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ORIGINAL ARTICLE

Prevalence and Disease-Specific Risk Factors for Lower Urinary Tract Symptoms in Systemic Sclerosis: An International Multicenter Study

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Objective. **To determine the prevalence of lower urinary tract symptoms (LUTS) in systemic sclerosis (SSc), to find specific risk factors, and to assess their impact on quality of life (QoL).**

Methods. **In a multicenter study, 334 patients completed a self-administered questionnaire on LUTS and QoL. LUTS were classified into 3 main categories: storage, voiding, and post-micturition symptoms. Digestive symptoms burden was captured by a visual analog scale, divided into 5 equal categories. Multivariable logistic regressions were performed to test association between risk factors and LUTS categories. Linear regression adjusted the association between LUTS and QoL.**

Results. **LUTS were recorded in 311 SSc patients (96.0%) and classified as severe in 120 (38.0%). The storage category of LUTS was the most prevalent (91.9%), followed by voiding (72.2%) and then by post-micturition symptoms (49.8%). Risk factors identified in the multivariable models were higher than the median Health Assessment Questionnaire disability index (HAQ DI; odds ratio [OR] 4.2 [95% confidence interval (95% CI) 1.4–12.9]) in the storage category; higher than the median HAQ DI (OR 2.4 [95% CI 1.2–4.9]) for digestive symptoms burden (OR 1.9 [95% CI 1.3–2.7]) and synovitis (OR 4.8 [95% CI 1.0–22.6) in the voiding category; and higher for digestive symptoms burden (OR 1.2 [95% CI 1.0–1.5]) in the post-micturition category of symptoms. These factors also increased the odds of having further severe symptoms. QoL was affected by the 3 categories of LUTS and decreased progressively with increasing frequency of symptoms.**

Conclusion. **Self-reported LUTS are among the most frequent symptoms in SSc and are associated with digestive symptoms. SSc patients with LUTS have lower QoL.**

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease driven by microvascular dysfunction and excessive synthesis of extracellular matrix (1). Antibodies specificities, extent of skin and internal organ involvement, functional consequences, complications, and prognosis distinguish the limited cutaneous (lcSSc) from the diffuse cutaneous (dcSSc) subset of systemic sclerosis (2–6). Of all the organ systems affected by the disease, the urinary tract has been poorly explored, and only small studies have reported on the prevalence of lower urinary tract symptoms (LUTS) (7,8).

Normal micturition requires coordination among the muscles of the bladder (detrusor), the sphincter mechanism, and the central, autonomic, and somatic nervous systems. This complex process may be affected by many urologic and nonurologic conditions in SSc. In fact, alterations in bladder volume have been found in more than two-thirds of patients when compared to healthy controls (9). The bladder may be small, thick, and noncompliant or large and hypoactive, depending on the fibrosis of the bladder wall (10,11) or urethra (12). Vascular abnormalities are also seen and can cause severe hematuria (11,13). Moreover, SSc exposes patients to many nonurologic conditions that are associated with LUTS. Disability secondary to muscle wasting, joint stiffness/inflammation, or skin fibrosis could affect coordination between the different micturition phases (e.g., the ability to void urine time-appropriately) and abdominal pressure

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Significance & Innovations

- Self-reported lower urinary tract symptoms (LUTS) are among the most frequent symptoms in systemic sclerosis (SSc) (96%).
- LUTS are described as severe by more than one-third of patients with SSc.
- Digestive symptoms and disability are associated with LUTS.
- SSc patients with LUTS have a lower quality of life.

(14,15). Lung and heart disease increase diuresis through fluid retention and diuretics use, and also impact micturition by increasing abdominal pressure through respiratory efforts and coughing (7,16). Gastrointestinal symptoms, which are seen frequently in SSc, are associated with LUTS (7,16). The involvement of the parasympathetic system probably plays a major role in such an association in SSc (17,18).

LUTS are classically grouped into 3 main categories: storage/filling, voiding, and post-micturition symptoms (19). Storage symptoms are related to the filling phase of the bladder and encompass increased daytime frequency (or pollakisuria), nocturia (the need to wake up 1 or more times per night to void), urgency (sudden compelling desire to pass urine that is difficult to defer), and urinary incontinence (any involuntary leakage of urine) (19). Voiding symptoms are experienced during micturition and may consist of a slow stream, straining (muscular effort needed to initiate or maintain the urinary stream), terminal dribble, intermittent stream, or hesitancy (difficulty in initiating micturition, resulting in a delay in the onset of voiding) (19). The complaints of incomplete emptying and post-micturition dribble (involuntary loss of urine immediately after having finished passing urine) are regrouped in post-micturition symptoms and are experienced just after voiding.

The associations between LUTS and the SSc main clinical subsets, i.e., the severity of skin fibrosis, vascular phenomena, digestive symptoms, pulmonary involvement, and disability, are unknown. The present study aimed to determine the prevalence of LUTS among SSc patients using a validated questionnaire, to find SSc-specific risk factors associated with storage/filling, voiding, or post-micturition symptoms, and to assess these symptoms' impact on quality of life (QoL).

PATIENTS AND METHODS

Overview of the study and patient population. All patients ages 18 years and older with a diagnosis of SSc who presented for a medical appointment at one of the tertiary participating centers in Bordeaux (France), Paris (France), Padua (Italy), Brescia (Italy), or Geneva (Switzerland) were asked to participate in the study. Those who were unable to understand the rules and implications of the study, patients receiving end-of-life care, pregnant women, and anuric patients were excluded. Most patients were included consecutively during their yearly visit. Participants were also recruited during the 2015 annual meeting of the Association des Sclérodermiques de France (ASF) in Les Sables d'Olonne, France. The ethics committee at each of the participating centers approved the study protocol. All included individuals gave written informed consent.

Participants completed a 30-minute self-administered questionnaire on LUTS, QoL, functional status, and disease activity, and a 5-minute investigator-administered questionnaire on medication, medical history, and demographic data. All patients except those included during the 2015 ASF annual meeting underwent a standardized physical examination including modified Rodnan skin thickness score (MRSS), 6-minute walking test, spirometry, echocardiography, and, when appropriate, computed tomography of the chest and/or right/left catheterization. Organ involvement was captured in a standardized questionnaire used by all centers. The presence of antinuclear, anticentromere, and anti–Scl-70 antibodies was determined via the medical database.

Symptoms and measurements. *LUTS.* The International Consultation on Incontinence Modular Questionnaire, long forms ([ICIQ-LF], female version and male version), are psychometrically robust patient-completed questionnaires for evaluating female and male LUTS and the impact of LUTS on QoL in research and clinical practice around the world (20). They explore LUTS for the last 4 weeks in 18 and 21 items, respectively. LUTS were defined and regrouped into 3 main categories (storage/filling, voiding, and post-micturition symptoms) according to a standard definition (19).

The severity of LUTS is related to its frequency and is self-rated for all symptoms in the ICIQ questionnaires as occurring occasionally, sometimes, most of the time, and all of the time. Symptoms were dichotomized on the basis of the frequency of symptoms, with symptoms classified as severe if participants answered "most of the time" or "all of the time" and mild if participants answered "occasionally" or "sometimes." Moreover, 3 sex-specific subscales, i.e., filling symptoms subscale, voiding symptoms subscale, and incontinence symptoms subscale, are computed in the ICIQ questionnaire (20).

SSc classification and symptoms. Diagnosis and classification in lcSSc, dcSSc, or other forms of SSc was done in accordance with Le Roy et al (21). SSc history, organ involvement (heart, lung, pulmonary arteries), skin extent, and antibodies were defined using standard criteria (22). Worsening of skin, Raynaud's phenomenon or cardiopulmonary symptoms were self-rated as binary variables. Digestive symptoms were explored through binary questions on the presence of esophageal (reflux, dysphagia), gastric (vomiting, early satiety), intestinal (bloating, diarrhea, constipation) symptoms, and fecal incontinence. The number of stools passed per day/week was also noted.

QoL and disability scores. The 36-item Short Form health survey (SF-36) is a reliable measure of physical and mental health, validated for use in SSc (23,24). The 8 dimensions (physical functioning, role physical, bodily pain, general health, vitality, social functioning, mental health, and role emotional) explored by the SF-36 were expressed in scales and summarized as physical component summary (PCS) and mental component summary (MCS) scores. Each scale is scored 0–100, with higher scores representing better health.

The Health Assessment Questionnaire disability index (HAQ DI) explores 8 categories of functioning, which represent a comprehensive set of functional activities (23–25). The scleroderma modified HAQ has 5 additional visual analog scales (VAS) to measure symptom activity over the last 7 days (Raynaud's phenomenon, digital ulcers, digestive symptoms, pulmonary symptoms, and overall symptoms burden) (26). The scales are 15-cm doubly anchored horizontal VAS scored from 0 (very well) to 100 (very poor). VAS were divided into 5 equal categories (of 20% increments each).

Statistics. The sample size was calculated to demonstrate a 33% relative difference of LUTS between the main clinical subsets of SSc, with a 2-sided level of significance of 0.05 and a power of 80%. Expecting LUTS in 45% of participants with lcSSc and 60% in other SSc participants, we initially planned to include 480 SSc patients (2,6).

The proportion of LUTS was compared across age and sex groups with chi-squared or exact tests when appropriate. A logistic regression–adjusted association between LUTS (binary) and SSc-related factors and an ordered logistic regression were used to test these factors on LUTS frequency/severity (ordinal variables). The SSc-related variables to be tested as potential risk factors for each LUTS category were chosen according to previous publications and the rationale described above (15,16,27–33). We assessed functional disability and articular involvement, digestive symptoms and burden (VAS), skin fibrosis and extent (MRSS), vascular anomalies and burden (VAS), and cardiopulmonary disease and severity of symptoms (VAS). Anticentromere antibodies (ACAs; recently found to be associated with urinary incontinence) (33), Scl-70, and the presence of other autoimmune diseases known to be potentially associated with antibodies against muscarinic receptors expressed in the bladder (17) were also explored. These factors were adjusted for age, sex, body mass index, presence of concomitant diabetes mellitus, urogenital disease, or neurological palsy, medication (corticoids, diuretics, opioids, or treatments with known LUTS side effects), and, for women, number of vaginal deliveries. Associated variables were entered into a multivariable logistic regression model. Continuous variables were tested for log linearity and incorporated as binary variables (cut in the median except for MRSS), or as categorical variables (e.g., VAS) as required. The cutoff for MRSS (cutoff = 14) was chosen to be similar to the one used in the European Scleroderma Study Group activity index (34).

The 8 dimensions of QoL were compared through the severity strata of LUTS categories with the Kruskal-Wallis test and the test for trend and presented in a radar graph. The radar graph allows for the appreciation of the effect of a factor on the different domains of the SF-36 in a single graph and has previously been used for that purpose in rheumatologic research (35). Linear regression and multivariate linear regression were used to adjust the association between LUTS and the PCS and MCS of the SF-36. Adjustment factors were chosen according to a published meta-analysis and previous reports: age, VAS of overall SSc symptom burden (continuous), dcSSc, use of antidepressant, antipsychotic, or anxiolytic medication, presence of heart or pulmonary disease, and fecal incontinence (binary) (33,36,37).

Table 1. Main characteristics of included patients*

No.	334
Age, median (IQR) years	61 (51–68)
Women	292 (87.4)
Body mass index, median (IQR), kg/m^2	23.2 (20.7–26.6)
Smoking status	
Current	25 (7.6)
Former	118 (35.5)
Never	189 (56.9)
Children, median (IQR)	2 (1–2)
Natural births, median (IQR)	1 (0–2)
Comorbid conditions	
Gastrointestinal symptoms†	266 (80)
Esophageal	215 (65.7)
Gastric	111 (33.9)
Intestinal	53 (16.2)
Fecal incontinence	78 (24.2)
Heart disease‡	61 (19.5)
Pulmonary disease§	143 (45.1)
Lung fibrosis	102 (32.4)
Pulmonary hypertension	33 (10.4)
Chronic obstructive pulmonary disease	19 (6.0)
Diabetes mellitus	15 (4.7)
Neurologic disease with palsy¶	17 (5.5)
Urologic/gynecologic disease#	16 (4.5)
Medication	
Corticoids	131 (40.6)
Diuretics	65 (20.3)
Opioids	39 (12.1)
Drugs with known urinary side effects**	43 (13.4)
SSc	
Diffuse cutaneous SSc	134 (40.1)
Limited cutaneous SSc	178 (53.3)
Antinuclear antibodies	270 (97.8)
ACA	98 (35.3)
Scl70 antibodies	103 (37.1)
MRSS, median (IQR)	4.0 (2.0–10)
Digital ulceration	144 (51.8)
Finger-skin thickening	137 (49.6)
Synovitis	24 (8.6)
HAQ DI, median (IQR)	0.625 (0.125–1.25)

* Values are the number (percentage) unless otherwise indicated. IQR = interquartile range; SSc = systemic sclerosis; ACA = anticentromere antibodies; MRSS = modified Rodnan Skin Score; HAQ DI = Health Assessment Questionnaire disability index.
† Number (percentage) of patients suffering from at least 1 symptom/disease composing the category. Since multiple symptoms/diseases are possible, the sum of each category is not always the sum of all items that compose the category. Gastrointestinal symptoms was composed of the following binary items: esophageal symptoms (reflux disease or dysphagia), gastric symptoms (vomiting or early satiety), intestinal symptoms (bloating, diarrhea, or constipation), and fecal incontinence.
‡ Any documented heart failure, arrhythmias, or ischemic heart disease.
§ Number (percentage) of patients suffering from at least 1 symptom/disease composing the category. Since multiple symptoms/diseases are possible, the sum of each category is not always the sum of all items that compose the category.
¶ Neurologic disease (central or peripheral) that results in palsy.
# Known urethral stricture, benign prostatic hyperplasia, prostatic cancer, prolapse (uterus, rectum, or bladder), or bladder cancer in the past.
** Tricyclic antidepressant, antipsychotic, anti-Parkinsonian, muscle relaxant, antihistamine, or antispasmodic drugs.

Two sensitivity analyses were performed. The first analysis excluded patients from the ASF annual meeting to test the consistency of the associations between potential risk factors and LUTS. The second adjusted the associations between LUTS and QoL for disability (HAQ DI). The significance level was set at 5% and all analyses were performed using Stata, version 12.0.

RESULTS

The participating centers recruited 334 patients from January 2013 to December 2015 (102 in Brescia, 96 in Paris, 61 in Padua, 17 in Geneva, 6 in Bordeaux, and 52 during the 2015 annual meeting of the ASF). The main characteristics of the patients are shown in Table 1. The dcSSc subtype was seen in 40% of patients, lcSSc in 53%, other forms of SSc in 4%, and 3% were unclassified.

LUTS prevalence and subtypes. LUTS questionnaires were available for all except for 5 patients (98.5%). Patients without information did not differ by age, sex, or clinical presentation compared to patients with available LUTS information. LUTS prevalence by age category for women and men is shown in Table 2 and Table 3, respectively. Except for daytime frequency for both sexes, straining for women, and intermittency and incomplete emptying for men, the proportion of most symptoms was constant across age categories. Slow stream (P = 0.012), hesitancy (P = 0.029), and alguria (P = 0.026) were statistically different between men and women.

Only 4% (95% confidence interval [95% CI] 1.9–6.2) of participants reported no LUTS symptoms. Patients had a median of 6 LUTS (interquartile range 3–8), which affected the 3 LUTS categories in 45.4% (95% CI 39.9–50.8), 2 of the 3 categories in 27.5% (95% CI 22.6–32.3), and a single category in 23.1% of participants (95% CI 18.5–27.8). The most frequent LUTS category was storage symptoms (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). Post-micturition symptoms alone were reported very rarely (only 1 participant); 98.2% and 92.5%, respectively, had additional storage or voiding symptoms. Similarly, 95.3% of patients with voiding symptoms had storage symptoms or post-micturition symptoms as well (Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

Of patients with LUTS, 38.0% (95% CI 32.6–43.3) reported at least 1 symptom occurring most of the time or all of the time (Figure 1 and Supplementary Table 1, at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). When considered individually, the most frequent LUTS was nocturia, followed by urinary incontinence for women and terminal dribble for men (Table 2 and Table 3).

Association between SSc-related factors and LUTS categories. There was no association between ACA and the 3 main categories of LUTS (see Supplementary Table 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). The unadjusted association between the potential SSc-related

Table 2. LUTS in women, by age group and according to International Conference on Incontinence standards*

	Entire cohort (n = 292)	Age group, years			
		<50 (n = 68)	50–59 (n = 64)	60–69 (n = 93)	≥70 (n = 67)
Any storage symptom	92.8 (89.8–95.7)	89.5 (82.0–97.1)	93.8 (87.6–99.8)	92.5 (87.0–97.9)	95.5 (90.4–100)
Increased daytime frequency	30.1 (24.8–35.4)	28.4 (17.3–39.4)	44.4 (31.8–57.1)	22.6 (13.9–31.2)	28.8 (17.6–40.0)†
Nocturia	74.5 (69.3–79.8)	62.7 (50.8–74.6)	73.0 (61.7–84.3)	79.6 (71.2–87.9)	80.6 (70.9–90.3)
Urgency	62.6 (57.0–68.2)	60.6 (48.5–72.7)	68.7 (57.1–80.4)	58.7 (48.4–68.9)	64.2 (52.4–76.0)
Incontinence	68.8 (63.5–74.2)	62.1 (50.1–74.1)	73.4 (62.3–84.6)	65.2 (55.3–75.1)	76.1 (65.6–86.6)
Any voiding symptom	71.0 (65.7–76.3)	72.3 (61.1–83.5)	67.7 (55.8–79.7)	66.3 (56.5–76.1)	79.1 (69.1–89.0)
Slow stream	27.1 (21.9–32.3)	16.7 (7.4–25.9)	24.5 (13.5–35.7)	32.9 (23.1–42.8)	31.8 (20.3–43.3)
Straining	24.5 (19.5–29.5)	12.1 (4.0–20.2)	31.7 (19.9–43.6)	23.9 (15.0–32.8)	30.8 (19.2–42.3)†
Terminal dribble	52.2 (46.4–58.1)	60.6 (48.5–72.7)	46.8 (34.0–59.5)	47.3 (36.8–57.7)	56.1 (43.8–68.4)
Intermittent stream	42.9 (37.2–48.7)	46.1 (33.7–58.6)	34.4 (22.1–46.7)	38.5 (28.3–48.6)	53.7 (41.5–66.0)
Hesitancy	28.1 (22.8–33.3)	29.2 (17.9–40.6)	29.5 (17.7–41.3)	22.8 (14.1–31.6)	32.8 (21.3–44.4)
Any post-micturition symptom	50.3 (44.5–56.2)	48.5 (36.1–60.9)	60.3 (47.9–72.7)	43.9 (33.6–54.3)	51.5 (39.1–63.9)
Incomplete emptying	40.2 (34.5–45.9)	37.9 (25.9–49.9)	47.6 (34.9–60.3)	37.4 (27.2–47.5)	39.4 (27.3–51.5)
Post-micturition dribble	52.3 (46.4–58.1)	60.6 (48.5–72.7)	46.8 (34.0–59.5)	47.3 (36.8–57.7)	56.1 (43.8–68.3)
Other symptoms/syndrome					
Bladder pain	27.8 (22.6–33.0)	24.6 (13.9–35.4)	40.6 (28.3–53.0)	23.9 (15.0–32.8)	23.9 (13.4–34.3)
Alguria	37.3 (31.6–42.9)	34.8 (23.0–46.6)	50 (37.2–62.8)	35.9 (25.9–45.8)	29.8 (18.6–41.1)
Urinary retention	3.8 (1.6–6.1)	3.1 (0.0–7.3)	0.0 (–)	4.3 (0.1–8.6)	7.5 (1.0–13.9)
Painful bladder syndrome‡	24.9 (19.9–29.9)	21.2 (11.1–31.3)	35.9 (23.9–48.0)	21.2 (13.1–30.3)	22.4 (12.1–32.6)
Overactive bladder§	66.1 (60.6–71.6)	63.6 (51.7–75.6)	70.3 (58.8–81.8)	63.0 (53.0–73.1)	68.7 (57.3–80.1)

* Values are the percentage (95% confidence interval). LUTS = lower urinary tract symptoms.
† $P < 0.05$ by chi-square test across age categories.
‡ Characterized by suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology.
§ Defined as urgency, with or without incontinence, usually with frequency or nocturia.

Table 3. LUTS in men by age group and according to International Conference on Incontinence standards*

	Entire cohort (n = 42)	Age group, years			
		<50 (n = 11)	50–59 (n = 14)	60–69 (n = 6)	≥70 (n = 11)
Any storage symptom	85.4 (74.1–96.7)	90.9 (70.6–100)	71.4 (44.4–98.5)	100	90.0 (67.4–100)
Increased daytime frequency	45.0 (28.9–61.1)	27.3 (0.0–58.6)	23.1 (0.0–49.6)	83.3 (40.5–100)	70.0 (35.4–100)†
Nocturia	77.5 (63.9–91.0)	72.7 (41.3–100)	69.2 (40.2–98.2)	83.3 (40.5–100)	90.0 (67.4–100)
Urgency	55.0 (38.9–71.1)	27.3 (0.0–58.6)	42.8 (13.2–72.5)	100 (–)	77.8 (43.9–100)
Incontinence	22.5 (9.0–36.0)	27.2 (0.0–58.6)	14.3 (0.0–35.3)	33.3 (0.0–87.5)	22.2 (0.0–56.1)
Any voiding symptom	80.5 (67.8–93.1)	63.6 (29.7–97.5)	71.4 (44.4–98.5)	100 (–)	100 (–)
Slow stream	46.3 (30.4–62.3)	27.3 (0.0–58.6)	50.0 (20.0–79.9)	66.7 (12.5–100)	50.0 (12.3–87.7)
Straining	31.7 (16.8–46.6)	18.2 (0.0–45.4)	50.0 (20.0–79.9)	50.0 (0.0–100)	10.0 (0.0–32.6)
Terminal dribble	63.4 (48.0–78.8)	54.5 (19.5–89.6)	64.3 (35.6–93.0)	66.7 (12.5–100)	70.0 (35.4–100)
Intermittent stream	52.5 (36.3–68.7)	9.1 (0.0–29.3)	61.5 (30.9–92.1)	83.3 (40.5–100)	70.0 (35.4–100)†
Hesitancy	45.0 (28.8–61.1)	27.3 (0.0–58.6)	46.1 (14.8–77.5)	83.3 (40.5–100)	40.0 (3.1–76.9)
Any post-micturition symptom	46.3 (30.4–62.3)	36.4 (2.4–70.3)	42.9 (13.2–72.5)	83.3 (40.5–100)	40.0 (3.1–76.9)
Incomplete emptying	34.1 (19.0–49.3)	9.1 (0.0–29.3)	28.6 (1.5–55.6)	83.3 (40.5–100)	40.0 (3.1–76.9)†
Post-micturition dribble	63.4 (48.0–78.8)	54.5 (19.5–89.6)	64.3 (35.6–93.0)	66.7 (12.5–100)	70.0 (35.4–100)
Other symptoms/syndrome					
Bladder pain	15.0 (3.4–26.6)	9.1 (0.0–29.3)	28.6 (1.5–55.6)	16.7 (0.0–59.5)	0.0 (–)
Alguria	19.0 (6.8–32.2)	27.3 (0.0–58.6)	28.6 (1.5–55.6)	16.7 (0.0–59.5)	0.0 (–)
Urinary retention	2.4 (0.0–7.4)	0.0 (–)	7.1 (0.0–22.6)	0.0 (–)	0.0 (–)
Painful bladder syndrome‡	12.5 (1.8–23.2)	9.1 (0–29.3)	21.4 (0–46.0)	16.7 (0–59.5)	0.0
Overactive bladder§	57.5 (41.5–73.5)	27.3 (0–58.7)	50.0 (20.0–80.0)	100	77.8 (43.9–100)†

* Values are the percentage (95% confidence interval). LUTS = lower urinary tract symptoms.
† $P < 0.05$ by chi-square test across age categories.
‡ Characterized by suprapubic pain related to bladder filling, accompanied by other symptoms, such as increased daytime and night-time frequency, in the absence of proven urinary infection or other obvious pathology.
§ Defined as urgency, with or without incontinence, usually with frequency or nocturia.

factors and the 3 LUTS categories, as well as the multivariable models adjusted for confounders and combining the factors identified in unadjusted analysis, are shown in Table 4. The adjusted association between factors and LUTS severity is shown in Supplementary Table 3, and a summary of the results can be found in Supplementary Table 4 (available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

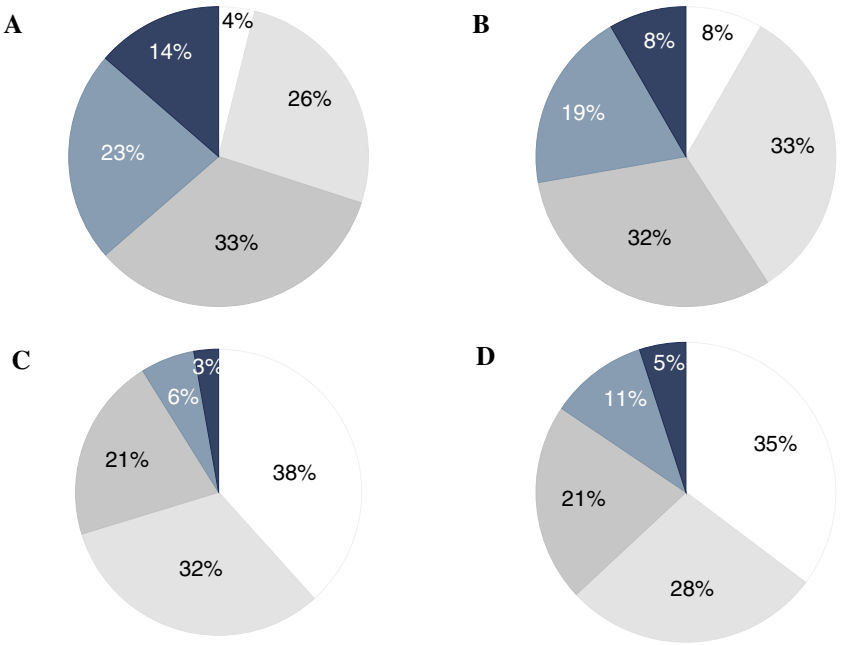

Figure 1. Proportion of lower urinary tract symptoms (LUTS) in the whole systemic sclerosis sample (n = 334). **A,** any LUTS, **B,** any storage symptoms, **C,** any voiding symptoms, and **D,** any post-micturition symptoms. White = no symptoms, light gray = symptoms occasionally, dark gray = symptoms sometimes, light blue = symptoms most of the time, and dark blue = symptoms all the time.

Table 4. Potential SSc-related factors associated with the 3 main categories of LUTS in the whole sample (n = 334)*

	Storage (n = 305)		Voiding (n = 236)		Post-micturition (n = 163)	
	Univariate	Multivariate†	Univariate	Multivariate†	Univariate	Multivariate†
Limited cutaneous SSc	1.0 (0.5–2.2)	–	1.2 (0.7–1.9)	–	1.4 (0.8–2.4)	–
ACA	1.2 (0.5–2.9)	–	1.1 (0.7–2.0)	–	1.1 (0.6–1.9)	–
General disability						
Disease > 10 years	1.5 (0.7–3.3)	–	1.2 (0.8–2.0)	–	1.3 (0.8–2.0)	–
Scl-70 antibodies	0.9 (0.4–2.0)	–	0.9 (0.5–1.5)	–	0.8 (0.4–1.2)	–
Overlapping disease	1.8 (0.4–7.9)	–	1.7 (0.7–4.2)	–	1.7 (0.8–3.6)	–
HAQ DI > median	3.5 (1.5–8.3)‡	4.2 (1.4–12.9)‡	3.0 (1.8–4.9)‡	2.4 (1.2–4.9)‡	1.6 (1.1–2.5)‡	1.4 (0.8–2.4)
VAS overall disease activity‡	1.2 (0.9–1.5)	–	1.3 (1.1–1.6)‡	0.8 (0.6–1.2)	1.1 (0.9–1.3)	–
Skin, vascular						
MRSS >14	1.5 (0.4–5.3)	–	1.3 (0.7–2.5)	–	1.2 (0.6–2.2)	–
Skin worse	1.5 (0.2–11.7)	–	3.2 (0.7–14.2)	–	1.1 (0.4–3.0)	–
Finger-skin thickening	2.6 (1.0–6.5)‡	2.7 (0.9–7.4)	1.0 (0.6–1.7)	–	1.2 (0.8–2.0)	–
Digital ulceration	1.2 (0.5–2.6)	–	1.2 (0.7–2.0)	–	0.9 (0.5–1.3)	–
Vascular worse	1.7 (0.5–5.9)	–	1.7 (0.8–3.4)	–	1.1 (0.6–2.1)	–
Synovitis	2.4 (0.3–18.6)	–	5.1 (1.2–22.4)‡	4.8 (1.0–22.6)‡	0.8 (0.3–1.8)	–
VAS for Raynaud's phenomenon§	1.2 (0.9–1.6)	–	1.3 (1.1–1.6)‡	1.2 (0.9–1.5)	1.1 (1.0–1.3)	–
VAS for finger ulcers§	0.9 (0.7–1.1)	–	1.1 (0.9–1.2)	–	0.9 (0.8–1.0)	–
Cardiopulmonary						
Lung fibrosis	0.7 (0.3–1.6)	–	1.2 (0.7–2.0)	–	1.4 (0.8–2.2)	–
Pulmonary hypertension	1.3 (0.3–5.9)	–	1.4 (0.6–3.3)	–	1.8 (0.8–3.8)	–
Dyspnea worse	–	–	3.0 (1.0–8.9)‡	2.0 (0.5–8.3)	2.0 (1.0–4.4)	–
VAS for breathing§	1.2 (0.8–1.6)	–	1.4 (1.1–1.7)‡	0.9 (0.6–1.2)	1.2 (1.0–1.3)	–
Digestive symptoms						
Esophageal	1.3 (0.6–3.1)	–	1.9 (1.1–3.1)‡	1.6 (0.8–2.9)	0.8 (0.5–1.3)	–
Gastric	3.2 (1.1–9.4)‡	2.5 (0.7–9.7)	1.4 (0.8–2.4)	–	1.2 (0.8–2.0)	–
Intestinal	5.4 (0.7–40.5)	–	1.2 (0.6–2.4)	–	0.9 (0.5–1.7)	–
Fecal incontinence	4.3 (1.0–18.7)‡	2.1 (0.4–10.7)	2.1 (1.1–4.0)‡	1.1 (0.4–2.6)	1.8 (1.1–3.1)‡	1.6 (0.9-3.1)
VAS intestinal problems§	1.3 (0.9–1.9)	–	1.8 (1.4–2.2)‡	1.9 (1.3–2.7)‡	1.3 (1.1–1.5) †	1.2 (1.0-1.5)‡
AUC (95% CI)	–	0.8 (0.7–0.9)	–	0.8 (0.7–0.8)	–	0.7 (0.6-0.7)

* Values are the odds ratio (95% CI). SSc = systemic sclerosis; LUTS = lower urinary tract symptoms; ACA = anticentromere antibody; HAQ DI = Health Assessment Questionnaire disability index; VAS = visual analog scale; MRSS = Modified Rodnan Skin Score; AUC = area under the curve; 95% CI = 95% confidence interval.
† Adjusted for age, sex, body mass index, presence of diabetes mellitus, urogenital disease or neurological palsy, medication (corticoids, diuretics, opioids, or treatment with known LUTS side effects), and number of vaginal deliveries.
‡ $P < 0.05$.
§ Visual analog scales are divided into 5 equal categories (each of 20% increments) and odds ratios are given for any increase in categories. Overlapping disease: concomitant systemic lupus erythematosus, rheumatoid arthritis, or Sjögren's syndrome (computed in a single binary variable).

Storage symptoms. Storage symptoms were associated with higher disability (HAQ DI), finger skin thickening, gastric symptoms, and fecal incontinence (Table 4). After adjustment for confounders, the association with HAQ DI scores greater than the median score (adjusted odds ratio [OR_{adj}] 3.9 [95% CI 1.4–10.6]) remained, but the associations with finger skin thickening (OR_{adj} 2.6 [95% CI 0.9–6.9]), gastric symptoms (OR_{adj} 3.0 [95% CI 0.8–10.4]), and fecal incontinence (OR_{adj} 2.9 [95% CI 0.6–13.1]) did not. In the multivariable model including the 4 previously mentioned potential factors, HAQ DI (OR_{adj} 4.2 [95% CI 1.4–12.9]) was the only statistically significant variable (Table 4). The area under the operative curve (AUC) of this model was 0.8 (95% CI 0.7–0.9). HAQ DI scores greater than the median score were also associated with a 2.1 OR (95% CI 1.1–4.0) of more severe storage symptoms (severe versus mild or mild versus no symptoms) (Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

Voiding symptoms. HAQ DI scores greater than the median score (OR_{adj} 2.6 [95% CI 1.5–4.6]), higher VAS of overall SSc symptoms (OR_{adj} 1.3 [95% CI 1.1–1.6]), higher VAS of Raynaud's phenomenon (OR_{adj} 1.3 [95% CI 1.1–1.6]), higher VAS of pulmonary symptoms (OR_{adj} 1.3 [95% CI 1.0–1.6]), higher VAS of digestive symptoms (OR_{adj} 1.8 [95% CI 1.4–2.4]), the presence of synovitis (OR_{adj} 4.6 [95% CI 1.0–20.6]), esophageal symptoms (OR_{adj} 2.0 [95% CI 1.1–3.4]), and fecal incontinence (OR_{adj} 2.2 [95% CI 1.1–4.6]) were all associated with voiding symptoms in univariate analysis (Table 4) and after adjustment for confounders. Worsening of dyspnea was not statistically significant after adjustment (OR_{adj} 2.7 [95% CI 0.8–9.6]) (Table 4).

Only synovitis (OR 4.8 [95% CI 1.0–22.6]), HAQ DI scores greater than the median score (OR 2.4 [95% CI 1.2–5.0]), and higher digestive symptoms VAS (OR 1.9 [95% CI 1.3–2.7]) were independent from the others and were statistically significant in the multivariable model (Table 4). These factors were further associated with the risk of having more severe

voiding symptoms with an OR of 2.9 (95% CI 1.1–7.4), 3.0 (95% CI 1.6–5.6), and 1.5 (95% CI 1.2–1.9), respectively (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

Post-micturition symptoms. HAQ DI scores greater than the median score (OR_{adj} 1.6 [95% CI 1.0–2.7]), higher VAS for digestive symptoms (OR_{adj} 1.3 [95% CI 1.1–1.6]) and fecal incontinence (OR_{adj} 2.0 [95% CI 1.1–3.7]) were associated with post-micturition symptoms in univariate (Table 4) and adjusted analysis. Higher VAS for digestive symptoms (OR 1.2 [95% CI 1.0–1.5]) remained statistically significant in the multivariable model including the 3 potential associated factors (Table 4). Higher VAS for digestive symptoms (OR_{adj} 1.3 [95% CI 1.1–1.6]) and rheumatologic overlapping disease (OR_{adj} 2.4 [95% CI 1.2–5.1]) increased the risk of severe post-micturition symptoms (see Supplementary Table 3, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

In women, in each additional subdivision in the VAS for digestive symptoms (20% increments), the filling and the voiding subscales of the ICIQ questionnaire increased by 0.36 (95% CI 0.17–0.56) and 0.40 points (95% CI 0.23–0.57), respectively. This association remained after adjustment and in multivariable models (see Supplementary Table 5, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

Association between QoL and LUTS in SSc. QoL, as measured by the specific score (Incontinence QoL questionnaire [IQoL]) and most of the SF-36 domains, was affected by LUTS, and decreased progressively with increasing frequencies of symptoms (see Figure 2 and Supplementary Table 6, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). In the storage category of LUTS, the bodily pain and role emotional domains were not statistically significant according to the Kruskal-Wallis test, but the trend across severity categories was significant.

The PCS was 5.4 points lower (95% CI 3.1–7.7, $P < 0.001$) and the MCS was 3.5 points lower (95% CI 1.6–5.5, $P < 0.001$) for each LUTS severity category. After adjustment, only voiding and post-micturition LUTS categories had statistically lower MCS, and the storage and voiding category had lower PCS (see Supplementary Table 7, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). For each additional LUTS, the PCS decreased by 0.92 unit (95% CI 0.52–1.33, $P < 0.001$) and the MCS by 0.87 unit (95% CI 0.53–1.21, $P < 0.001$). This association persisted after adjustment, with respective decreases of 0.59 unit (95% CI 0.25–0.93, $P = 0.001$) and 0.64 unit (95% CI 0.28–1.00, $P = 0.001$).

Sensitivity analyses. The sensitivity analyses excluding ASF patients resulted in similar conclusions for factors associated with LUTS compared to the main analysis (data not shown). Adding HAQ DI in the adjusted regression analysis had only a small impact on the link between LUTS and PCS and MCS (see Supplementary Table 8, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract).

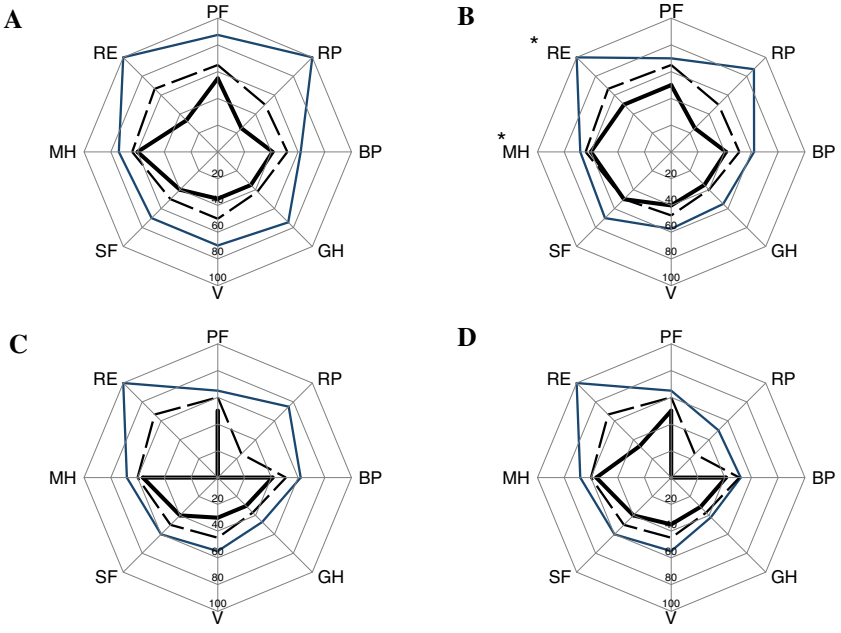

Figure 2. Radar diagrams of quality of life according to lower urinary tract symptoms (LUTS) severity for patients with **A,** any LUTS, **B,** any storage symptoms, **C,** any voiding symptoms, or **D,** any post-micturition symptoms. In each panel, median scores of the 8 domains of the Short Form 36 are represented for all LUTS categories, for patients without symptoms (solid blue line), patients with mild symptoms (broken black line), and patients with severe symptoms (solid black line). $P < 0.01$ for trend for all. * = $P < 0.05$ for all (Kruskal-Wallis), except for MH and RE in the storage symptoms, in which $P > 0.05$. PF = physical functioning; RP = role physical; BP = bodily pain; GH = general health; V = vitality; SF = social functioning; MH = mental health; RE = role emotional. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract.

DISCUSSION

This large international multicenter study demonstrates that self-reported LUTS are among the most frequent symptoms (96%) in SSc patients, more prevalent than cardiovascular (48%) or gastrointestinal symptoms (80%) (Supplementary Table 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). All LUTS categories affect QoL, and their impact increases with symptom severity.

The 3 categories of LUTS are overrepresented in the SSc population and tend to occur in combination. This is in agreement with a French study that found a prevalence of 92% for any LUTS in SSc patients using the Urinary Symptom Profile. High prevalence of LUTS is also seen among patients with other autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome (38), and rheumatoid arthritis (14). In the general population, LUTS vary greatly depending on age and disability/comorbidity distribution. The European Prospective Intervention Into Cancer and Nutrition (EPIC) study, exploring LUTS in 4 European countries and in Canada, found an increasing prevalence with age (the highest being 81% across men older than 60 years) (39). By contrast, our report shows a high and constant prevalence of LUTS even among younger patients. However, a direct comparison between the EPIC study and ours should be made with caution, since different instruments to assess LUTS were used and many confounders exist (e.g., disability and comorbidity).

This study shows that there are specific (disease-related) factors associated with LUTS and their severity (Supplementary Table 4, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). However, it failed to find a direct or independent link between skin fibrosis, SSc vascular involvement (e.g., pulmonary hypertension, Raynaud's phenomenon, and ulceration), or cardiopulmonary symptoms and LUTS (Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). The 2 most important mechanisms generating LUTS in SSc appear to be the functional impairment (resulting from the different disease manifestation) and dysfunction of the autonomous nervous system. The latter could explain why digestive symptoms are closely associated with voiding and post-micturition symptoms (7,16,40). The association between joint inflammation (synovitis) and LUTS probably results from a greater functional disability or a shared inflammatory mechanism with the voiding category of LUTS (Supplementary Figure 2, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23454/abstract). The involved mechanisms and their interactions are probably more complex than the proposed model, since there are discrepancies when bladder histology, urodynamic measures, severity of autonomic deficit, and urinary symptoms are taken into consideration (13, 40). Further studies are needed to better understand the physiopathology of LUTS in SSc.

LUTS have a real impact on many aspects on daily life (29). Quality of life is lower in patients with symptoms in any LUTS category, especially when symptoms are severe or when patients suffer from several LUTS. However, confounders explain some of the association between low QoL and LUTS. The association is less dramatic in models adjusted for comorbid conditions and disability. Nevertheless, even after adjustment, the lower MCS for patients suffering from voiding or post-micturition symptoms, and the lower PCS for patients suffering from storage or voiding categories of symptoms, are statistically significant and clinically relevant (41). The PCS score has complex interactions with LUTS, since disability increases the risk of having these symptoms and LUTS limit daily activity because of embarrassing situations or frequent toileting needs. Nevertheless, the sensitivity analysis, adjusted for disability, showed an independent association between storage symptoms and PCS.

Physicians often overlook LUTS. A recent report showed that less than one-quarter of incontinent SSc patients remembered having been interviewed by a health care provider about their urinary symptoms (33). The present study provides a rationale for including LUTS screening and severity assessment in any SSc patients. However, data are lacking on LUTS management in this specific population. Thus, further studies should explore the impact of LUTS screening, the benefits of LUTS treatment by symptoms and severity, and, finally, propose disease-specific management guidelines.

The present study has some limitations. First, 2 factors affected the statistical power of the analysis: the predefined sample size was not reached, and the proportion of LUTS was unexpectedly high. The impact was maximal when considering LUTS as a binary variable, and for the storage category, since very few participants were free of symptoms. Second, we did not include a control group, which would had been interesting for the assessment of SSc-related factors, but we primarily aimed to assess LUTS prevalence. Third, we did not account for multiple analyses performed in the study. Nevertheless, secondary analysis on potential risk factors was meant to be strictly exploratory, since scarce information on LUTS and SSc-related factors were available at the time of the study.

Fourth, we chose to explore LUTS by categories (storage, voiding, and post-micturition). Every symptom in each category might result from different mechanisms, with no common risk factors. Of note, urinary incontinence was recently associated with ACAs and the limited cutaneous form of SSc, but the same association was not found in the storage category (33). Nevertheless, analyzing all symptoms separately would generate many statistical tests and could expose it to spurious association (type I error). Furthermore, the fact that post-micturition symptoms, storage symptoms, and voiding symptoms were systematically associated with one another argues for a common risk factor/mechanism. In addition, 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. Finally, we used a self-administered questionnaire to measure LUTS and did not perform urodynamic exploration. However, the ICIQ questionnaires have been proven to correlate with objective measures of LUTS in different studies and are highly recommended to measure symptoms in men and women (42,43). In conclusion, self-reported LUTS are among the most frequent symptoms in SSc. More than one-third of

patients describe them as severe. Digestive symptoms and disability are associated with LUTS. SSc patients with LUTS have a lower QoL.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. John had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. John, Chizzolini.

Acquisition of data. John, Avouac, Piantoni, Polito, Fredi, Cozzi, Airò, Truchetet, Franceschini, Allanore, Chizzolini.

Analysis and interpretation of data. John, Cozzi, Airò, Truchetet, Franceschini, Allanore, Chizzolini.

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