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The limited cutaneous form of systemic sclerosis is associated with urinary incontinence: an international multicentre study

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Abstract

Objectives. The aim of this study was to explore the association between urinary incontinence (UI) and the main clinical and serological subsets of SSc, to assess risk factors for UI and its impact on quality of life (QoL).

Methods. UI and QoL were assessed through self-administered questionnaires in 334 patients with SSc from five European tertiary centres. Logistic regressions were performed to test the association between clinical forms, serological status and UI and to adjust for confounders. Further independent predefined SSc risk factors for UI were tested through a multivariable logistic model.

Results. The prevalence of UI was 63% (95% CI: 60, 68%). lcSSc and ACAs were both significantly associated with UI even after adjusting for age, sex, disability, diabetes, BMI, caffeine consumption, dyspnoea, faecal incontinence, abnormal bowel movement, presence of overlapping rheumatological disease and pulmonary hypertension [adjusted odds ratio (OR) = 2.4; 95% CI: 1.2, 4.7]. ACA and lcSSc doubled the risk of frequent and heavy urinary leaks. Factors independently associated with UI were as follows: lcSSc (OR = 2.2; 95% CI: 1.1, 3.2), ACA (OR = 2.8; 95% CI: 1.4, 5.8), female sex (OR = 10.8; 95% CI: 2.8, 41.3), worsening of dyspnoea (OR = 6.8; 95% CI: 1.2, 36.7), higher HAQ-DI (OR = 3.2; 95% CI: 1.5, 6.7), BMI (OR = 1.1; 95% CI: 1.0, 1.1) and active finger ulceration (OR = 0.3; 95% CI: 0.1, 0.7). Patients suffering from UI had decreased QoL.

Conclusion. Self-reported UI is frequent in SSc and disproportionally affects the limited cutaneous form of the disease and patients positive for ACA.

Trial registration: ClinicalTrials.gov, http://clinicaltrials.gov, NCT01971294.

Key words: systemic scleroderma, urinary incontinence, quality of life, anti-centromere antibodies

CLINICAL SCIENCE

Rheumatology key messages

- Urinary incontinence is frequent in SSc (63%) and affects the quality of life.
- SSc patients positive for ACAs are at increased risk of urinary incontinence.
- Urinary incontinence is found more often among SSc patients suffering from the limited cutaneous form.

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Introduction

SSc is characterized by vascular alterations and widespread tissue fibrosis [1]. The functional impact and prognosis varies with the extent of skin fibrosis, the antibody constellation and the affected internal organ [2, 3]. More than 60% of patients have lcSSc and 30% have dcSSc. lcSSc is associated with ACAs and has a relatively good prognosis. However, the proportion of pulmonary arterial hypertension, which is ~9% (95% CI: 6, 12%) in SSc increases in patients with ACA [3–5]. dcSSc is defined by skin involvement proximal to the elbows or knees and is preferentially associated with anti-topo I antibodies (Scl-70) and poor survival [2, 3]. Internal organs may be involved in both dcSSc and lcSSc; however, patients with dcSSc are at greater risk for clinically significant organ dysfunction [6].

Based on predictions of population ageing, it has been estimated that by 2018, 423 million individuals will be affected by urinary incontinence (UI) worldwide [7]. Furthermore, UI has been associated with many unfavourable outcomes and decline in quality of life (QoL), to the extent that two recent meta-analyses concluded that patients with UI are at higher risk of death [8, 9]. This association is probably indirect, UI being more frequent among frail individuals, but could also result from a direct association (e.g. urinary infection).

Urinary symptoms in SSc could result from two distinct, not mutually exclusive mechanisms. On the one hand, disability caused by skin sclerosis or joint contractures/inflammation [10, 11], heart and pulmonary involvement [11–13] and medication use (CSs, diuretics and opioids) [13, 14] increases the risk of lower urinary tract symptoms (LUTS). On the other hand, a few case reports [15–18] and small sample observational studies [19–21] have identified a specific fibrotic process of the urinary tract, vascular thrombosis [17, 21] and autonomic dysfunction [19] in SSc patients. Those two mechanisms should be more frequent in dcSSc, but some evidence suggests that lcSSc might increase the risk of UI [19]. However, the distribution of UI among the main forms of SSc and its prevalence are not well characterized.

The aim of the present study was to determine the difference in prevalence of UI among patients suffering from the lcSSc and dcSSc, exploring the impact of UI on QoL and finding risk factors associated with UI.

Methods

This is the first (cross-sectional) report from a longitudinal observational study exploring LUTS among individuals suffering from SSc in five European tertiary centres [Bordeaux, Paris (France), Padova, Brescia (Italy) and Geneva (Switzerland)]. The ethical committee of each participating centre approved the study protocol. Participating patients provided written consent.

Overview of the study and population

Eligible patients were individuals aged ⩾18 years and presented at the participating centres, with SSc according to the ACR/EULAR criteria [22]. Those unable to understand the rules and implications of the study, end-of-life patients, pregnant women and anuric patients were excluded.

Diagnosis of lcSSc, dcSSc or other form of SSc was made according to LeRoy *et al.* [23]. Patients were included consecutively in the participating centres. Additional participants were included during the 2015 annual meeting of the Association des Sclérodermiques de France (ASF), in Les Sables d'Olonne, France. After the consent form was signed, participants fulfilled a 30 min self-administered questionnaire on LUTS, QoL, functional status, disease activity, medication, medical history and demographic data. The self-administered questionnaire was checked for completeness and supplemented with a 5 min investigator-administered questionnaire about medication and protocol-specified co-morbid conditions. All patients, except those included during the 2015 annual meeting of the ASF, underwent a standardized physical examination. Organ involvement, presence of ACA or Scl-70 antibodies, modified Rodnan skin score, 6-min walking test, spirometry, CT of the chest and echocardiography were part of the annual clinical visit.

Symptoms and measurement

UI

UI was derived from the International conference on incontinence questionnaire female/male lower urinary tract symptoms (ICIQ-FLUTS and ICIQ-MLUTS) [24]. ICIQ-FLUTS and ICIQ-MLUTS are psychometrically robust patient-completed questionnaires for evaluating lower urinary tract symptoms and impact on QoL in research and clinical practice across the world in females and males, respectively. All questions/urinary symptoms are completed with a second question exploring how much the urinary symptom is bothersome to the subject (0–10). The questions concerning incontinence are computed in an incontinence summary subscale that is sex dependent. The methods, definitions and units conform to the standards recommended by the International Continence Society. UI was defined as any involuntary leakage of urine and subdivided into stress, urge, mixed and other UI according to a standard definition [25].

Severity of leakage was further stratified according to the quantity of urine loss (from a few drops of urine to an important leak that wets clothing) and frequency of leakages (monthly, weekly or daily leakages).

QoL and disability scores

The Short form 36 (SF-36) is a reliable measure of physical and mental health, validated for SSc [24]. The eight dimensions explored by the SF-36 were expressed in scales and summarized into physical and mental component summary scores. Each SF-36 scale is scored 0–100, with a higher score representing better health.

The incontinence quality of life (questionnaire) (I-QOL) is a self-administered questionnaire of 22 items addressing the specific impact of urinary symptoms for men and women in Italian, English and French [26]. The result is

provided within a single transformed scale ranging from 0 to 100 points. A higher score indicates a higher QoL.

Impairment and co-morbid conditions

The HAQ and Disability Index (HAQ-DI) explores eight categories of functioning, which represent a comprehensive set of functional activities [27]. The eight category scores are averaged into an overall HAQ-DI scale. The scleroderma modified HAQ has five additional visual analog scales to measure symptom activity over the last 7 days (Raynaud, digital ulcer, digestive symptoms, pulmonary symptoms and overall symptom burden) [28]. The scales are 15 cm doubly anchored horizontal visual analog scales that are scored from 0 (very well) to 100 (very poor).

Lung fibrosis was diagnosed on CT scan. Pulmonary hypertension was screened with echocardiography. Right heart catheterization was performed only when indicated according to screening protocols based on echocardiography or in the event of unexplained dyspnoea. Disease duration was defined as time since the first non-Raynaud symptom (cutaneous, musculoskeletal or SSc-related internal organ involvement).

Statistical analysis

The initial sample size of the cohort was calculated to demonstrate a 33% relative decrease prevalence of all LUTS in the lcSSc group (60% in non-lcSSc and 45% in lcSSc patients), with a two-sided significant level of 0.05 and a power of 80% [2, 3]. However, after the extension of the study to a fifth centre (Bordeaux) and to the annual meeting of the ASF, the participating centres could not reach the expected 480 participants, and 334 patients were recruited.

To test the proportion of UI between different forms of SSc, the population was divided into subgroups determined by clinically assessed lcSSc *vs* other forms of SSc. Patients with missing information on SSc subtype were excluded from this analysis. A second subdivision was made based on immunological status (presence *vs* absence of ACA). Chi-squared or exact tests were used to compare binary variables between groups when appropriate. The Mann–Whitney *U*-test was used for continuous variables. A logistic regression was used to adjust the association for potential confounders. The adjustment variables chosen were the following known risk factors for UI: age, sex, disability (HAQ-DI), diabetes, BMI, caffeine consumption $>$204 mg/day, presence of concomitant SLE, RA or SS (computed in a single binary variable), altered bowel movement (more than three stools per day or fewer than three stools per week) and faecal incontinence [8, 11, 29–34]. The final model was also adjusted for the presence of pulmonary arterial hypertension and worsening of dyspnoea, two factors associated both with UI and clinical forms of SSc and/or the presence of ACA. Continuous variables were tested for log linearity and, with the exception of BMI, were incorporated as binary variables (cut at the median). No variables were collinear or had interaction.

Five sensitivity analyses were performed to test the consistency of the associations between subgroups of SSc or ACA and UI. First, we excluded all patients included during the ASF annual meeting because some information was missing for these patients, and they might represent a subset of patients more motivated to understand their disease and physically fit enough to join an annual meeting. Second, we performed multiple imputations (see supplementary Table S1 and Multiple imputations section of supplementary data, available at *Rheumatology* Online). Third, we restricted the definition of UI to patients who scored one or more in the bother scale of any of the UI questions of the ICIQ questionnaires. Fourth, we performed a fully adjusted model including history of vaginal delivery, gynaecological/urological disease, medication use (opioids, CSs, diuretics and medication with known urinary tract side-effects) and centre of inclusion. Fifth, we excluded patients having received a medication or a surgery to correct UI, which resulted in similar results (data not shown).

Association between lcSSc or ACA and the frequency of urinary leaks or the quantity of leakage (ordinal variables) was performed through a generalized ordered logit model estimate [35]. Linear regression was used to adjust the relationship between lcSSc/ACA and the female incontinence subscale of the ICIQ questionnaire. This analysis was restricted to women, because the proportion of male participants precluded subgroup analysis.

A multivariable logistic regression model was constructed to assess risk factors of UI other than the main predictors (lcSSc/ACA). According to the number of continent patients and a requested number of 10 events per variable, we expected a maximum of five additional variables in the final adjusted model (see supplementary Table S2 and Choice of risk factors for UI section of supplementary data, available at *Rheumatology* Online) [36].

A multivariable linear regression was performed to adjust the relationship between UI and the two SF-36 summary component scores, with age, HAQ-DI, SSc overall symptom burden scale (continuous), dcSSc, use of anti-depressant, anti-psychotic or anxiolytic medication, presence of any heart or pulmonary disease and faecal incontinence (binary) [37].

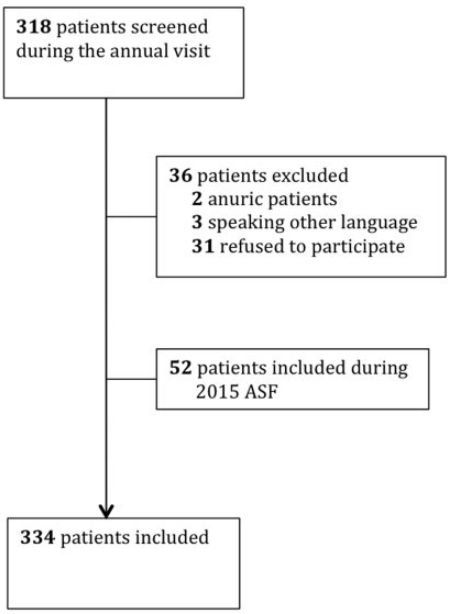
Summary scores and I-QOL were compared between different subtypes of UI through Kruskal–Wallis rank test, and adjusted with a multivariable linear regression. The significance level was set at 5%, and all analyses were performed using STATA statistical software, version 12.0 (StataCorp LP, College Station, TX, USA).

Results

Three hundred and thirty-four patients with SSc were included from January 2013 to December 2015 (Fig. 1). Patients from Brescia (102) and Paris (96) represented two-thirds of the study population. The rest of the cohort was composed of patients from Bordeaux (6), Padova (61) or Geneva (17) or who were included during the 2015 annual meeting of the ASF (52). Main characteristics of the patients are given in Table 1.

dcSSc and lcSSc were diagnosed in 134 and 178 patients, respectively. Twelve patients were classified as

Fig. 1 Flowchart of study population



ASF: 2015 annual meeting of the Association des Sclérodermiques de France.

other form of SSc [sine scleroderma (3), early SSc (1), not specified (8)], and 10 patients were not classified. ACA was present in 35% of patients and mostly among lcSSc (92%, $P < 0.001$). Anti-Scl-70 was present in 37.1% of patients, but only in 16% with lcSSc ($P < 0.001$). SS was found in 9.7% of lcSSc and in 1.8% of other SSc participants ($P = 0.011$) and was the most frequent overlapping rheumatological disease (Table 1).

UI prevalence and subtypes

The continence status was known for all except five patients (98.5%), and 63% (95% CI: 60, 68%) of the included patients were incontinent. There was no inclusion centre difference in UI proportion (see supplementary Table S3, available at *Rheumatology* Online). Incontinent patients were older, more often female, with lcSSc or with pulmonary hypertension compared with patients without UI (Table 1).

The most frequent mechanism of urinary leakage was stress UI, with 51% (95% CI: 46, 57%) of patients complaining of this symptom. Urge UI was found in 41% (95% CI: 35, 46%) of patients. The majority of patients suffered from a combination of stress and urge episodes of urinary leakage (Fig. 2). Thus, mixed UI was found in 30% (95% CI: 25, 35%) of patients.

Only 24% of the UI patients remembered having been questioned once on their urinary symptoms by their care provider. Thirty-six per cent did seek advice from their primary care physician, and 21% met a specialist dealing with UI. Overall, 7% received a medical treatment and 8% a surgery to correct UI, but only two patients were continent after treatment. Fifty-three per cent of the incontinent patients believed that UI is a normal condition of ageing.

Association between UI and the main clinical forms of SSc or ACA

UI was more frequent in patients clinically classified as having lcSSc or in patients positive for ACA (Fig. 2 and Table 2). The odds ratio (OR) for UI remained statistically significant after adjustment (Table 2). Furthermore, patients with both lcSSc and ACA were more likely to suffer from UI than patients with only one of lcSSc or ACA (OR = 2.1; 95% CI: 1.1, 3.9, $P = 0.02$; and adjusted OR = 3.4; 95% CI: 1.5, 7.8, $P = 0.004$).

lcSSc was associated with more frequent UI episodes [OR = 1.9 (95% CI: 1.2, 3.1, $P < 0.01$) for presenting daily episodes compared with weekly or monthly episodes, or for presenting weekly or daily episodes compared with monthly episodes of UI] and heavier urine loss (OR = 1.8; 95% CI: 1.1, 2.9, $P = 0.02$). The results were similar for patients with ACA and after adjustment, as well as when considering the female incontinence subscale of the ICIQ (see supplementary Table S4, available at *Rheumatology* Online).

Sensitivity analyses

The sensitivity analyses resulted in similar conclusions compared with the main analysis (Table 2). However, the associations between stress UI and lcSSc, urge UI and ACA, or mixed UI and ACA were not statistically significant through all sensitivity analyses.

Association between QoL and UI in SSc

UI was associated with a decreased QoL assessed by many of the SF-36 domains and I-QOL (Table 3). The physical component summary score of the SF-36 was 4.7 points (95% CI: 2.1, 7.3, $P < 0.001$) lower in incontinent patients. This difference was reduced to 2.3 points (95% CI: 0.2, 4.3, $P = 0.03$) after adjustment. The mental component summary score was not statistically affected by UI.

Compared with patients suffering from stress UI, participants with urge UI and mixed UI scored 6.3 points (95% CI: 0.4, 12.2, $P = 0.03$) and 13.4 points (95% CI: 8.9, 17.8, $P < 0.001$) lower in the I-QOL scale (see supplementary statistics in Table S5, available at *Rheumatology* Online). Those differences persisted after adjustment: 6.0 points (95% CI: 0.5, 11.5, $P = 0.03$) and 10.8 points (95% CI: 6.6, 15.0, $P < 0.001$), respectively.

Risk factors for UI

UI was associated with worse functional status and SSc-related symptoms, especially respiratory and digestive symptoms (Table 1). In multivariable logistic regression, six variables were independently associated with UI: ACA/lcSSc, female sex, worsening of dyspnoea, HAQ-DI, BMI and active finger ulceration (Table 4). Those results were constant across sensitivity analyses (see supplementary statistics in Table S6, available at *Rheumatology* Online).

Table 1 Main characteristics and their differences between groups with or without urinary incontinence

Variables	Whole cohort (334)	Urinary incontinence		P-value
		Present (208)	Absent (121)	
General				
Age, median (IQR), years	61 (51–68)	63 (51.5–70)	59 (48–66)	0.043
Men	42 (12.6)	9 (4.3)	31 (25.6)	<0.001
BMI, median (IQR), kg m^{-2}	23.2 (20.7–26.6)	23.6 (20.8–27.5)	22.8 (20.4–25.6)	0.139
Smoking status				
Current	25 (7.5)	18 (8.7)	7 (5.8)	
Former	118 (35.5)	66 (31.9)	48 (40.0)	0.292
Never	189 (56.9)	123 (59.4)	65 (54.2)	
Children, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	0.791
Birth, natural route, median (IQR)	1 (0–2)	2 (0–2)	1 (0–2)	0.653
Co-morbid conditions				
Other rheumatological disease	36 (12.9)	22 (13.2)	13 (12.1)	0.804
SS	18 (6.4)	9 (5.4)	8 (7.5)	
SLE	4 (1.5)	4 (1.5)	0 (0)	
RA	8 (2.9)	5 (3.0)	3 (2.8)	
Diabetes	15 (4.7)	10 (5.0)	4 (3.5)	0.777
Heart disease	61 (19.5)	38 (19.4)	21 (18.7)	0.891
Pulmonary disease	143 (45.1)	92 (46.5)	49 (43.0)	0.552
Neurological palsy[a]	17 (5.5)	13 (6.6)	4 (3.6)	0.309
Urological/gynaecological disease[b]	16 (4.5)	10 (5.1)	4 (3.6)	0.777
Faecal incontinence	78 (24.1)	62 (30.4)	16 (13.9)	0.001
Bowel movement				
<3 stools/week	27 (8.9)	19 (9.8)	8 (7.4)	
Normal	246 (81.2)	149 (77.2)	95 (88.0)	0.039
>3 stools/day	30 (9.9)	25 (12.9)	5 (4.6)	
Medication				
CSs	131 (40.6)	74 (37.2)	55 (46.2)	0.112
Diuretics	65 (20.3)	47 (23.7)	18 (15.2)	0.071
Opioids	39 (12.1)	25 (12.6)	13 (11.0)	0.651
Side-effect[c]	43 (13.4)	32 (16.2)	11 (9.3)	0.086
SSc				
dcSSc	134 (40.1)	74 (36.8)	56 (47.5)	0.062
lcSSc	178 (53.3)	123 (61.2)	54 (45.8)	0.007
ANAs	270 (97.8)	163 (98.8)	102 (96.2)	0.167
ACA	98 (35.3)	68 (41.0)	29 (27.4)	0.022
Scl-70 antibodies	103 (37.1)	60 (35.9)	41 (38.7)	0.646
Disease duration, median (IQR),[d] years	11.5 (6.3–18.1)	12.1 (6.8–19.2)	10.6 (5.3–16.1)	0.143
Age at first Raynaud symptom, median (IQR), years	43.3 (31.9–52.4)	43.3 (34.0–52.3)	42.8 (30.3–52.4)	0.667
Age at first non-Raynaud symptom, median (IQR), years	47.5 (36.7–55.7)	47.9 (38.1–56.0)	46.3 (34.9–54.4)	0.253
MRSS, median (IQR)	4.0 (2.0–10)	4.0 (2.0–9.0)	5 (2.0–11.0)	0.587
Digestive symptoms	248 (75.8)	163 (80.7)	82 (68.3)	0.012
Digital ulceration	144 (51.8)	78 (47.0)	62 (57.9)	0.077
Active ulceration	41 (14.7)	20 (12.0)	21 (19.6)	0.117
Finger-skin thickening	137 (49.6)	90 (54.2)	45 (42.9)	0.068
Synovitis	24 (8.6)	16 (9.6)	8 (7.5)	0. 547
Lung fibrosis	102 (32.4)	65 (33.0)	35 (31.0)	0.801
Pulmonary hypertension[e]	33 (10.4)	26 (13.1)	6 (5.3)	0.033
Disease activity				
Vascular worse	55 (17.4)	38 (19.4)	16 (13.9)	0.211
Skin worse	17 (5.3)	11 (5.5)	6 (5.1)	0.999
Dyspnoea worse	32 (9.9)	27 (13.5)	4 (3.4)	0.003
VAS Raynaud %, median (IQR)	30.7 (6–63.3)	36.3 (6.3–66.7)	30.0 (4.7–61.3)	0.746
VAS Finger %, median (IQR)	7.3 (0–52.7)	3.7 (0–50.0)	13.3 (0.0–62.7)	0.075
VAS Gut %, median (IQR)	10 (0–46.7)	22 (0.0–50.0)	6.7 (0.0–26.7)	0.007
VAS Lung %, median (IQR)	7 (0–42.7)	13.3 (0.0–46.7)	3.3 (0–33.3)	0.059
VAS Overall %, median (IQR)	42 (11.3–63.3)	46.7 (15.0–66.7)	32.0 (3.3–58.0)	0.035

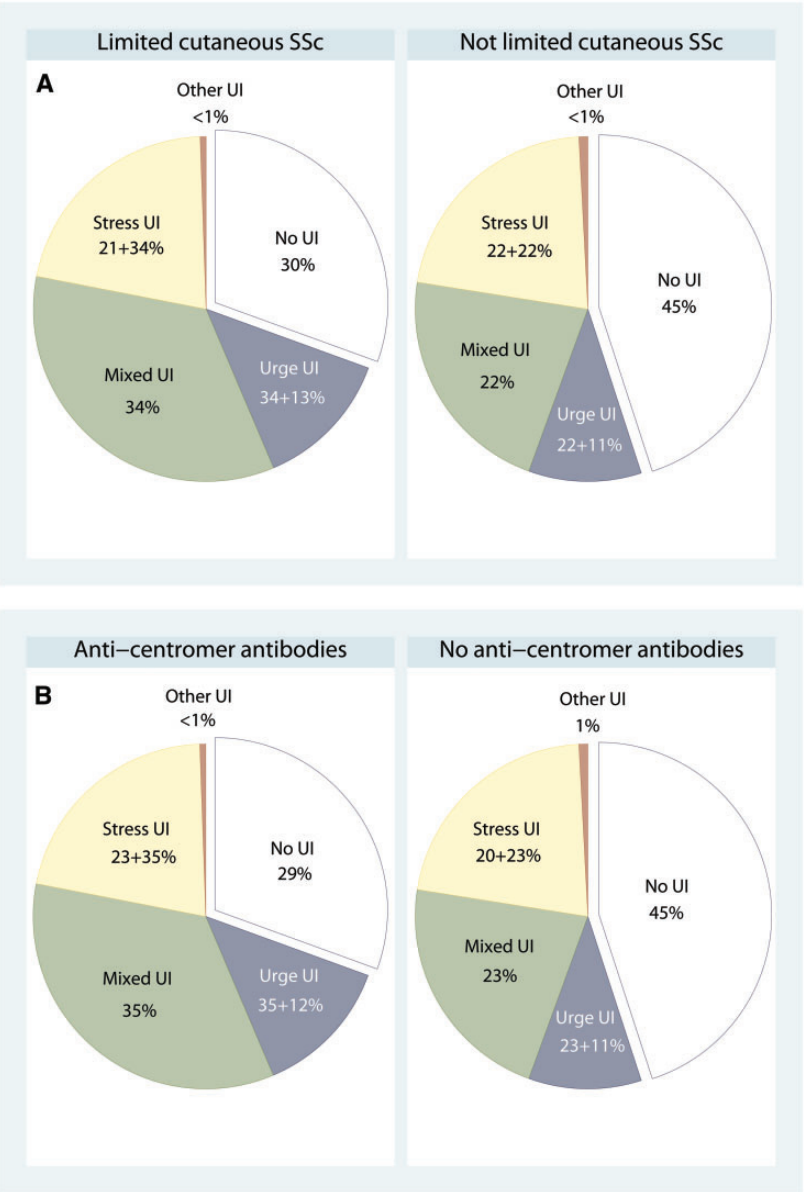
(continued)

Table 1 Continued

Variables	Whole cohort (334)	Urinary incontinence		P-value
		Present (208)	Absent (121)	
Disability				
HAQ-DI, median (IQR)	0.625 (0.125–1.25)	0. 75 (0.375–1.5)	0.375 (0.0–1.125)	<0.001
6MWT, m, median (IQR)	478 (370–538)	456 (340–520)	500 (380–574)	0.034

Values are numbers (%) unless stated otherwise. [a]Neurological disease (central or peripheral) that results in palsy. [b]Known urethral stricture, benign prostatic hyperplasia, prostatic cancer, prolapse (uterus, rectum or bladder) or bladder cancer in the past. [c]Medical drugs with known urinary side-effect (e.g. tricyclic antidepressant, anti-psychotic, anti-parkinsonian, muscle relaxant, antihistamine, antispasmodic). [d]Right heart catheterization was performed only when indicated according to screening protocols based on echocardiography or unexplained dyspnoea. [e]Defined as first non-Raynaud symptom (cutaneous, musculoskeletal or SSc-related internal organ involvement). MRSS: modified Rodnan skin score; 6MWT: 6-min walking test; VAS: visual analog scale.

Fig. 2 Prevalence of urinary incontinence



Prevalence is given by clinical subtypes of SSc (A) and presence of antibodies (B).

Table 2 Prevalence of urinary incontinence subtypes and differences between lcSSc and other forms of SSc

Type of UI	Prevalence of UI, % (95% CI)		OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR[b] (S1)	Adjusted OR[b] (S2)	Adjusted OR[b] (S3)	Adjusted OR[b,c] (S4)
	lcSSc	Other SSc						
Any UI	69 (63, 76)	55 (47, 63)	1.9 (1.2, 3.0)	2.4 (1.2, 4.7)	2.4 (1.2, 4.7)	2.2 (1.2, 4.0)	2.8 (1.4,5.6)	2.5 (1.1, 5.4)
Urge	47 (40, 55)	33 (25, 40)	1.9 (1.2, 2.9)	3.5 (1.7, 7.1)	3.5 (1.7, 7.1)	2.1 (1.2, 3.7)	4.1 (1.9, 8.6)	6.2 (2.5, 15.4)
Stress	57 (49, 64)	43 (35, 52)	1.7 (1.1, 2.7)	1.7 (0.9, 3.4)	1.7 (0.9, 3.4)	2.1 (1.2, 3.7)	2.1 (1.1, 4.2)	1.7 (0.8, 3.5)
Mixed	35 (28, 42)	22 (15, 29)	1.9 (1.1, 3.1)	3.3 (1.5, 7.2)	3.3 (1.5, 7.2)	2.3 (1.3, 4.2)	3.8 (1.6, 8.7)	4.9 (1.9, 12.9)
Nocturnal enuresis	9 (4, 13)	7 (3, 12)	1.1 (0.5, 2.5)	1.1 (0.3, 3.8)	1.1 (0.3, 3.8)	1.4 (0.6, 3.3)	1.5 (0.4, 5.3)	1.2 (0.3, 5.0)
	ACA	No ACA						
Any UI	70 (61, 79)	56 (49, 63)	2.0 (1.2, 3.4)	2.7 (1.4, 5.4)	2.7 (1.4, 5.4)	2.2 (1.2, 4.0)	1.9 (1.1, 3.6)	2.8 (1.3, 5.8)
Urge	46 (36, 56)	32 (25, 39)	1.9 (1.1, 3.2)	2.2 (1.2, 4.1)	2.2 (1.2, 4.1)	1.6 (0.9, 2.7)	2.1 (1.1, 4.0)	2.2 (1.1, 4.3)
Stress	58 (48, 68)	43 (36, 51)	1.9 (1.1, 3.1)	2.1 (1.1, 4.0)	2.1 (1.1, 4.0)	2.0 (1.1, 3.6)	1.9 (1.1, 3.6)	2.2 (1.1, 4.3)
Mixed	34 (25, 44)	21 (15, 27)	2.1 (1.2, 3.7)	2.2 (1.1, 4.4)	2.2 (1.1, 4.4)	1.7 (0.9, 3.1)	2.4 (1.2, 4.8)	2.3 (1.1, 4.7)
Nocturnal enuresis	9 (3, 15)	6 (3, 10)	1.5 (0.6, 3.8)	1.1 (0.3, 3.8)	1.1 (0.3, 3.8)	1.5 (0.6, 3.8)	1.3 (0.4, 4.4)	1.0 (0.3, 3.7)

Prevalence of UI is also compared between patients with and without ACA. [a]OR of UI for lcSSc *vs* other SSc or presence *vs* absence of ACA. [b]Adjusted for age, sex, disability, dyspnoea, diabetes, BMI, caffeine consumption, pulmonary hypertension, faecal incontinence, abnormal bowel movement (normal *vs* more than three stools per day *vs* fewer than three stools per week) and presence of other rheumatological disease. [c]Adjusted for history of vaginal delivery, gynaecological/urological disease, medication use (CSs, opioids, diuretics and medication with known urinary tract side-effects) and centre of inclusion. OR: odds ratio; S1: sensitivity analysis 1: exclusion of the 2015 annual meeting of the Association des Sclérodermiques de France patients; S2: sensitivity analysis 2: multiple imputation; S3: sensitivity analysis 3: restriction of UI definition to UI with impact on the bother scale. UI: urinary incontinence; S4: sensitivity analysis 4: model with complete adjustment.

Discussion

This international multicentre study demonstrates that self-reported UI is frequent in SSc (63%) and disproportionally affects the limited cutaneous form of the disease or patients positive for ACAs. lcSSc and ACA are further associated with frequent and heavy urine loss.

Involvement of the urinary tract in SSc was once believed to be rare [17]. The first reports were based on post-mortem examinations [38] or urodynamic measures [20, 39]. However, changes in bladder volume and function can be found in more than two-thirds of SSc patients when compared with healthy controls [20]. Fibrosis affects the bladder wall [21, 40] and/or urethra [15]. The pattern of deposition of fibrosis probably explains the two morphological extremes seen among SSc patients: a small, thick and not compliant bladder or a large hypoactive bladder. Vascular anomalies have also been reported. These anomalies could sometimes cause severe micro- or macro-haematuria [17, 21]. The above studies revealed frequent changes in the urinary tract. However, there are discrepancies between bladder histology, urodynamic anomalies and symptoms [17, 19].

The prevalence and type of UI found in the present cohort (mostly women) suffering from SSc is in accordance with smaller recent reports [41–43]. It seems higher than the prevalence found among the general population or among other rheumatological diseases (see supplementary Fig. S1, available at *Rheumatology* Online), but this observation deserves a direct comparison using the same instrument and adjusting for confounders.

In addition to disability, increased BMI, dyspnoea or female sex, which are also risk factors in non-SSc patients [30], this study revealed that SSc-related factors (clinical form and antibodies) affect continence. The increased proportion of UI in lcSSc or in patients positive for ACA cannot be explained solely by the burden of

Table 3 Quality of life by presence of urinary incontinence

Quality of life measure	No UI (121)	Any UI (208)
SF-36 domains		
Physical functioning	70 (50, 95)	55 (35, 75)**
Role physical	62.5 (0, 100)	25 (0, 75)*
Bodily pain	52 (41, 84)	46.5 (41, 72)*
General health	42 (30, 62)	38.5 (25, 52)*
Vitality	50 (35, 65)	45 (30, 55)*
Social functioning	60 (40, 70)	50 (40, 70)
Mental health	68 (56, 72)	60 (56, 68)*
Role emotional	100 (33.3, 100)	66.7 (0, 100)*
SF-36 component summary		
Physical	41.5 (31.9, 50.6)	36.3 (28.0, 43.9)**
Mental	46.2 (38.2, 50.5)	42.5 (35.9, 49.7)
SF-36 Health transition		
Feel better, n (%)	27 (22.5)	57 (28.9)
The same, n (%)	69 (57.5)	99 (50.2)
Worse than last year, n (%)	24 (20)	41 (20.8)
I-QOL		
Score	100 (98.2, 100)	92.7 (81.4, 98.2)**

Values are numbers (95% CI) unless stated otherwise. *$P < 0.05$; **$P < 0.001$. I-QOL: incontinence quality-of-life questionnaire; SF-36 MCS; the 36-item short form health survey, mental component summary; SF-36 PCS: the 36-item short form health survey, physical component summary; UI: urinary incontinence.

Table 4 Multivariable logistic regressions of risk factors for urinary incontinence

Predictors	Univariate analysis	Multivariable model	
		lcSSc	ACA
Main predictor			
ACAs	2.01 (1.18, 3.41)	–	2.79 (1.35, 5.77)
lcSSc	1.87 (1.13, 3.23)	2.16 (1.04, 4.48)	–
SSc-related factors			
Finger-skin thickening	1.58 (0.96, 2.58)	NS	NS
Dyspnoea worse (%)	4.45 (1.52, 13.05)	6.77 (1.25, 36.73)	7.45 (1.34, 41.33)
Digital ulceration			
Past	0.69 (0.40, 1.18)	NS	NS
Active	0.48 (0.23, 0.97)	0.27 (0.10, 0.73)	0.23 (0.09, 0.61)
Gastro-oesophageal symptoms	1.91 (1.07, 2.68)	NS	NS
Faecal incontinence	2.70 (1.47, 4.95)	NS	NS
Abnormal bowel movement			
Fewer than three stools per week	1.51 (0.64, 3.60)	NS	NS
More than three stools per day	3.19 (1.18, 8.61)	NS	NS
Adjustment variables			
>60 years old	1.30 (0.83, 2.04)	NS	NS
Men	0.13 (0.06, 0.29)	0.09 (0.02, 0.35)	0.07 (0.02, 0.27)
BMI	1.03 (0.98, 1.08)	1.07 (1.01, 1.15)	1.08 (1.01, 1.15)
HAQ-DI more than the median	2.71 (1.07, 4.30)	3.17 (1.49, 6.72)	3.14 (1.49, 6.63)
Caffeine consumption[a]	1.15 (0.72, 1.84)	NS	NS
Diabetes	1.43 (0.44, 4.66)	NS	NS
Presence of overlapping rheumatological disease	1.10 (0.53, 2.28)	NS	NS

Values are odds ratio (95% CI) unless stated otherwise. [a]More than 204 mg/day of caffeine. HAQ-DI: HAQ-Disability Index; NS: not statistically significant; VAS: visual analog scale.

co-morbidities, the prevalence of other rheumatological disease, concomitant gastrointestinal involvement, the presence of pulmonary arterial hypertension or the worsening of dyspnoea. Autonomic nervous system dysfunction, which has been shown to be frequent in SSc patients, is a promising candidate to fill the gap and explain the association [19]. Indeed, antibodies inhibiting parasympathetic neurotransmission have been shown to be directly responsible of urinary symptoms in another autoimmune disease (SS) [44]. However, further studies are needed to understand the real physiopathology of UI in SSc and test this hypothesis.

An increase in UI among patients with lcSSc and patients positive for ACA was not observed in previous reports. The difference could result from the fact that previous studies were all underpowered, used very different instruments to measure UI and explored the association between lcSSc/ACA and the presence of any lower urinary tract symptoms [42], only severe urinary tract symptoms (Urogenital Distress Inventory > 6) [43] or without adjustment [41].

Urinary symptoms are seldom reported spontaneously and are rarely part of a systemic evaluation [45]. In the present report, a minority of UI patients had sought medical attention for urological complaints. The reason could be that in a threatening disease, assessment of urinary symptoms might seem to be of low priority. Another explanation could be the false belief that UI is a normal process of ageing. LUTS have a real impact on many aspects of everyday living. Urinary tract involvement might predispose to urinary tract infection because of flow limitation and stagnation, which has been associated with mortality [8]. In this cohort, the QoL of SSc patients suffering from UI was statistically lower that seen in SSc patients without UI. However, after adjustment, the difference in the physical summary score was small and probably not clinically relevant [46].

The present study presents some limitations. First, the predefined sample size was not reached, and this could have affected the statistical power of the analysis. However, the latter was calculated based on the proportion of LUTS and characteristics of the EULAR scleroderma trial and research group population previously published; two assumptions that did not reflect the reality of the studied population. The resulting statistical power turned out to be better than expected. Second, we included patients during the annual meeting of the ASF, which could cause a selection bias. However, excluding those patients from the analysis did not alter the conclusions. Third, we used a subjective self-administered questionnaire to measure UI and its severity, and we performed no urodynamic exploration or pad test to confirm UI. However, the ICIQ questionnaires have been correlated with those objective measures of UI in other studies [47, 48]. ICIQ questionnaires are highly recommended to measure UI symptoms in men and women. Moreover,

the sensitivity analysis restricted to bothersome UI, as measured in the bother scale of the ICIQ, resulted in similar results to the main analysis. Finally, we did not include a control group, and thus comparison of UI prevalence between SSc and other populations cannot be assessed formally.

Conclusion

UI is frequent in SSc, especially among patients suffering from the limited cutaneous form of the disease and those positive for ACAs.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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