%, and 75.0% vs 60.7%, during the first, second, and third 3-yr intervals from disease onset, respectively), albeit not reaching significance. Moreover, lung function tests in surviving patients during followup did not differ between sexes (Table 2). Women presented a somewhat higher frequency of upper GI tract involvement than men in the second and third intervals (52.4% vs 37.5%, 61.5% vs 33.3%; findings in esophageal manometry performed in 39 women and 9 men always confirmed the reported symptoms), as well as of lower GI tract involvement (17.5% vs 11.8%, 24.1% vs 14.3%) in the second and third intervals; these differences were not statistically significant. There was no difference between the sexes in the presence of arrhythmias, of LVEF ≤ 60%, or of the prevalence of PASP ≥ 40 mm Hg by ultrasound (right heart catheterization performed in 5 women and 2 men confirmed the presence of PAH in 4 patients).

On the other hand, significant sex-related differences were found for features of vasculopathy other than PAH. Analysis of data showed that renal crisis and digital ulcers occurred more frequently in men than women during the first 3 years after disease onset. As shown in Table 1, 17.4% of men presented renal crisis in the first 3 years compared to only 2.9% of women in the same period (p = 0.006). In addition, digital vasculopathy in the first 3 years after disease onset developed in 54.2% of men compared to 31.5% of women (p = 0.036). In the following 3-year intervals, no significant differences between sexes were noted.

Finally, no significant differences were noted between sexes regarding social history, smoking (34.1% of women vs 35.7% of men at disease onset), and medical history of diabetes mellitus, dyslipidemia, coronary artery disease and thyroidopathy (data not shown). Moreover, there were no significant differences regarding disease management in men versus women in terms of medications and doses during the 3-year intervals, with the exception of intravenous treatment with iloprost, which was more frequent among men (p = 0.04) during the first 3 years after disease onset. Also, during this period more men than women received bosentan, albeit not to the point of statistical significance.

Survival. During the study period, 35 deaths occurred. After excluding non-SSc-related deaths (5 women and 1 man from cancer, 1 woman from sepsis, and 1 woman from anaphylactic shock), 27 patients (21 women) died from SSc-related causes. Deaths were considered related to renal crisis in 2 men, heart involvement in 7 women, pulmonary fibrosis in 12 women, pulmonary hypertension in 3 patients (2 men), and severe GI tract involvement in 3 patients (2 men). In all 3-year intervals, men had worse survival rates than women (Table 3). As shown in Figure 1, Kaplan-Meier analysis confirmed the statistical difference in survival between sexes (Mantel-Cox test, p = 0.005).

Table 2. Mean values (% of predicted ± SD) of forced vital capacity (FVC), total lung capacity (TLC), and diffusion capacity for CO (DLCO) at the third, sixth, and ninth year after disease onset in surviving patients, stratified by sex.

	Women, n = 91	Men, n = 16	p*
FVC			
Third	89.9 ± 16.1	90.9 ± 15.0	0.849
Sixth	87.8 ± 19.5	83.3 ± 18.1	0.594
Ninth	84.5 ± 21.1**	68.2 ± 19.3***	0.157
TLC			
Third	85.1 ± 14.7	82 ± 17.1	0.549
Sixth	81.1 ± 18.2	74.6 ± 14.5	0.416
Ninth	73.5 ± 16.7**	63 ± 18.4***	0.398
DLCO			
Third	66.0 ± 15.4	72.4 ± 20.9	0.249
Sixth	63.1 ± 18.4	63.5 ± 25	0.967
Ninth	57.4 ± 19.8**	58.7 ± 22.3***	0.923

* By t-test; ** n = 64; *** n = 11.

DISCUSSION

Older data from SSc referral centers indicated that the male/female ratio was around 1:4–5[16,17], whereas clear differences in disease expression and/or progression between sexes were not identified. According to more recent data from several studies of ethnic cohorts[21,23,24] and from a global analysis published in 2009[29], the male/female ratio is considerably lower (1:7–8). This difference suggests that a referral bias may be present in the older studies, due to underrepresentation of women with milder forms of SSc in the examined patient populations. On the other hand, few

Table 3. Survival rates (by percentage) in 231 patients with systemic sclerosis (2904 patient-yrs) stratified by sex. No. patients who completed each period of followup are shown in parentheses.

	Women	Men	p*
3-year survival	98.8 (177 of 179)	85.7 (24 of 28)	**0.0001**
6-year survival	97.3 (143 of 147)	77.2 (17 of 22)	**0.0001**
9-year survival	92.4 (109 of 119)	64.3 (9 of 14)	**0.001**
12-year survival	89.2 (74 of 84)	53.8 (7 of 13)	**0.001**

Numbers in bold type are statistically significant. * Chi-square.

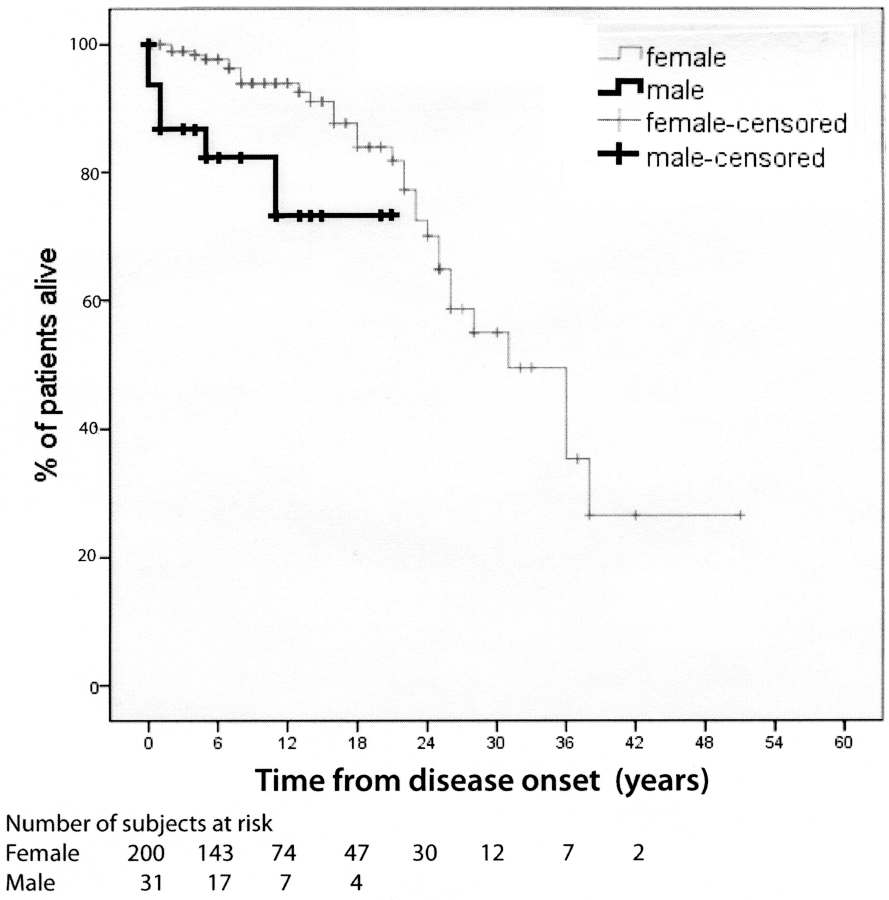

Figure 1. Kaplan-Meier analysis confirmed the statistical difference in survival between sexes. Mantel-Cox log-rank test, p = 0.005.

studies[11,12,13,14,15] have attempted to directly address the differences in expression of SSc between men and women, and most of the available data represent circumstantial evidence, or at best, secondary outcomes of trials. Until now, data regarding the effect of sex on the clinical severity of SSc are limited and inconclusive. Existing data are also controversial regarding differences in survival: there are studies reporting similar survival rates between sexes[15,30] and studies demonstrating significantly higher mortality in men compared to women with SSc[17,31].

Our primary endpoint was to detect possible sex-related differences in the clinical manifestations of SSc, at any stage of the disease course. For that purpose we arbitrarily divided disease progression into consecutive 3-year intervals. We tried to eliminate any relevant confounding factors, such as differences in social background, treatment strategies, or medical history between men and women, by including only Greek patients who received the same standardized care in a single center. The clinical characteristics of patients in our cohort are consistent with a previously published Greek cohort[32], with Canadian[33] and German registries[34], and with other ethnic cohorts[8,23,24]. Moreover, survival rates in our cohort are comparable with those reported elsewhere[7,24,32]. Therefore, it seems that our cohort is representative of the general SSc population, not only in our country, possibly permitting extrapolation of our findings to other white patient groups.

We found that musculoskeletal symptoms, pulmonary fibrosis, and GI tract and cardiac involvement were comparably prevalent in both sexes. But renal crisis and digital ulcers occurred significantly earlier in men than women. These results indicate that vasculopathy, one of the 2 main underlying pathophysiologic processes in SSc, develops earlier in men than women, suggesting that the pattern of clinical expression in SSc depends on sex. Moreover, our data also imply that SSc progresses faster and more severely in men than in women. In one study, diagnosis of SSc after RP presentation occurred earlier in men than in women, possibly reflecting more severe expression and more rapid evolution of SSc in men[35]. Consistent with the proposal that

SSc is expressed more aggressively in men is our finding that survival rates in men were significantly lower than in women for all consecutive 3-year intervals.

The first study to search for clinical differences between men and women with SSc was published in 1996 by Simeon, *et al*[11]. In that cohort of 91 patients with SSc, prospectively followed for a mean of 5.8 years, men displayed a significantly higher prevalence of myositis and a lower prevalence of arthritis compared to women. In addition, men more frequently presented a nucleolar pattern of antinuclear antibody immunofluorescence, a finding that was significantly associated with myositis in the multiple logistic regression analysis. However, this study did not show significant sex-related survival differences.

Two additional studies published in 2011[13] and 2010[14] also reported a significant sex-related variance in the clinical manifestations of SSc. In the first of these studies[13], a higher frequency of diffuse skin involvement, lung involvement, and estimated PAH, by echocardiographic finding of PASP > 35 mm Hg, were found among men, and a higher frequency of calcinosis was found among women. In the Canadian study[14], diffuse disease subtype and renal crisis were more common in men, who also had a younger age at diagnosis compared to women. Finally, in 2 additional studies presented in abstract form[15,36], comparison of clinical expression of SSc between men and women revealed several significant differences. Specifically, myopathy, arrhythmias, and renal failure were more prevalent among men in the first study[15], and lung fibrosis, arrhythmias, and diffuse skin involvement were more prevalent among men in the second study[36]. To our knowledge, an earlier development of digital ulcers in men than in women has not been previously reported.

The limitations of our study should be addressed. Its retrospective design makes it hard to apply strict criteria for the recognition of GI tract involvement or PAH. Not all patients had undergone esophageal manometry and very few had the diagnosis of PAH confirmed by right heart catheterization. In addition, the milder course of vasculopathy in women should have been confirmed by longitudinal capillaroscopic studies. Because capillaroscopy was not routinely performed, while available data in 45 patients did not derive from the same timepoints in the course of the disease, a comparison between men and women is not meaningful.

We conclude that vasculopathy develops earlier in male patients with SSc and that survival in men is worse compared to that in women. The results support the notion that SSc is expressed more severely in men and that male sex is a poor prognostic factor in SSc, which is also the case in systemic lupus erythematosus[37]. To elucidate the possible mechanisms that underlie the excessive vasculopathy in men with SSc, further study is required of genetic, hormonal, vascular, immunologic, and environmental factors affecting the course of SSc.

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