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## **Epidemiology of cutaneous involvement in Sjögren syndrome: Data from three French pSS populations (TEARS, ASSESS, diapSS)**

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## **ABSTRACT**

### **Objective**

To determine the prevalence and significance of dermatological disorders in primary Sjögren syndrome (pSS).

### **Methods**

We used 2 pSS French cohorts (ASSESS, in which prevalence of skin disorders in 395 patients was evaluated; and diapSS, in which 76 on 139 pSS patients had an examination by a dermatologist) and baseline data of the TEARS randomized trial (110 patients with recent or active pSS treated with rituximab or placebo and evaluated for skin dryness using a visual analogue scale (VAS) out of 100).

### **Results**

Skin manifestations included in the EULAR Sjögren syndrome disease activity index (ESSDAI) were rare in the ASSESS cohort (n=16/395, 4.1%, mainly purpuras; only 3 had high activity), but they were associated with activity in the other ESSDAI domains (peripheral neurological (p<0.001), muscular (p<0.01), haematological (p<0.05), biological (p<0.05), history of arthritis (p<0.01), splenomegaly (p<0.05) and higher gamma globulin levels (p<0.01)). In the diapSS cohort, compared to pSS patients not receiving a dermatological consultation, the pSS patients who had a dermatological consultation had significantly more dermatological involvement outside the ESSDAI score [38.2% (29/76) versus 15.9% (10/63); p<0.01]. The TEARS study showed a high prevalence of cutaneous dryness (VAS>50; 48.2%) and found that patients with dry skin had higher VAS pain (p<0.01) and drought (p<0.01) scores.

### **Conclusion**

ESSDAI skin activity is rare and associated with hypergammaglobulinemia and ESSDAI activity. Systematic dermatological examination is informative for non-specific lesions. The most common skin disorder is skin dryness, which is associated with a higher pain and overall subjective dryness.

### **Key words:**

skin; cutaneous involvement; dryness; sicca; Sjogren syndrome; disease activity; visual analogic score; rheumatology; cohort; rituximab

# 1. Introduction

Sjögren syndrome is a systemic autoimmune disease characterized by lymphoid infiltration of the salivary glands and lacrimal glands resulting in secretory dysfunction, and is clinically manifested as xerostomia, xerophthalmia, dry skin, vaginal, respiratory (1–3) and extraglandular involvement of skin, joints, lungs, nervous system and kidneys (1,4–6). Sjögren syndrome may be primary or associated with another systemic autoimmune disease (lupus, inflammatory myopathy or scleroderma) or organ-specific autoimmune disease (such as autoimmune thyroiditis or primary biliary cirrhosis). At present, pSS is classified using the 2002 Americano-European Criteria Group (AECG) criteria (7) or 2016 American College of Rheumatology /European Ligue Against Rheumatism (ACR–EULAR) criteria (8,9).

The EULAR task force on pSS has created two new tools for assessing disease activity and patient-reported outcomes. The EULAR Sjögren syndrome disease activity index (ESSDAI) (1) is the sum of scores for each organ-specific domain multiplied by the activity level (range 0–3). The EULAR Sjögren syndrome patient reported index (ESSPRI) (10) combines visual analogue scales (VASs) for dryness, pain and fatigue.

Cutaneous involvement is common during primary Sjögren syndrome (pSS), but prevalence and characteristics are difficult to establish precisely because of the limited number of patients studied in most cohorts, the variability of the disorders evaluated in each cohort, the rarity of some of these disorders, and the heterogeneity of evaluations from previous studies (11).

The main objective of this study was to determine, using 3 French groups of patients suffering from pSS (ASSESS, diapSS, TEARS) in which different evaluation criteria were used, the prevalence of dermatological disorders and the clinical and paraclinical parameters associated with them. We sought to assess, on the one hand, the prevalence of cutaneous lesions according to the ESSDAI score at inclusion (cutaneous manifestations contributing to the ESSDAI value are erythema multiforme and cutaneous vasculitis, the most frequent being vascular purpura, and urticarial vasculitis (1)); and on the other hand, the other dermatological features since the cutaneous domain of ESSDAI is limited to few signs and does not include skin and mucosal dryness.

## 2. Methods

We used data from two French cohorts (*ASSESS*, which evaluated the prevalence of skin disorders in 395 pSS patients, and *diapSS* including 139 patients who had Sjögren syndrome diagnosed according to 2016 ACR-EULAR criteria among 325 patients suspected of having primary Sjögren syndrome and baseline data from the *TEARS* randomized trial (110 patients with recent or active pSS treated with rituximab or placebo evaluated for skin dryness using a visual analogue scale out of 100).

## **2.1. Patients**

### 2.1.1. Evaluating Systemic Signs and Evolution of Sjögren Syndrome (*ASSESS*)

*ASSESS* was a prospective multicentre national cohort study. Its primary objective was to identify factors predicting systemic complications and lymphoma in pSS during a prospective 5-year follow-up. This cohort was created in 2006 (Hospital Clinical Research Program 2005, P060228). A total of 395 consecutive patients who met the American-European Consensus Group (AECG) criteria were included in 15 centres of tertiary autoimmune diseases between 2006 and 2009. The study, promoted by the Assistance Publique des Hôpitaux de Paris, was approved by the Ethics Committee of Bichat Hospital and the National Commission for Computing and Liberties in 2006. All patients gave their written consent with full knowledge of the facts.

### 2.1.2. *DiapSS*

*DiapSS* was a single-centre Brittany cohort study of patients suspected of having a diagnosis of pSS who were prospectively included between January 2006 and September 2016 at the University Hospital Brest, France. The criteria for inclusion in the cohort were subjective ocular or mouth dryness, major salivary gland swelling, extraglandular manifestations suggestive of pSS, or suggestive antibodies or biological abnormalities. The patients were referred to our multidisciplinary clinics by their family doctor, rheumatologist, internist, oral specialist or ophthalmologist. A total of 325 patients were included prospectively, 139 of whom fulfilled the ACR/EULAR criteria of pSS (8). All participants signed an informed consent form, and the study was approved by the local ethics committee (Brest University Hospital).

### 2.1.3. *TEARS*

*TEARS* was a French national multicentre cohort study whose objective was to evaluate the efficacy of rituximab in terms of improvement in absolute value of + 30% on at least two of the following four visual analogue scales: drought, pain, fatigue, and global evaluation. A total of 110 patients with pSS meeting the criteria of AECG and having active disease (defined by score > 50 mm on at least two of the four visual analogic scores (VASs): overall assessment of the disease, pain, dryness, fatigue) were included prospectively between 2008 and 2011 by French internists and rheumatologists in 14 French university hospitals. All patients had to have recent (less than 10 years after the first manifestation reported to or observed by a physician) or active Sjögren syndrome with active visceral involvement. This study was approved by the relevant ethics committee (PPC West VI), and all patients gave their written consent prior to study enrolment. The protocol was registered on ClinicalTrials.gov (NCT00740948).

## **2.2. Methods**

For the three cohorts, all systemic manifestations [skin, joints, lungs, kidneys, peripheral nervous system (PNS), central nervous system (CNS), muscles and vessels] were prospectively documented through a standardized paper report (CRF) by a pSS expert clinician at inclusion. The systemic activity of the disease was evaluated by the ESSDAI score (range: 0 to 123), including 12 domains (1). The ESSPRI score (patient-related index linked to the EULAR Sjögren syndrome score), a consensus result obtained by the patient assessing dryness, fatigue and pain, was completed by all patients each year (10). In the *TEARS* cohort, we also included a VAS score for cutaneous dryness collected at baseline. In the *DiapSS* cohort, a dermatologist examined patients with suspicion of pSS when possible.

## **2.3. Statistical analysis**

We analysed the baseline patient characteristics for which the relevant data were available. In the *diapSS* cohort, we compared patients having a dermatological examination with those who did not. In the *ASSESS* cohort, we compared patients with skin manifestations, either past and/or present, to patients with no cutaneous manifestations. In the *TEARS* cohort, we compared patients with a VAS cutaneous dryness score  $\geq 50$  to those with VAS cutaneous dryness <50.

Continuous variables were described as the mean  $\pm$  SD and were compared using the Mann-Whitney test. Categorical variables were described as n (%) with the 95% confidence interval and compared using the Pearson's chi-square test. SPSS software version 25.0 [IBM, Armonk, NY, USA] was used for all analyses. All significance tests were two-tailed, and values of  $p < 0.05$  were considered significant.

### **3. Results**

#### **3.1. Studied population**

We evaluated data from 644 pSS and 186 sicca patients without pSS. Table 1 lists the main characteristics of the patients in the three cohorts. The patients were mainly women. The mean age at diagnosis was between 54.3 and 57.9 years in the three cohorts. The mean ESSDAI score was higher in the TEARS study than in the two cohorts, and the prevalence of cutaneous manifestation according to the ESSDAI score was also slightly higher.

#### **3.2. Cutaneous involvement**

In the ASSESS cohort, cutaneous manifestations contributed to the ESSDAI value in 16/395 (4.1%) patients, including 3 with high, 12 with moderate, and 1 with low disease activity. Forty-four patients had a history of purpura, including 9 with purpura present at baseline; 16 patients had a history of livedo, including 4 with livedo present at baseline; and 4 patients with a history of ulcer, including 1 patient with ulcer present at baseline. In total, cutaneous manifestations contributing to the ESSDAI at baseline and/or previously have been reported at any visit value in 64/391 patients (16.4%) (Table 2). Data about cutaneous manifestations outside the ESSDAI were not collected and we cannot describe them.

In the diapSS cohort of 319 patients, 91 had cutaneous involvement (in score ESSDAI and out of score ESSDAI; 46 pSS and 45 patients suspected of pSS but not fulfilling the ACR/EULAR criteria of pSS). Cutaneous manifestations contributed to the ESSDAI value in 7/139 (5.0%) pSS patients. In pSS patients, 39 had a cutaneous involvement not taken account in the ESSDAI score (28.1%) (Table 3). Thirty two of 139 pSS patients (27.3%) had Raynaud's syndrome. In the diapSS cohort, 139 pSS patients fulfilled the ACR/EULAR

criteria of pSS and 76 of them received a dermatological consultation. Compared to pSS patients not receiving a dermatological consultation, the pSS patients who had a dermatological consultation did not present more cutaneous involvement included in the ESSDAI score but they had significantly more dermatological involvement outside ESSDAI score ( $p < 0.01$ ) (Table 4).

In the TEARS cohort, cutaneous manifestations contributed to the ESSDAI value in 7/110 (6.4%) patients, including 3 with high, 3 with moderate, and 1 with low disease activity. The mean VAS score for cutaneous dryness was 45.1 (SD, 31.5). Fifty-three of 110 patients (48.2%) had a VAS skin dryness score  $\geq 50$ .

### **3.3. Factors associated with dermatological disorders**

In the ASSESS cohort (Table 5), patients with active cutaneous involvement in the ESSDAI domain had a higher prevalence of peripheral neuropathy ( $p < 0.001$ ), muscular involvement ( $p < 0.01$ ), biological involvement ( $p < 0.05$ ) and haematologic involvement ( $p < 0.05$ ) compared with that in the control group. These patients more often had a history of arthritis ( $p < 0.01$ ) and splenomegaly ( $p < 0.05$ ) and had a higher level of gamma globulin ( $p < 0.01$ ) compared with the control group. Patients with dermatological activity did not differ from the others in terms of the use of immunosuppressive medications. The mean ESSDAI score was higher in patients with cutaneous involvement than in those without ( $p < 0.001$ ), even after exclusion of the cutaneous domain ( $p < 0.05$ ).

In the TEARS cohort, patients with a VAS cutaneous dryness score  $\geq 50$  had significantly higher pain scores on the VAS ( $p < 0.01$ ), global dryness scores on the VAS ( $p < 0.001$ ) and ESSPRI scores ( $71.1 \pm 15.2$  vs  $58.9 \pm 15.3$ ,  $p < 0.001$ ) than those with VAS cutaneous dryness  $< 50$  (Table 6).

## **4. Discussion**

In our study, the prevalence of cutaneous signs included in the cutaneous domain of the ESSDAI score at inclusion was 4.1%, 5.3% and 6.4% in the ASSESS, DiapSS and TEARS cohorts, respectively. However, the cutaneous domain of ESSDAI is limited to few signs and does not include dryness, which is the most common manifestation of the disease. Moreover,

as in many studies, two of our three study populations were not systematically examined by a dermatologist, and although most specific signs of pSS were detected by the rheumatologists, some other unspecific signs were probably not detected.

Cutaneous manifestations contributing to the ESSDAI value are erythema multiforme, cutaneous vasculitis, the most frequent being vascular purpura, and urticarial vasculitis (1).

Vasculitis corresponds to necrotizing or inflammatory lesions of the vascular walls linked to an immunological mechanism. According to the recent dermatologic addendum to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012)(12), Sjögren syndrome vasculitis is often either recurrent macular vasculitis in hypergammaglobulinemia or cryoglobulinemic vasculitis.

There is wide variability in the prevalence of cutaneous vasculitis in previous studies, ranging from 4.3% to 30.6% (5,13–29). In the ASSESS cohort, the prevalence of cutaneous vasculitis in the ESSDAI score was 16.4%. These results are consistent with previous reports indicating that approximately 15% of patients with pSS have manifestations of cutaneous vasculitis reported in the ESSDAI score (30,31). Recently, Retamozo et al. (32) reported that cutaneous ESSDAI was the 4th most common extraglandular manifestation (10%) in a cohort of 6331 patients with pSS in order of frequency.

Moreover, in the ASSESS cohort, cutaneous involvement in the ESSDAI domain including cutaneous vasculitis is associated with a more severe disease and systemic disease activity; these results are consistent with those of Kittridge et al. in 2011 (33).

Subcutaneous lupus (SCLE), also known as annular erythema, has long been considered an exclusive cutaneous feature of Asian patients with pSS, but Brito-Zerón (13), in a retrospective study, found annular erythema in nearly 35/377 (9%) pSS patients, including Caucasian patients. None of the patients in the ASSESS cohort had any current or past SCLE, but that observation can be explained by the fact that patients have not been systematically examined by dermatologists and consequently there may have been underdiagnosed cases of SCLE.

In the ASSESS cohort, patients with active cutaneous involvement in the ESSDAI domain had a higher prevalence of peripheral neuropathy and muscular involvement; these patients also more often had a history of arthritis; these results are consistent with 2004 Spanish study (15). Furthermore, patients in our cohort with active cutaneous involvement in the ESSDAI domain had a higher level of gamma globulin. Quartuccio et al, in 2017 (30), confirmed that purpuras associated with hypergammaglobulinemia were associated with benign proliferation of B cells, whereas purpura with cryoglobulinemia was associated with systemic vasculitis

with complement activation and increased risk of lymphoma. In the ASSESS cohort, none had lymphoma at the time of inclusion.

Cutaneous dryness, xeroderma or cutaneous xerosis is partly genetically determined. It is a part of the phenotype of each individual, and it changes in the course of life. Nevertheless, it is also clearly associated with Sjögren syndrome, in which it is the most frequently found skin manifestation (23-67%)(34–37). In the TEARS cohort, the VAS scores for cutaneous dryness were collected at baseline. Defining skin xerosis according to the VAS score corresponding to the patient's perception is an interesting approach to evaluating the impact on the patient's quality of life, which can be underestimated if the xerosis is not objectified by the clinician; indeed, in the TEARS cohort, patients with VAS cutaneous dryness  $\geq 50$  had significantly higher VAS pain scores, VAS global dryness scores and ESSPRI scores. Approximately half of the patients had a cutaneous dryness VAS  $\geq 50$ , which is consistent with the results of previous studies (27,34,35,38,39).

Moreover, patients with cutaneous EVA dryness  $\geq 50$  did not have more eye or oral dryness, which is consistent with the pathophysiological mechanism defended by Bernacchi and Engelke (36,40).

In the DiapSS cohort, nearly one-third of the pSS patients had cutaneous involvement, but only 5.3% had cutaneous involvement considered in the ESSDAI. Patients who had a dermatological visit had more skin involvement not taken into account in the ESSDAI. The evaluation of the cutaneous lesions was carried out in general by Sjögren syndrome experts, often rheumatologists and internists, using the ESSDAI score, which can underestimate non-specific cutaneous effects of this syndrome. According to a recent study (32), the percentage of patients with pSS with cutaneous features outside of the ESSDAI was 0.9%. The ESSDAI score is an interesting tool to judge the activity of the disease but does not seem to be suitable for the diagnosis of pSS or for the routine evaluation of all skin disorders. Close collaboration with the dermatologist is justified for detecting nonspecific lesions and for the management of these disorders (34,35).

Our study has several limitations. First, all the study centres were located in France. Second, patients in the 3 cohorts did not meet the same inclusion criteria, which may have led to selection bias. Finally, the evaluation of dermatological involvement was different in our 3 cohorts. Our study also has strengths, including 3 cohorts with a large number of patients, sufficient for the evaluation of the most common cutaneous manifestation and good representativity given the distribution of the included centres throughout France. The different criteria for assessing the dermatological involvement between the 3 cohorts may be a

weakness of the study but also a strength, as it allowed a more general vision of the cutaneous lesions in the pSS population.

To conclude, the dermatological signs included in the ESSDAI activity index are rare. These active skin disorders are associated with ESSDAI activity in various domains (muscle, peripheral neurological, haematological and biological). Systematic examination by a dermatologist would give a better estimation of specific and non-specific cutaneous manifestations of Sjögren syndrome [Appendix A, Figure S1; See the supplementary material associated with this article online]. The most common cutaneous involvement, skin dryness, is not included in the disease endpoints, so it should be evaluated by a specific VAS.

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**Table 1:** Characteristics of patients with pSS included in the three cohorts: ASSESS, TEARS and diapSS

	<b>ASSESS N=395 pSS</b>	<b>TEARS N=110 pSS</b>	<b>diapSS N=180 sicca</b>	<b>diapSS N=139 pSS</b>
<b>Mean (SD)</b>				
Age, years	57.9 (+/-12.1)	54.3 (13.7)	55.4 (+/-13.9)	56.3 (+/-13.2)
time since first symptom	6.5 (+/-5.8)	8.0 (+/-6.7)	5.9 (+/-6.5)	7.1 (+/-7.9)
ESSDAI score	4.8 (+/-5.5)	10.1 (+/-6.8)	3.9 (+/-5.7)	5.1 (+/-5.7)
ESSPRI score	53.5 (+/-21.2)	64.2 (+/-16.2)	56.3 (+/-25.8)	59.4 (+/-25.8)
<b>n/N (%)</b>				
Female sex F/M (% F)	367/25 (92.9)	109/1 (99.1)	213/18 (92.2)	87/7 (92.6)
Anti-SSA antibodies	228/385 (59.2)	90/110 (81.8)	64/230 (27.8)	29/94 (30.8)
Anti-SSB antibodies	129/385 (33.5)	-	29/229 (12.7)	13/94 (13.8)
Cutaneous involvement on ESSDAI score	16/389 (4.1)	7/110 (6.4)	9/228 (3.9)	8/91 (8.8)

ESSDAI= European League Against Rheumatism Sjögren syndrome disease activity index  
disease activity index

ESSPRI = European League Against Rheumatism Sjögren Syndrome Patient Reported Index

Anti-SSA = anti-Sjögren syndrome A antibodies

Anti-SSB = anti-Sjögren syndrome B antibodies

**Table 2:** Prevalence of cutaneous manifestations in the ASSESS cohort

	<b>Present at inclusion</b> <b>N=391</b>	<b>Previous involvement</b> <b>N=391</b>	<b>Any moment</b> <b>N=391</b>
<b>n/N (%)</b>			
Purpura, n (%)	9 (2.3)	35 (8.9)	44 (11.3)
Livedo, n (%)	4 (10.2)	12 (3.1)	16 (4.1)
Ulcer, n (%)	1 (0.2)	3 (0.8)	4 (1.0)

**Table 3:** Cutaneous involvement observed by a rheumatologist in the diapSS cohort

	<b>pSS</b>	<b>Sicca or other manifestations suggestive of pSS without pSS</b>
	<b>N = 139</b>	<b>N = 180</b>
<b>n/N (%)</b>		
Cutaneous involvement on ESSDAI score	7 (5.0)	10 (5.5)
- Low activity	0	3
- Moderate activity	6	6
- High activity	1	1
Cutaneous involvement not taken into account in the ESSDAI score	39 (28.1)	35 (19.4)

**Table 4:** Cutaneous involvement detected in patients with pSS in the diapSS cohort

	<b>Dermatological examination</b> N =76	<b>No dermatological examination</b> N = 63
<b>n/N (%)</b>		
Cutaneous involvement on ESSDAI score	5/76 (6.6)	2/63 (1.6)
Cutaneous involvement not taken into account in the ESSDAI score **	29/76 (38.2)	10/63 (15.9)

\*\*P < 0.01

**Table 5:** Characteristics of patients and factors associated with dermatological involvement in the ASSESS cohort

	<b>Cutaneous manifestations</b>	<b>No cutaneous manifestations</b>
<b>n/N (%)</b>		
Lymphadenopathy	1/16 (6.3)	11/374 (2.9)
Glandular	3/16 (18.8)	44/374 (11.8)
Articular	6/16 (37.5)	67/374 (17.9)
Pulmonary	0/16 (0)	57/372 ( 15.3)
Renal	1/16 (6.3)	10/374 (2.7)
Muscular**	3/16 (18.8)	10/373 (2.7)
Peripheral nervous system (PNS)***	4/16 (25)	34/373 (9.1)
Central nervous system (CNS)	0/16 (0)	8/374 (2.1)
Biological*	8/16 (50)	138/371 (37.2)
Haematologic*	7/16 (43.8)	55/373 (14.7)
History of arthritis**	12/16 (75)	154/374 (41.2)
History of splenomegaly*	2/16 (12.5)	10/37 (2.7)
Cryoglobulinemia	4/16 (25)	53/321 (16.5)
Anti-DNA	1/16 (6.3)	37/320 (11.6)
Anti-SSA	13/16 (81.3)	215/369 (58.3)
Anti-SSB	9/16 (56.3)	120/369 (32.5)
History of lymphoma	0/16 (0)	18/379 (4.7)
Corticosteroids <sup>1</sup>	8/16 (50)	207/376 (55.1)
Corticosteroids of the last visit	2/16 (12.5)	38/252 (15.1)
Plaquenil <sup>1</sup>	11/16 (68.8)	209/376 (55.6)
Plaquenil of the last visit	4/12 (33.3)	60/257 (23.3)
Methotrexate <sup>1</sup>	1/16 (6.3)	50/375 (13.3)
Rituximab <sup>1</sup>	2/16 (12.5)	19/375 (5.1)
<b>Mean +/-SD</b>		
Gamma globulin levels**	23.1 +/-7.3	18.5 +/-8.1
ESSDAI score***	14.5 (6.8)	4.4 (5.1)
ESSDAI score excluding skin points*	8.1 (6.2)	4.4 (5.1)

\*\*\* P < 0.001

\*\*P < 0.01

\* P < 0.05

<sup>1</sup> Current use and prior to inclusion.

Anti-DNA = deoxyribonucleic acid antibodies, Anti-SSA = anti-Sjögren syndrome A antibodies, Anti-SSB = anti-Sjögren syndrome B antibodies

**Table 6:** Factors associated with dermatological involvement in the TEARS cohort

	<b>VAS cutaneous dryness score <math>\geq</math> 50 N = 53</b>	<b>VAS cutaneous dryness score &lt; 50 N = 57</b>
<b>n/N (%)</b>		
Cutaneous involvement on ESSDAI	3 (5.7)	4 (7.0)
Raynaud's Syndrome	17 (32.1)	21 (36.8)
Oral symptoms	53 (100)	55 (96.5)
Dry mouth	50 (94.3)	52 (94.5)
Ocular symptoms	51 (96.4)	52 (91.2)
Dry eyes	46 (90.2)	46 (88.5)
Lymphadenopathy	5 (9.4)	2 (3.5)
Glandular	31 (59.6)	39 (68.4)
Articular	17 (32.1)	14 (24.6)
Pulmonary	5 (9.4)	10 (17.5)
Renal	1 (0.2)	3 (0.5)
Muscular	2 (0.4)	1 (0.2)
Neurologic	6 (11.3)	10 (17.5)
<b>Mean +/-SD</b>		
Pain VAS score, <i>mm</i> **	61.7 +/- 28.2	46.8 +/-27.0
Dryness VAS score, <i>mm</i> ***	79.4 +/- 15.2	62.5 +/-21.7
Fatigue VAS score, <i>mm</i>	72.2 +/- 18.2	67.5 +/- 18.9
ESSPRI score ***	71.1 +/- 15.2	58.9 +/- 15.4

\*\*\* P < 0.001

\*\*P < 0.01

VAS = visual analogue scale, ESSPRI = EULAR Sjögren Syndrome Patient Reported Index