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Original Article

A pilot study of skin barrier function in patients with systemic sclerosis and primary Sjögren's syndrome

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Objective: Although the close interactions between the epidermis and dermis of the skin have been widely explored, the skin barrier functions of the stratum corneum (SC) in patients with systemic sclerosis (SSc) and primary Sjögren's syndrome (pSS) are not well known. We aimed to investigate the biophysical characteristics of the skin, including transepidermal water loss (TEWL), the SC water content, erythema, and the melanin index, in patients with SSc and pSS.

Methods: This case-control study included 34 patients with SSc, 31 patients with pSS, and 25 healthy controls. All parameters were measured on the extensor surface of the forearm and compared between patients and healthy controls. In patients with SSc, we performed subgroup analyses by disease subtype (diffuse and limited cutaneous SSc), the modified Rodnan skin sclerosis score (>6 or ≤6), and comorbid secondary SS status. In patients with pSS, subgroup analyses were performed by anti-Ro/SSA antibody status and the findings of salivary gland ultrasound.

Results: No statistically significant differences were observed in TEWL or skin hydration between patients with SSc and pSS and healthy controls. In the pSS group, only the erythema index was significantly increased compared to the control group. In subgroup analyses, no significant differences were observed in the extent of TEWL or skin hydration by disease subtype, severity, autoantibody profile, or comorbidities.

Conclusion: Patients with SSc or pSS did not exhibit specific impairments of skin barrier function or skin hydration. Further studies with larger sample sizes and age-matched controls are required.

Keywords: Skin, Skin physiological phenomena, Systemic sclerosis, Sjögren's syndrome

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disease characterized by microvasculopathy, immune dysregulation, and fibrosis of the skin and visceral organs [1]. Skin thickness is the hallmark, and the extent of skin thickness is classified into two major subsets: limited cutaneous systemic sclerosis (lcSSc) and diffuse cutaneous systemic sclerosis (dcSSc) [2]. Notably, pruritus is a common symptom in SSc, affecting 40%~65% of patients, though its pathophysiology remains poorly understood [3]. Indeed, the prevalence of Sjögren's syndrome (SS) in patients with SSc, known as secondary SS, has been reported to be approximately 14% to 51% [4]. Xerosis is the most frequent cutaneous manifestation in patients with SS [5], and pruritus is

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significantly associated with xerosis in patients with SSc [6].

Primary Sjögren's syndrome (pSS) is a systemic, chronic autoimmune disorder characterized by immune-mediated damage to the lacrimal and salivary glands that triggers ocular and oral dryness [7]. pSS patients present various cutaneous features including xerosis, pruritus, annular erythema, and cutaneous vasculitis [5]. However, the underlying cause is not clear, suggesting that more dermatological research is required. Epithelial–fibroblast interactions have been suggested to play an important role in profibrotic diseases [8]. Abnormal skin fibrosis in SSc results from a complex interplay between immune cells, endothelial cells, and fibroblasts [9,10]. However, most previous studies of SSc focused exclusively on dermal change; the epidermis was ignored. Despite the high prevalence of skin complaints in patients with SSc or pSS, there are scarce reports regarding barrier function characteristics in SSc and pSS.

MP6 skin quality evaluation instrument (Courage+Khazaka GmbH, Cologne, Germany) can quantify stratum corneum (SC) functionswith non-invasive probes including transepidermal water loss (TEWL) as an objective indication of skin barrier function, skin hydration, and amount of skin melanin and erythema [11]. These methods can easily detect functional changes of the SC in various skin conditions such as atopic dermatitis (AD) [12], and psoriasis [13]. The measurement of skin homeostasis and epidermal barrier function in SSc and pSS patients could help clinicians to understand the complex and still incomplete etiopathogenesis of these diseases.

We aimed to investigate TEWL, the water content of the SC, erythema, and melanin production in patients with SSc and pSS compared to those of healthy controls using MPA6 Multi Probe Adapter.

MATERIALS AND METHODS

Participants

We enrolled 34 patients with SSc, 31 patients with pSS, and 25 healthy controls in this pilot study conducted at Soonchunhyang University Seoul Hospital, between March 2020 and December 2021. Definitive diagnoses of SSc and pSS were made using the 2013 criteria of the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR), i.e., the 2013 ACR/EULAR [14] and 2016 ACR/EULAR [15]. The study was approved by the ethics committee of Soonchunhyang University Seoul Hospital (IRB no. 2020-10-021) and adhered to the principles of the Declaration of Helsinki. All participants provided written informed consent.

Subjects under 19 or over 70 years of age with underlying skin diseases (AD or psoriasis) who received systemic antibiotics or prednisolone at a dose above 10 mg/day in the previous 4 weeks or applied topical steroids or retinoid ointment in the previous 2 weeks were excluded. The workup included a thorough physical examination including evaluation of the Raynaud phenomenon, laboratory tests, the Schirmer's test, and salivary gland ultrasound (SGUS) (for pSS patients only). A single rheumatologist (KAL, with 7 years of experience in SGUS) performed all SGUS procedures, which reveal structural abnormalities of the major salivary glands in pSS patients [16]. Each of the four salivary glands was individually graded using the 2019 scoring system of the US Outcome Measures in Rheumatology (OMERACT) [17]. An SGUS score ≥2 for the most affected salivary gland indicated pSS [18].

All patients were asked yes/no questions about their history of dry skin and ocular and oral dryness. Laboratory tests measured the levels of ANA and the anti-centromere, -scl-70, -RNA polymerase III, -Ro/SSA, and -La/SSB autoantibodies. We assessed the extent of skin thickening in SSc patients using the modified Rodnan skin score (mRSS) (range: 0~51 over 17 body sites), which uses a scale of 0~3 (0: normal, 1: mild thickening, 2: moderate thickening, and 3: severe thickening) [19].

Noninvasive measurements

Functional skin barrier properties were measured on the low-

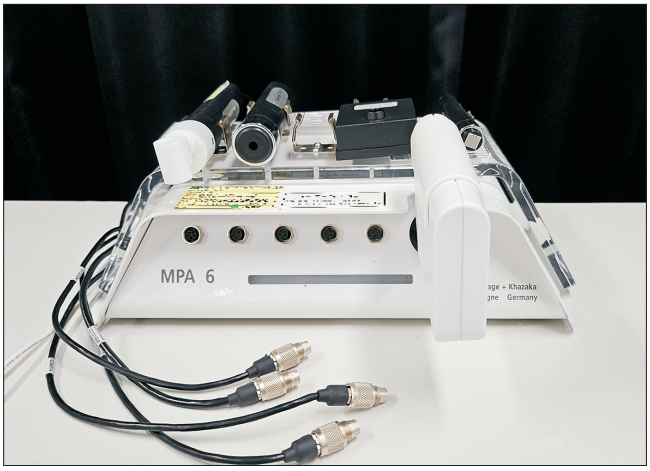

Figure 1. MPA6 Multi Probe Adapter (Courage+Khazaka GmbH). MPA6 Multi Probe Adapter was used to evaluate the parameters necessary for assessing the skin condition.

er one-third of the extensor sides of all forearms using the MPA6 Multi Probe Adapter (Figure 1). Skin SC hydration was measured with the Corneometer CM825 device (Courage+Khazaka GmbH). The skin electrical capacitance reflected the water content of the horny layer. The SC water content was measured in Corneometer units; a value <30 U indicated dry skin. Arm TEWL was determined using the Tewameter TM300 device (Courage+Khazaka GmbH) (unit = g/m^2/h; normal range: 0~25 g/m^2/h). The water evaporation gradient is measured in an open chamber. The extents of pigmentation and skin rash were measured using a Mexameter (Courage+Khazaka GmbH) and the results are presented as a melanin index (MI) and an erythema index (EI). All skin measurements were performed by a trained physician at a room temperature of 22°C~25°C and a relative humidity of 50% after 20 minutes of subject acclimatization. All parameters were measured three times and the mean values calculated. All participants were instructed not to use emollients for 12 hours prior to measurements.

Statistical analysis

All data were analyzed with IBM SPSS software (ver. 20; IBM Corp., Armonk, NY, USA) and are expressed as median interquartile range (IQR) or mean (standard deviation [SD]) for continuous variables (as appropriate) and as absolute frequencies with percentages for qualitative variables. Data were compared using the unpaired Student t-test, Mann–Whitney U-test, chi-

Table 1. Clinical and laboratory characteristics of patients with SSc and primary pSS, and healthy controls

	SSc (n=34)	pSS (n=31)	Control (n=25)	p-value
Age (yr)	51.8 (13.4)	60.8 (8.8)	30.0 (7.3)	<0.001
Female, n (%)	32 (94.1)	31 (100.0)	16 (64.0)	<0.001
BMI, (kg/m^2)	21.9 (3.0)	22.3 (2.9)	22.1 (2.5)	0.883
Disease duration (yr)	2.7 (1.6)	4.4 (2.8)		
Ocular dryness, n (%)	34 (100.0)	25 (80.7)	5 (20.0)	<0.001
Oral dryness, n (%)	19 (55.9)	26 (83.9)	0 (0)	<0.001
Skin dryness, n (%)	21 (61.8)	18 (58.1)	6 (24.0)	0.006
Raynaud's phenomenon, n (%)	30 (88.3)	7 (23.3)	0 (0)	<0.001
Diffuse cutaneous SSc, n (%)	17 (50.0)			
mRSS, median (Q1, Q3)	6 (3, 10)			
Secondary SS syndrome	18 (52.9)			
SGUS positive		12/29 (41.4)		
Positive anti-Ro/SSA (%)	12 (35.3)	19 (61.3)		
Positive anti-La/SSB (%)	1 (2.9)	5/30 (16.7)		
Positive anti-centromere, n (%)	12 (35.3)	4 (13.3)		
Positive scl-70, n (%)	13 (38.2)	0 (0)		
Positive RNA polymerase III, n (%)	3 (8.8)			
Therapy, n (%)				
Glucocorticoids	21 (61.8)	14 (45.2)	0 (0)	<0.001
Mycophenolate mofetil	17 (50.0)	0 (0)	0 (0)	<0.001
Hydroxychloroquine	0 (0)	9 (29.0)	0 (0)	<0.001
Comorbidities, n (%)				
Hypertension	6 (17.6)	5/30 (16.1)	0 (0)	0.056
Diabet	0 (0)	5/30 (16.1)	0 (0)	0.064
Dyslipidemia	4 (11.8)	2/30 (6.7)	0 (0)	0.196
Interstitial lung disease	15 (44.1)	2/30 (6.7)	0 (0)	<0.001

Values are presented as mean (standard deviation) unless otherwise stated. BMI: body mass index, mRSS: modified Rodnan skin score, pSS: primary Sjögren's syndrome, SGUS: salivary gland ultrasound, SSc: systemic sclerosis, SS: Sjögren's syndrome.

squared test, and Fisher's exact test, as appropriate. Demographic data were analyzed to generate descriptive statistics. A p-value <0.05 was taken to indicate a statistically significant difference.

RESULTS

The study included 34 patients with SSc (32 [94.1%] females and 2 [5.9%] males), 31 patients with pSS (all females), and 25 healthy controls (16 [64%] females and 9 [36%] males). The mean±SD ages of patients with SSc, patients with pSS, and healthy controls were 51.8±13.4, 60.8±8.8, and 30.0±7.3 years, respectively. The mean disease durations±SD were 2.7±1.6 and 4.4±2.8 years for patients with SSc and pSS, respectively. SSc patients were taking two agents: 21 (61.8%) had been prescribed glucocorticoids and 17 (50%) were given mycophenolate mofetil. Fourteen (45.2%) patients with pSS were treated with glucocorticoids, and nine (29%) with hydroxychloroquine (HCQ).

In the SSc group, 21 (61.8%), 34 (100%), and 19 (55.9%) patients reported skin, ocular, and oral dryness respectively. In the pSS group, 18 (58.1%) patients reported skin dryness, 25 (80.7%) ocular dryness, and 26 (83.9%) oral dryness. Half of all SSc patients had dcSSc and the other half had lcSSc. In the SSc group, the median mRSS was 6 (3, 10). Eighteen patients (52.9%) with SSc exhibited secondary pSS. In the pSS group, 12 (41.4%) patients were positive on SGUS, defined as a maximum OMERACT SGUS grade ≥2 (Table 1).

Of SSc patients, 13 (38.2%) were positive for anti-scl-70, 12 (35.3%) for anti-centromere, and 3 (8.8%) for RNA polymerase III autoantibodies. Of pSS patients, 19 (61.3%) and 5 (16.7%) were positive for anti-Ro/SSA and anti-La/SSB antibodies, respectively.

The water contents of the SC and TEWL did not differ significantly among the three groups (p>0.05) (Table 2). There was no correlation between the skin hydration or TEWL level, skin thickness, or mRSS score in patients with SSc (all p>0.05).

The MI values in patients with SSc and pSS did not differ significantly from the control value, but the EI of pSS patients was significantly higher than that of the controls (Table 2).

We performed subgroup analyses of the SSc and pSS groups. When SSc was stratified into dcSSc and lcSSc, the dcSSc subgroup tended to exhibit less SC hydration and an increased TEWL compared to the lcSSc subgroup, but the differences were not statistically significant. Similarly, when stratified by the median mRSS score, the mRSS >6 group tended to evidence decreased SC hydration and an increased TEWL compared to the mRSS ≤6 group but the differences were again not statistically significant. Secondary SS did not significantly affect the SC hydration or TEWL levels of SSc patients (Table 3). In the analysis of SSc patients based on the presence of interstitial lung disease and pulmonary arterial hypertension, no significant differences were observed in TEWL, SC water content, MI, and EI (data not shown).

In subgroup analyses of the pSS group by anti-Ro/SSA antibody and SGUS status, no significant difference was observed (Table 4). In patients with pSS, the group taking HCQ showed significantly higher MI compared to the group not taking HCQ (median [IQR], 174.6 [149.3~204.6] vs. 138.3 [109.0~161.6]) (p=0.014).

DISCUSSION

Neither the TEWL nor the extent of SC hydration of the extensor surface forearms of patients differed significantly from those of healthy controls, although approximately 60% of patients with SSc and pSS complained of dry skin in the current study. In subgroup analyses of patients with SSc, tendencies toward a decreased SC water content and increased TEWL were found in the dcSSc and high-mRSS (mRSS >6) subgroups compared to the lcSSc and low-mRSS (mRSS ≤6) subgroups,

Table 2. The biophysical properties in patients with SSc and primary pSS, and healthy controls

Function	Control (n=25)	SSc (n=34)	p-value	pSS (n=31)	p-value
Skin hydration (U)	39.6 (13.1)	38.6 (10.9)	0.75	39.5 (12.1)	0.98
TEWL (g/m^2/h)	12.1 (10.1)	15.4 (10.7)	0.24	11.7 (6.5)	0.86
Melanin index	137.1 (28.6)	149.8 (29.2)	0.10	147.2 (36.6)	0.27
Erythema index	200.6 (39.1)	224.0 (53.4)	0.14	235.0 (50.7)	0.03

Values are presented as mean±standard deviation. pSS: primary Sjögren's syndrome, SSc: systemic sclerosis, TEWL: transepidermal water loss.

Table 3. Skin hydration and TEWL according to the subtypes in patients with SSc

	Cutaneous type			mRSS			Secondary SS		
	Diffus (n=17)	Limited (n=17)	p-value	>6 (n=17)	≤6 (n=17)	p-value	with (n=18)	without (n=16)	p-value
Hydration (U)	37.4 (33.0, 42.7)	40.7 (32.6, 49.4)	0.50	35.2 (29.3, 43.3)	42.3 (33.4, 51.5)	0.18	41.8 (33.8, 49.4)	37.7 (32.8, 43.7)	0.34
TEWL (g/m^2/h)	12.4 (9.4, 18.9)	11.4 (9.8, 14.1)	0.65	13.06 (9.10, 22.15)	11.4 (9.5, 51.5)	0.87	11.1 (9.4, 13.7)	12.7 (10.4, 22.0)	0.32

Values are presented as the median (Q1, Q3). mRSS: modified Rodnan skin score, SS: Sjögren's syndrome, SSc: systemic sclerosis, TEWL: transepidermal water loss.

but the differences were not statistically significant. In subgroup analyses of patients with pSS according to anti-Ro/SSA antibody status and the SGUS score, no statistically significant difference was apparent, suggesting that skin barrier function was not associated with the immune profile or extent of major glandular duct damage caused by pSS.

Previously, Sogabe et al. [20] found that neither the TEWL nor the skin surface high-frequency conductance of patients with SSc measured at the forearm differed significantly from that of normal controls. Moreover, no correlation was observed between the level of TEWL or high-frequency conductance and the degree of skin thickening in patients with SSc [20]. On the other hand, Bernacchi et al. [21] showed no difference in skin hydration and TEWL in patients with pSS compared to healthy controls. In addition, Olewicz-Gawlik et al. [22] compared TEWL and SC hydration in patients with primary and secondary SS, AD, and normal controls. According to the study, TEWL was not significantly different between the three groups, while SC hydration was significantly decreased only in AD [22]. Consistent with previous studies, we could not find alterations in skin barrier function or corneal hydration in patients with SSc and pSS compared to healthy controls. This study is the first to evaluate skin barrier function in two representative rheumatic diseases, SSc and pSS, which are characterized by frequent skin symptoms. Additionally, we conducted a subgroup analysis for the first time based on various clinical and auto-antibody profile parameters related to disease severity. Although statistical significance was not found, there was a trend indicating a decrease in SC water content and an increase in TEWL depending on the severity of skin thickness. Therefore, further studies recruiting a larger number of patients, including those with more severe conditions, are necessary.

Skin barrier disruption (increased TEWL) and decreased water content have been widely investigated in patients with AD. In particular, TEWL increased not only in dry, non-eczematous skin but also in clinically normal skin in AD, indicating a primary defect of the epidermal barrier in AD. In AD, decreased intercellular phospholipids and ceramides account for the altered SC functions to some extent [23]. However, no alterations in skin barrier function and skin hydration in SSc and pSS suggest a distinct underlying mechanism for subjective skin dryness and related-pruritus in patients with SSc and pSS.

Dermal fibrosis is the hallmark of SSc. Profibrotic cytokines and growth factors such as type 1-interferon, transforming

Table 4. Skin hydration and TEWL according to the subtypes in patients with pSS

	anti-Ro/SSA			SGUS		
	Positive (n=19)	Negative (n=12)	p-value	Positive (n=12)	Negative (n=17)	p-value
Hydration (U)	37.1 (31.7, 43.1)	37.01 (33.9, 49.0)	0.69	36.0 (29.6, 42.9)	38.1 (35.6, 47.5)	0.24
TEWL (g/m^2/h)	11.9 (8.6, 13.6)	10.91 (9.0, 11.9)	0.92	11.2 (7.8, 13.4)	11.6 (9.1, 12.4)	0.95

Values are presented as the median (Q1, Q3). pSS: primary Sjögren's syndrome, SGUS: salivary gland ultrasound, TEWL: transepidermal water loss.

growth factor-β (a key driver of fibrosis), platelet derived growth factor, connective tissue growth factor, and endothelin-1 all play important roles in SSc [9,10]. In addition, the T helper cell 2 subtype infiltrates and increases the related cytokines (interleukin [IL]-4, IL-13, IL-5, IL-31, and IL-33), which have been associated with fibrosis in animal studies [10,24]. This, in turn, induces activation, differentiation, and survival of mesenchymal cells (fibroblasts, myofibroblasts), resulting in tissue fibrosis through increased extracellular matrix protein deposition such as collagen [8,10,25]. Th2 cytokines, particularly IL-13, IL-31, and IL-33, have been shown in animal studies to play a critical role in skin fibrosis [10,24,25], and these cytokines are also important in the pathogenesis of AD and other pruritic diseases (i.e., prurigo nodularis). Thus, skin problems, including dry skin and pruritus, in SSc can be attributed to Th2 cytokines. On the other hand, Nikitorowicz-Buniak et al. [26] found hypertrophic epidermis and altered expression of terminal differentiation markers, including involucrin, loricrin, and filaggrin, suggesting that these are responsible for dry skin and related pruritus in SSc. Moreover, the authors found that the SSc epidermis generates profibrotic CCN2 and pro-inflammatory S100A9, contributing to skin fibrosis and inflammation [26]. Further studies are required to address the underlying mechanism of immune-mediated inflammation and fibrosis as well as epidermal-dermal interactions in the patients' skin with SSc and SS.

Skin barrier function and SC water content have also been evaluated in other fibrotic diseases. In hypertrophic scars and keloids, both TEWL and SC water content were significantly elevated compared to the corresponding control skin of the same patients [20,27]. Although SSc and hypertrophic scars have dermal fibrosis and collagen deposition in common, several features are different. The excessive accumulation of collagen is more marked in hypertrophic scars and keloids than in SSc. Histopathologically, hypertrophic scars and keloids show increased cellularity and aberrant collagen arrangement that does not exist in normal skin or SSc skin, while sclerotic changes in SSc are characterized by hyalinization or homogenization of collagen with poor cellularity [20].

On the other hand, Ďurčanská et al. [28] measured TEWL in localized scleroderma (LSc) plaques at three stages: inflammatory, sclerotic, and atrophic. TEWL was significantly elevated in all three stages of LSc plaques compared to contralateral non-lesional skin and decreased from the inflammatory stage, through the sclerotic stage and to the atrophic stage [28]. In contrast, in a study of 27 patients with LSc, no alteration was detected in TEWL, but decreased SC hydration and increased epidermal thickness were found in the LSc plaques [29]. Despite the similarity in the development of abnormal fibrosis, these results suggest various natures of alterations in epidermis and dermis and diverse interactions might exist between those profibrotic diseases.

Regarding the patients with pSS, xerosis is the most frequent cutaneous manifestation in pSS, with 23%~67% of reported prevalence [21]. One study suggested that the xerotic skin in patients with SS complicated with AD is related to hypohidrosis due to eccrine gland dysfunction resulting from an autoimmune mechanism mediated by $CD8^+$ T cells [30]. However, Bernacchi et al. [21] obtained skin biopsy specimens from patients with pSS with severe xerosis and found no lymphocytic infiltration, no morphological alterations and reduction in the numbers of sebaceous and eccrine sweat glands. Instead, altered cytokeratin expression and premature involucrin demonstration were found in pSS skin, suggesting that these may be responsible for xerosis of patients with pSS [21]. An advantage of this study is that it measured not only TEWL and SC water content but also EI and MI. Erythema is an inflammatory skin condition commonly used as a marker to monitor the progression of cutaneous diseases or treatment-induced side effects [31]. Among Asian patients with pSS, a specific cutaneous finding known as annular erythema has been reported in a relatively high proportion of cases [32]. Various other erythematous lesions may also be found, including vasculitic lesions and recurrent urticarial.

Notably, increased EI in patients with pSS might reflect the underlying skin inflammatory reaction of the disease. We showed the higher MI observed in pSS patients taking HCQ compared to those not taking HCQ can be explained by HCQ binding to melanin. A recent study reported that the occurrence of HCQ-induced pigmentation is relatively common, with an incidence rate of 26.3% [33]. We did not observe typical HCQ-induced pigmentation at forearm lesions in enrolled patients. Our study demonstrated an association between HCQ use and increased melanin production even before noticeable pigmentation occurred.

The limitations of the study included a small sample size and lack of age-matched controls, which would have allowed for better comparisons. A recent study showed that TEWL and SC hydration showed only very low correlation with age and the sebum production decreased significantly with age in female subjects [34]. A meta-analysis showed TEWL in elderly patients (aged ≥65 years) was either similar to or lower than values in the younger group (18 to 64-year-old subjects) [35]. In our study, six patients (17.6%) in the SSc group and 10 patients (32.2%) in pSS group were over 65 years old, respectively, while there were no patients over 65 years old in the control group. When analyzing patients within the SSc and pSS groups by dividing them into those above and below 65 years old, there were no statistically significant differences in TEWL, SC hydration, MI, or EI. Although current studies suggest that the impact of age on skin barrier function is minimal, further investigation is needed to explore the impact of age on the skin barrier in rheumatic diseases, including age- and sex-matched controls. Second, all the SSc and pSS patients were under treatment. Inclusion of newly diagnosed patients (before initiation of any systemic treatment) might have yielded different results. Third, we measured the severity of whole-body skin involvement, but not the severity the distal one-third of the extensor side of the left forearm. However, we believe that the one's disease severity and stage might better reflect the general skin conditions (subjective skin dryness and skin barrier function) of patients with SSc and pSS.

CONCLUSION

In conclusion, neither the skin barrier function nor the extent of SC skin hydration differed among patients with SSc, patients with pSS, and controls in this pilot study; the alteration could be found in more systemic involvement of the disease, dcSSc type, or in patients with more severe skin fibrotic changes. Further well-designed studies with larger sample sizes and age-matched controls are required. In addition, newly diagnosed patients should be included, and more precise treatment history should be taken. Molecular studies of cytokine profiles, markers of epidermal differentiation, and epidermal lipid profiles would provide more information on skin barrier function and subjective pruritus and skin dryness in patients with SSc and pSS.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

K.A.L., S.K., and H.S.K. contributed to the study design and data collection, analysis, and interpretation. H.Y.S. and M.K.C. contributed to the data interpretation. All authors revised the manuscript and gave final approval for submission.

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