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Increased serum uric acid levels are associated with digital ulcers in patients with systemic sclerosis

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Abstract

Endothelial injury/dysfunction is thought to be one of the earliest events in the development of vascular diseases in systemic sclerosis (SSc). Although hyperuricemia is also known to induce endothelial dysfunction and vascular inflammation, the effect of uric acid on the microvascular involvement in SSc has not been well established. We investigated whether increased serum uric acid (SUA) levels are associated with digital ulcers (DUs) in SSc. In this cross-sectional study, we consecutively recruited 71 women with SSc and 349 age- and sex-matched healthy subjects, and SUA levels were measured in all study subjects. SSc patients had significantly higher mean SUA levels than healthy subjects (4.5 ± 1 mg/dL vs 4.2 ± 0.9 mg/dL, $p = 0.017$), although a significantly lower body mass index (BMI) was observed in SSc patients than in controls. Among 71 SSc patients, 22 (31%) had DUs ever (active DUs, 8; healed DUs, 14). SSc patients presenting with DUs ever showed significantly higher SUA levels than those without this feature (median, 5.2 mg/dL vs 4.1 mg/dL, $p = 0.009$). In multivariable logistic regression models adjusted for confounders such as BMI and estimated glomerular filtration rate, increased SUA levels were associated with a significantly higher risk for the presence of DUs ever (OR 2.3, 95% CI 1.16–4.57, $p = 0.018$). Our data revealed that elevated SUA levels are independently associated with the presence of DUs in SSc patients, thereby suggesting the potential role of hyperuricemia in the pathogenesis of SSc vasculopathy.

Keywords Systemic scleroderma · Uric acid · Ulcers · Vascular endothelium

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Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown causes characterized by fibroproliferative vasculopathy, extensive fibrosis of skin and internal organs, and the presence of autoantibodies [1, 2]. Vasculopathy in SSc, which is regarded to be a hallmark of the disease, primarily affects the microcirculation and is characterized by perivascular mononuclear cell infiltration, vascular wall remodeling, and loss of capillaries leading to luminal narrowing [3–5]. Vasculopathy can occur in the early disease course and contribute to the pathogenesis of later fibrotic process in SSc [4]. Endothelial injury/dysfunction along with vascular instability and excessive production of reactive oxygen species (ROS) caused by chronic hypoxia is thought to be the earliest events in vascular diseases in SSc [6]. SSc vasculopathy manifests as Raynaud's phenomenon, digital ulcers (DUs), and pulmonary arterial hypertension (PAH). Among them, DUs, which are common in SSc patients, can cause significant pain and serious complications such as infection, gangrene, loss of digits, and an increased risk of internal organ involvements [7, 8]. In addition, DUs are often difficult to treat and represent one of the greatest therapeutic challenges in rheumatology. Thus, it is important to identify SSc patients at a higher risk for development of DUs in clinical practice.

Uric acid is the final oxidation product of purine metabolism in humans and responsible for gout and urolithiasis because of the deposition of monosodium urate crystal. Uric acid was known to be potent endogenous antioxidant, but it can act as pro-oxidant and pro-inflammatory factor at higher levels [9]. Accordingly, hyperuricemia has been reported to be associated with metabolic syndrome, chronic kidney disease, non-alcoholic fatty liver disease, and dyslipidemia [9, 10]. In addition, growing evidences have emerged in recent decades that hyperuricemia is linked with atherosclerotic cardiovascular diseases (CVDs) including coronary heart disease and stroke [11–13] through the endothelial injury/dysfunction as a consequence of excessive production of ROS, smooth muscle cell proliferation, and inflammation induced by uric acid in the blood vessel [9, 11, 14]. Uric acid, an endogenous damage-associated molecular pattern (DAMP), can also lead to inflammasome activation which has been implicated in the onset of fibrosis [15, 16]. This suggests a potential link between uric acid and SSc-related fibrosis. Considering these data, it is assumed that uric acid may contribute to the initiation and perpetuation of SSc vasculopathy. Recently, DETECT study indicated that elevated serum uric acid (SUA) levels could be predictive of the development of PAH in SSc patients [17]. However, the effect of hyperuricemia on the microvascular involvement in SSc has not been well established. Therefore, in the present study, we investigated whether increased SUA levels are associated with DUs in SSc patients.

Methods

Study design and subjects

This was a cross-sectional study conducted at a rheumatology center in a tertiary care university-affiliated hospital in Busan, South Korea. This study recruited 71 consecutive female patients with SSc and 349 healthy controls matched for sex and age (± 2 years) as outpatients in our center from July 2014 to June 2017. Only female SSc patients were recruited because of the limited number of male patients in our rheumatology department. Patients with SSc were defined as those who meet the 1980 preliminary classification criteria of the American College of Rheumatology for SSc [18] and those who were diagnosed with rheumatic or autoimmune diseases other than SSc were excluded. SSc was classified as limited or diffuse subtypes based on the extent of skin involvement according to the established criteria of LeRoy et al. [19] Healthy controls were selected from individuals undergoing annual health check-ups in the same center and all controls were female. Inclusion criteria for healthy controls were no history of any rheumatic or autoimmune diseases. The following study subjects including both patients with SSc and controls were excluded: (1) those with a diagnosis of gout or uric acid stones, (2) those taking xanthine oxidase inhibitors such as allopurinol and febuxostat or uricosuric agents such as benzbromarone and probenecid, (3) those with estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2, and (4) those who refused to participate in this study. All participants signed written informed consent forms based on the principles of Helsinki Declaration, and this study was reviewed and approved by the Research and Ethical Review Board of Pusan National University Hospital (IRB no. H-1402-005-014).

Clinical and laboratory data collection

Demographic and clinical data such as age, height, weight, body mass index (BMI), blood pressure (BP), and the presence of type 2 diabetes mellitus (DM) and hypertension (HTN) were obtained via interviews and physical examinations. BMI was calculated as weight in kilograms divided by the square of the height in meters (kg/m2). BP was measured by a TM-2655P apparatus (A&D Company Ltd, Tokyo, Japan) as the mean of two measurements taken at an interval of 5 min. HTN was defined as BP ≥ 140/90 mmHg or current use of antihypertensive mediations. Type 2 DM was defined as ≥ 126 mg/dL or use of oral hypoglycemic agents

or insulin. Laboratory data including SUA, serum creatinine, low-density lipoprotein (LDL), triglyceride (TG), high-density lipoprotein (HDL), and C-reactive protein (CRP) were obtained using overnight fasting blood samples collected from all study subjects. SUA levels were determined by enzyme colorimetric assay using the Roche-Hitachi Cobas 8000 c702 chemistry autoanalyzer (Cobas 8000, Roche Diagnostics, Switzerland). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKI-EPI) equation, as follows: $eGFR = 141 \times \min(\text{serum creatinine}/0.7, 1)^{-0.329} \times \max(\text{serum creatinine}/0.7, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) [20].

Disease-related data including disease duration, age at diagnosis, SSc subtype, modified Rodnan skin score (MRSS), organ involvement such as DUs, interstitial lung disease (ILD), PAH, and gastrointestinal (GI) involvement, autoantibody profile such as anti-nuclear antibody (ANA), anti-centromere antibody, and anti-Scl70 antibody, and concomitant medications were collected from SSc patients. MRSS was evaluated by a well-trained rheumatologist, blinded to all clinical and laboratory data, at 17 body areas by palpation, and each area was scored 0–3, with a maximum total score of 51 [21]. DUs ever included both active and healed ulcers [22–25]. Active DUs were defined as loss of epithelialization and tissues involving the underlying epidermis, dermis, subcutaneous tissue, and sometimes the bone according to the criteria by Amanzi et al. [26] Healed DUs were defined as complete epithelialization of an ischemic ulcer regardless of residual pain [22, 25]. ILD was defined by the presence of diffuse ground-glass opacity or bibasilar pulmonary fibrosis on chest X-ray examination or high-resolution computed tomography without evidence of another pulmonary disorders. PAH was defined as a systolic pulmonary arterial pressure (PAP) > 40 mmHg on echocardiography or mean PAP over 25 mmHg on right-sided heart catheterization. GI involvement was defined if an SSc patient had clinical symptoms such as dysphagia, heartburn, reflux esophagitis, or small bowel bacterial overgrowth or had required proton-pump inhibitor. The presence of ANA was evaluated by indirect immunofluorescence on HEp-2 cells, and anti-centromere antibody and anti-topoisomerase I antibody were detected using immunoblot assay (EUROLINE anti-ENA profile 1).

Statistical analysis

Continuous data were expressed as mean ± standard deviation (SD) or medians and interquartile range (IQR) and categorical data as number of cases with percentages (%), as appropriate. Groups were compared using Student's *t* test or Mann–Whitney *U* test for continuous data and using Chi-square test or Fisher's exact test for categorical data, as appropriate. Correlations between SUA and clinical parameters were assessed by Pearson's or Spearman's correlation analyses, as appropriate. To investigate independent association between SUA and the presence of DUs ever, we used multivariable backward logistic regression models which included variables with p value < 0.1 in univariable logistic regression analyses. BMI and eGFR were considered as a *priori* confounding factors, which were also adjusted in our multivariable logistic regression models. All statistical tests were two-sided, and p values < 0.05 were considered statistically significant. All analyses were performed using STATA v. 11.1 for Windows (StataCorp LP, College Station, TX, USA).

Result

Table 1 shows the comparisons of clinical and laboratory characteristics between 71 SSc patients and 349 healthy controls. SUA levels in SSc patients were significantly higher than those in healthy controls (4.5 ± 1 mg/dL vs 4.2 ± 0.9 mg/dL, $p = 0.017$), although SSc patients have a significantly lower BMI than controls (21.8 ± 2.8 kg/m^2 vs 22.9 ± 2.9 kg/m^2, $p = 0.003$). There were no differences in age, serum creatinine levels, and eGFR between the two groups. SSc patients had a significantly higher serum CRP and TG levels and lower systolic BP and serum LDL and HDL concentrations than healthy subjects (Table 1).

Demographic and clinical features in SSc patients are presented in Table 2. The mean age at diagnosis was 45.6 ± 12.2 years, and the frequencies of diffuse and limited subtypes were 45.1% and 54.9%, respectively. Most patients with SSc had positive results for ANA (98.6%), and the frequencies of anti-centromere antibody and anti-Scl70 antibody were 23.9% and 33.8%, respectively. DUs ever were observed in 22 (31%) SSc patients: 8 (11.3%) were active DUs and 14 (19.7%) were healed DUs. Current medications taken are also listed in Table 2.

When SSc patients were divided into two groups according to the mean SUA level of SSc patients (4.5 mg/dL), the frequency of DUs ever in SSc patients with SUA level ≥ 4.5 mg/dL was significantly higher than those with SUA level < 4.5 mg/dL (45.5% vs 18.4%, $p = 0.02$), as depicted in Supplementary Table 1. However, no significant differences were found in disease duration, MRSS, frequency of ILD, PAH, GI and involvement, and anti-centromere antibody and anti-Scl70 autoantibody positivity according to the SUA levels in SSc patients. SSc patients with SUA level ≥ 4.5 mg/dL had significantly higher serum TG levels than those with SUA level < 4.5 mg/dL, whereas eGFR, BMI, and serum LDL, HDL and CRP levels did not differ between the two groups (Supplementary Table 1).

Figure 1 shows the comparisons of SUA levels in SSc patients according to clinical features. SUA levels in SSc

Table 1 Comparisons of clinical and laboratory characteristics between patients with systemic sclerosis and healthy controls

	Patients with SSc ($n=71$)	Healthy controls ($n=349$)	p value
Age, years	53.4 ± 10.8	52.3 ± 8.2	0.413
SUA, mg/dL	4.5 ± 1	4.2 ± 0.9	0.017
Serum creatinine, mg/dL	0.7 ± 0.12	0.71 ± 0.1	0.506
eGFR, mL/min/1.73 m^2, mean ± SD	95.2 ± 14.9	95.4 ± 11.2	0.917
BMI, kg/m^2, mean ± SD	21.8 ± 2.8	22.9 ± 2.9	0.003
SBP, mmHg	112.4 ± 15.8	117.7 ± 16.8	0.015
DBP, mmHg	69.6 ± 11.8	72.2 ± 11	0.074
HTN, n (%)	6 (8.5)	39 (11.2)	0.499
Serum glucose, mg/dL	88.8 ± 14.4	89 ± 15.7	0.934
Type 2 DM, n (%)	2 (2.8)	5 (1.4)	0.406
LDL, mg/dL	110.7 ± 31.7	125.7 ± 35.5	0.02
TG, mg/dL, median (IQR)	107 (73.8–161.3)	80 (58–113)	< 0.001
HDL, mg/dL	53 ± 14.6	57.6 ± 13.5	0.011
CRP, mg/dL, median (IQR)	0.09 (0.04–0.31)	0.04 (0.02–0.09)	< 0.001

SSc systemic sclerosis, *SUA* serum uric acid, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HTN* hypertension, *DM* diabetes mellitus, *LDL* low density lipoprotein, *TG* triglyceride, *HDL* high density lipoprotein, *CRP* C-reactive protein

Table 2 Demographic and clinical features in patients with systemic sclerosis

	Patients with SSc ($n=71$)
Disease duration, months, median (IQR)	84 (36–124)
Age at diagnosis, years, mean ± SD	45.6 ± 12.2
Subtype	
Diffuse SSc, *n* (%)	32 (45.1)
Limited SSc, *n* (%)	35 (54.9)
MRSS, median (IQR)	10 (7–15)
Anti-centromere antibody, *n* (%)	17 (23.9)
Anti-Scl70 antibody, *n* (%)	24 (33.8)
DUs ever, *n* (%)	22 (31)
Active DUs, *n* (%)	8 (11.3)
Healed DUs, *n* (%)	14 (19.7)
ILD, *n* (%)	38 (53.5)
PAH, *n* (%)	10 (14.1)
GI involvement, *n* (%)	36 (50.7)
Anti-nuclear antibody, *n* (%)	70 (98.6)
Current medications	
Vasodilators, *n* (%)	34 (47.9)
Anti-platelet agents, *n* (%)	53 (74.6)
Methotrexate, *n* (%)	6 (8.5)
D-penicillamine, *n* (%)	19 (26.8)
Glucocorticoids, *n* (%)	31 (43.7)

SSc systemic sclerosis, *MRSS* modified Rodnan skin score, *DUs* digital ulcers, *ILD* interstitial lung disease, *PAH* pulmonary arterial hypertension, *GI* gastrointestinal

patients with DUs ever were significantly higher than in those without DUs (median [IQR], 5.2 [4.1–5.6] mg/dL vs 4.1 [3.6–5] mg/dL, $p=0.009$). There was no significant difference in SUA levels according to SSc subtype and the presence of anti-centromere antibody. Of note, SSc patients having positive results for anti-Scl70 antibody had significantly lower SUA levels than those having negative results for anti-Scl70 antibody (median [IQR], 4 [3.6–4.6] mg/dL vs 4.7 [3.8–5.4] mg/dL, $p=0.045$) (Fig. 1). In simple correlation analyses, SUA levels did not significantly correlate with age ($\gamma = -0.097$, $p=0.419$), disease duration ($\rho=0.098$, $p=0.417$), MRSS ($\rho=0.105$, $p=0.382$), BMI ($\gamma=0.034$, $p=0.78$), eGFR ($\gamma = -0.143$, $p=0.233$), and CRP levels ($\rho=0.121$, $p=0.347$).

Association between SUA levels and DUs ever in SSc patients was analyzed by logistic regression models (Table 3). Backward multivariable logistic regression models for adjusting confounding factors revealed that higher SUA levels were independently associated with the presence of DUs ever (OR = 2.3, 95% CI = 1.46–4.57, $p=0.018$). In addition, MRSS (OR = 1.14, 95% CI = 1.03–1.27, $p=0.013$) and disease duration (OR = 1.01, 95% CI = 1–1.02, $p=0.023$) also showed significant relationship with DUs ever in multivariable logistic regression analyses.

Discussion

In this study, despite the lower BMI, SSc patients had significantly higher SUA levels than healthy subjects. We found that elevated SUA levels were independently associated with the presence of DUs ever in SSc patients. SSc

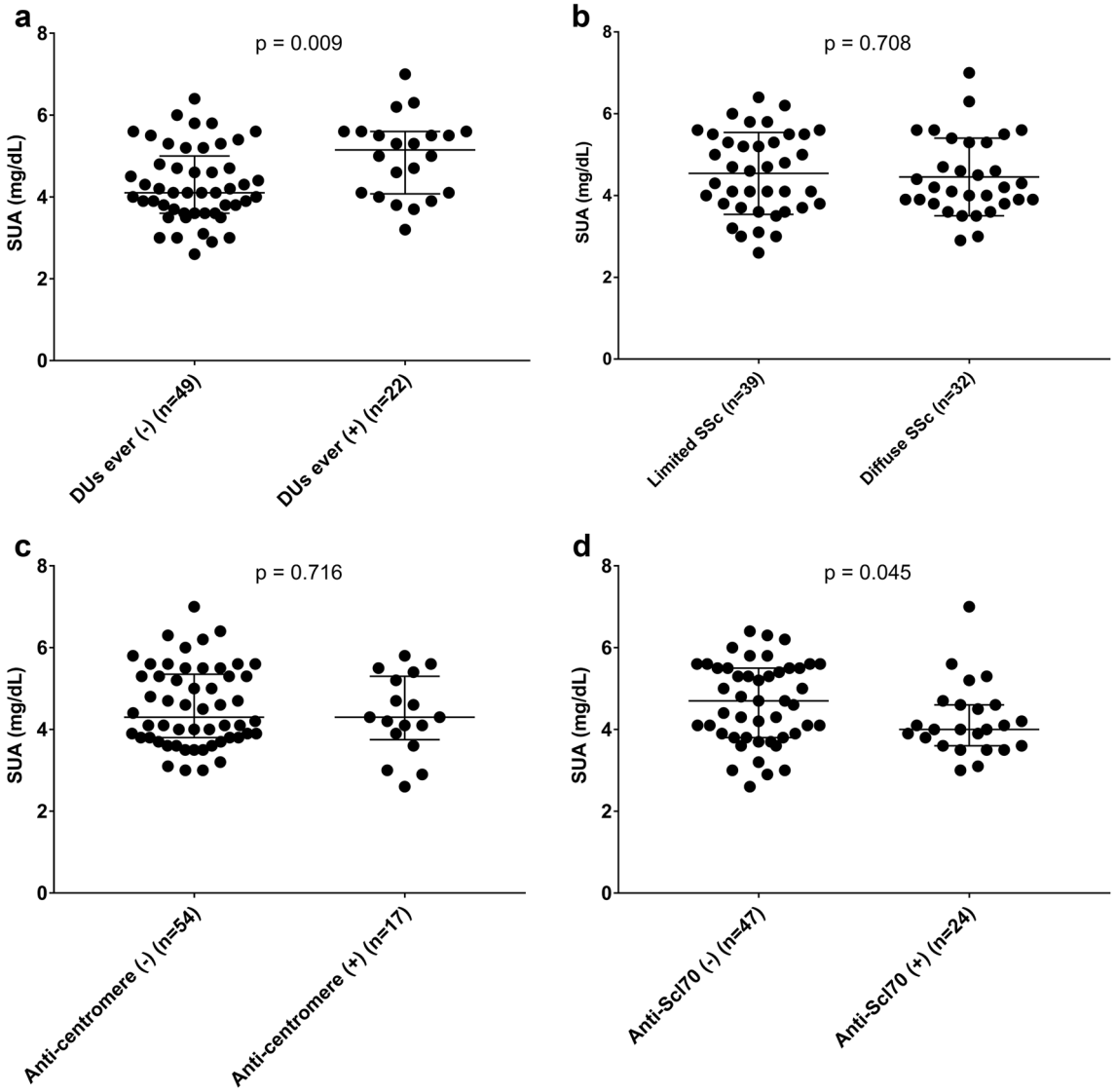

Fig. 1 Comparisons of serum uric acid levels in patients with systemic sclerosis according to the presence of DUs ever (**a**), subtype of systemic sclerosis (**b**), and presence of anti-centromere antibody (**c**) and anti-Scl70 antibody (**d**). Short horizontal lines and bars in **a, c, d** are the median and interquartile range and those in **b** are the mean ± standard deviation

patients having anti-Scl70 antibody had significantly lower SUA levels than those without this feature, but SUA levels did not differ according to SSc subtype or presence of anti-centromere antibody. In addition, no significant association between SUA levels and MRSS in SSc patients was observed; thus, we assumed that uric acid may be more closely linked with vasculopathy than fibrosis in SSc. In line with previous researches [7], higher skin score and longer disease duration were also significantly associated with DUs in the patients with SScin our analysis.

The major finding in this study was a significant association between increased SUA levels and the presence of DUs in patients with SSc after adjusting confounding factors. Similar to our results, previous studies reported that increased SUA levels were reported to be associated with higher risk of vascular involvement in SSc such as PAH and nailfold videocapillaroscopy damage [27, 28]. Uric acid can induce oxidative stress by generation of ROS during its production through xanthine oxidase activity, induce endothelial dysfunction as determined by the reduction in nitric oxide production, and stimulate vascular inflammation leading to activation of vasoconstrictive mediators such as endothelin-1 [9, 14, 29], which are strikingly similar to those found in the pathological process during SSc vasculopathy. In addition, uric acid can stimulate inflammasome activity which is known to trigger inflammatory response in vascular wall [30]. Thus, it is assumed that uric acid may contribute to the disease mechanism in SS vasculopathy.

Table 3 Association between serum uric acid level and digital ulcers ever in patients with systemic sclerosis

Variables	Univariable model		Multivariable model	
	Crude OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value
SUA level, mg/dL	2.19 (1.23–3.92)	0.008	2.3 (1.16–4.57)	0.018
MRSS	1.14 (1.04–1.25)	0.004	1.14 (1.03–1.27)	0.013
Disease duration, months	1.01 (1–1.02)	0.02	1.01 (1–1.02)	0.023
ILD	3.27 (1.1–9.78)	0.034	–	–
eGFR, mL/min/1.73 m^2	1.01 (0.97–1.04)	0.831	–	–
BMI, kg/m^2	0.97 (0.81–1.16)	0.72	–	–
PAH	0.51 (0.1–2.6)	0.424		
Anti-centromere antibody	0.38 (0.1–1.51)	0.169		
Anti-Scl70 antibody	0.65 (0.21–1.95)	0.437		
Diffuse SSc (ref. limited SSc)	1.33 (0.49–3.66)	0.576		

MRSS disease duration, *ILD* eGFR and BMI, *SUA* serum uric acid, *MRSS* modified Rodnan skin score, *ILD* interstitial lung disease, *eGFR* estimated glomerular filtration rate, *BMI* body mass index, *PAH* pulmonary arterial hypertension, *SSc* systemic sclerosis

[a]Estimated using backward multivariable logistic regression models including SUA levels

However, because all previous studies including ours had cross-sectional design, the relationship between SUA levels and vascular involvements in SSc may be observed as a result of reverse causality, implying that elevated SUA level was not a cause but rather a consequence of SSc vasculopathy. Further longitudinal or experimental studies are needed to support our findings.

Of note, significantly higher SUA levels in SSc patients than in healthy controls were found in this study. Obesity, renal impairment and older age are known to be the major causes of hyperuricemia [31, 32]. However, SSc patients had significantly lower BMI and comparable eGFR and age than controls in our data. The higher SUA levels in SSc patients than controls cannot be explained by these factors. Positive association between circulating inflammatory markers such as CRP and SUA levels was observed in previous studies [33], and striking similarities between serum CRP and SUA levels as markers of CVDs and inflammation have been suggested [34]. Because SSc patients had significantly higher CRP levels than controls in our study, we assumed that inflammatory state triggered by autoimmunity in SSc patients may be linked with increased SUA levels. However, it is yet unclear whether uric acid is only a maker for pro-inflammatory state or whether it can cause inflammation or vice versa [34]. In addition, we found no correlation between CRP and SUA levels in our study. Thus, this hypothesis should be validated by further research. It is known that uric acid is released by ischemic tissues and is a marker of damaged cells [15]. Thus, chronic ischemia due to obliterative vasculopathy in SSc may raise SUA levels in patients with SSc compared with controls. In addition, as patients with SSc might have other unknown sources of uric acid that are related to disease severity and hyperuricemia can be induced by high intake of alcohol, fructose, red meat, and certain drugs including thiazide, which were not fully assessed in this study. Therefore, whether SUA levels are more elevated in SSc patients than in general populations warrants further investigations.

The association of SUA levels with clinical features other than DUs in SSc patients was also investigated in this study. First, unexpectedly, SUA levels in SSc patient with anti-Scl70 antibody positivity were significantly lower than in those without this feature. However, this may be an incidental finding because of the small sample size, and replications are required in further larger studies. Second, the extent of skin thickness evaluated by MRSS did not correlate with SUA levels, implying the limited role of uric acid in skin fibrosis in SSc. A large body of evidence supports that uric acid could lead to renal fibrosis by inducing inflammation, oxidative stress, and fibroblast activation [35, 36] whereas no significant association between SUA and development of liver fibrosis was found in a recent meta-analysis [37]. Thus, the effect of uric acid on the fibrotic process may differ between organs and diseases. More insight into the relationship between uric acid and pathologic fibrosis is needed. Third, unlike the general population, SUA levels did not significantly correlate with eGFR in SSc patients in this study. The exact causes for this finding are uncertain. Renal tubular handling or regulation of uric acid may be different between SSc patients and healthy subjects. Moreover, we calculated eGFR based on CKI-EPI equation which has been suggested as a more accurate tool than other formulae to assess renal function in SSc patients with normal serum creatinine levels [38]. However, there is yet no gold standard for measurement of kidney function in SSc patients, and eGFR calculated based on serum creatinine levels can be affected by muscle wasting which is highly prevalent among SSc patients [38, 39]. Thus, eGFR assessed based on serum

creatinine levels may not exactly represent renal function in SSc patients in our data. Beyond the issue of the accuracy in the eGFR calculations, it is possible that SSc might cause different rates of elevation of uric acid levels depending on their disease process. Fourth, no significant positive association between BMI and SUA levels in SSc patients was observed. This finding appears to be inconsistent with previous epidemiologic studies showing that obesity along with insulin resistance is closely associated with hyperuricemia in the general population [40]. SSc patients showed significantly higher insulin resistance than healthy subjects despite their significantly lower BMI [23] and SSc-related factors such as malnutrition, muscle wasting, and physical inactivity can reduce BMI in this population. Thus, it is difficult to use BMI as a clinical index of obesity or insulin resistance, which could explain our results. Finally, in contrast to data from previous research such as the DETECT study [17], we did not find an association between SUA levels and PAH in our study. These discordant results may be due to the small numbers of PAH cases in patients with SSc in our study. In addition, serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) is considered a biomarker for PAH in SSc [17, 41]. Because the pathophysiologies of PAH and DUs in SSc are similar, it is possible that NT-proBNP could also be associated with DUs. Otherwise, SUA levels were reported to be correlated with serum NT-proBNP levels in patients with systemic lupus erythematosus and PAH [42, 43]. Thus, further researches are needed to investigate the relationship between NT-proBNP and SUA levels and DUs in patients with SSc.

Potential limitations in the present study must be considered. First, given its cross-sectional nature, this study did not fully determine the cause–effect relationship between SUA levels and DUs, as mentioned above. Second, only female SSc patients were recruited. Thus, further studies are needed to investigate whether our results also hold true for male counterparts. Third, information regarding smoking, alcohol use, and physical activity which may act as confounding factors for the association between SUA levels and DUs was not fully obtained in this study. Fourth, almost a quarter of patients with SSc (26.8%) were receiving D-penicillamine in our study. Although there is no evidence for the efficacy of D-penicillamine in the treatment of skin fibrosis, this medication has been routinely prescribed for SSc patients in our center. However, we conjecture that the use of D-penicillamine is unlikely to have had a significant impact on the association between SUA levels and DUs in this study. Finally, the controls-to-patients ratio seems to be high in the present study. It was difficult to recruit enough patients with SSc in this study due to its rarity. Instead, we tried to recruit as many healthy controls as possible in this study.

In conclusion, this study revealed that SSc patients had significantly increased SUA levels than controls, and elevated SUA levels are associated with DUs regardless of confounding factors. Along with recent data supporting hyperuricemia as an emerging risk factor in vascular diseases such CVDs and PAH, our results may be able to give an insight into the potential role of uric acid as a biomarker or contributor for microvascular involvement in SSc such as DUs. However, given the cross-sectional nature of our study, further studies are needed to ascertain whether increasing SUA levels may have direct causal effect on the development of SSc vasculopathy.

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Author contributions EK: study design, data collection, analysis and interpretation and writing manuscript, HNL: data collection and analysis, YKK: data interpretation, GTK: data interpretation, MWS: data analysis and interpretation, EA: data analysis and interpretation, DHS: revision of manuscript, SGL: study design, data analysis and interpretation, writing manuscript and coordination of entire study.

Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

Ethical standards The present study was approved by the Research and Ethical Review Board of Pusan National University Hospital (IRB no. H-1402-005-014). All study participants provided written informed consent in accordance with the principles of the Declaration of Helsinki.

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