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Influence of systemic sclerosis on periodontal health: A case–control study

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Abstract

Aim: Patients with systemic sclerosis (SSc) present various clinical and radiological oral manifestations. However, precise evaluation of the oral features associated with diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc) is limited. The objective of this study was to evaluate the periodontal ligament (PDL) surface in SSc patients in comparison with controls. Assessment of oral-health-related quality of life (OHRQoL) and the levels of different biomarkers in the gingival crevicular fluid (GCF) was performed.

Materials and Methods: SSc patients and matched controls underwent standardized oral examination and cone-beam computed tomography (CBCT). Levels of interleukin-6 (IL-6), chemokine (C-X-C motif) ligand 4 (CXCL-4) and matrix metalloproteinase-9 (MMP-9) in the GCF were determined by enzyme-linked immunosorbent assay. PDL surface was measured on CBCT axial views. OHRQoL was quantified using the Mouth Handicap in SSc Scale (MHISS).

Results: Thirty-nine SSc patients and 39 controls were included. SSc patients exhibited increased PDL surface, higher number of missing teeth as well as elevated IL-6, MMP-9 and CXCL-4 levels. Reduced mouth opening was observed in dcSSc but not in lcSSc patients. MHISS score was higher in dcSSc than in lcSSc patients. Although worse periodontal parameters were found in both subgroups compared with controls, dcSSc patients presented lower gingival inflammation.

Conclusions: SSc is associated with PDL space widening, impaired oral health and OHRQoL.

KEYWORDS
autoimmunity, gingival crevicular fluid, periodontal diseases, periodontitis, systemic sclerosis

Clinical Relevance

Scientific rationale for study: Systemic sclerosis (SSc) is an autoimmune disease characterized by excessive deposition of extracellular matrix proteins leading to tissue fibrosis. The aim of this study was to evaluate the oral condition of patients with limited (lcSSc) and diffuse (dcSSc) forms of SSc compared with the general population.

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Principal findings: SSc patients presented increased periodontal ligament (PDL) surface, as well as higher levels of plaque and attachment loss than controls. Increased levels of interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and chemokine (C-X-C motif) ligand 4 (CXCL-4) were measured in the gingival crevicular fluid (GCF) of SSc patients. Interestingly, patients with dcSSc showed reduced mouth opening but less gingival inflammation.
Practical implications: PDL widening is associated with SSc and could be a hallmark of SSc severity. SSc patients exhibit worsened periodontal status and should be monitored frequently. In patients with dcSSc, severe fibrosis of the gingival tissue may mask the signs of acute inflammation, making the diagnosis of periodontal disease more difficult. Screening and management of oral diseases in this specific group of patients should be performed to improve their quality of life.

1 | INTRODUCTION

Systemic sclerosis (SSc) is a rare and complex autoimmune disease affecting predominantly women and characterized by tissue fibrosis, vasculopathy and immune dysfunction (Cutolo et al., 2019). SSc is divided into two subsets based on the extent of skin fibrosis. In limited cutaneous SSc (lcSSc), skin involvement is restricted to the face and the distal extremities, whereas diffuse cutaneous SSc (dcSSc) is characterized by proximal skin fibrosis (LeRoy et al., 1988) and a more severe clinical course.

SSc has been associated with orofacial manifestations including microstomia, xerostomia, tooth decay and periodontitis (Jung et al., 2017), most of them impacting the quality of life (QoL) (Baron et al., 2014). Periodontitis and SSc present a comparable disease course and involve various proinflammatory mediators (Skaug & Assassi, 2019). Interleukin-6 (IL-6) is increased in SSc patients' sera (Khan et al., 2012) and participates in the degradation of the extracellular matrix (ECM) (Brown & O'Reilly, 2019; Dufour et al., 2018; Khan et al., 2012). Chemokine (C-X-C motif) ligand 4 (CXCL-4) is a potent anti-angiogenic chemokine implicated in the initiation and progression of fibrosis (Silva-Cardoso et al., 2020) and can be used as a predictive biomarker for severe SSc (van Bon et al., 2014). Matrix metalloproteinases (MMPs) degrade the ECM components and contribute to periodontal tissue destruction. They may represent a risk factor for periodontitis, and their monitoring could be useful for the early detection of periodontal disease (Checchi et al., 2020; Yang et al., 2019). Considering their crucial role in tissue remodelling, MMPs have also been involved in SSc. Elevated circulating MMP-9 concentrations were correlated with skin thickness, suggesting that MMP-9 contributes to the fibrotic process (Kim et al., 2005). To date, the levels of these biomarkers have not been measured in the gingival crevicular fluid (GCF) in the context of SSc.

Several radiographic features have also been described in SSc patients, in particular periodontal ligament (PDL) widening. However, most of the descriptions are based on case reports or subjective analyses of radiographs, and only a few studies present objective measurements of the PDL space (Alexandridis & White, 1984; Dagenais et al., 2015; Iordache et al., 2019; Leung et al., 2011; Marmary et al., 1981; Wood & Lee, 1988).

The main objective of this case–control study was to evaluate the PDL surface in SSc patients using cone-beam computed tomography (CBCT) in comparison with controls. We also aimed to assess the oral status, the oral-health-related QoL (OHRQoL), as well as the levels of biomarkers in the GCF obtained from SSc patients and controls.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This case–control study (ClinicalTrials.gov identifier: NCT02371005) was conducted in the University Hospital of Strasbourg and approved by Ethical Committee ('Comité de Protection des Personnes Est IV' no. 15/09). Written informed consent was obtained from all participants before enrolment to the study.

SSc patients fulfilling the following criteria were invited to participate in the study: age ≥18 years; diagnosis based on the American College of Rheumatology/European League Against Rheumatism criteria (van den Hoogen et al., 2013); >12 teeth suitable for evaluation (third molars were excluded). Sex-matched controls with similar age (±10 years) were recruited from patients attending the same dental clinic who underwent or had to undergo CBCT examination for third molar extraction, impacted teeth assessment or implant planning. Exclusion criteria are described in the Supplementary Methods.

2.2 | Recorded data and parameters

Demographic characteristics as well as oral hygiene habits were recorded. SSc-related clinical and biological parameters were assessed, including severity (lcSSc: skin involvement restricted to the face, neck and area distal to elbows and knees; dcSSc: skin fibrosis also involving the proximal limbs and/or trunk) (LeRoy et al., 1988), clinical manifestations, modified Rodnan skin score (mRSS; skin thickness) (Clements et al., 1993), disease duration and treatments. SSc disease duration was measured as the time (in years) between the onset of the first non-Raynaud manifestation attributable to SSc and inclusion in the

study (early stage <2 years; late stage >2 years). The results of blood tests were also recorded.

2.3 | Oral examination

Plaque index (PI), gingival index (GI) (Loë & Silness, 1963), periodontal probing depth (PPD) and clinical attachment level (CAL) were measured in all teeth (except the third molars) at six sites per tooth to the nearest millimetre using a PCPUNC 15 periodontal probe (Hu-Friedy, Chicago, IL, USA). The number of missing teeth as well as the Decayed, Missing, Filled Teeth-Index (DMFT) were recorded (Klein, 1946). Evaluation of the maximum mouth opening and salivary production is described in the Appendix (Supplementary Methods).

2.4 | Periodontal diagnosis

Periodontal diagnosis was performed according to Tonetti et al. (2018). Periodontal status was defined as healthy, gingivitis and periodontitis stages I/II and III/IV.

2.5 | CBCT examination

CBCT examinations were performed using a NewTom VGI CT device (Quantitative Radiology, Verona, Italy) with high-resolution acquisition (12 × 7.5 cm) centred on the maxilla and mandible. Images were obtained at 110 kV and 12 mA with a 0.2 voxel size and a typical exposure of 5.4 s.

2.6 | PDL surface measurement

PDL surfaces were evaluated on CBCT axial sections (0.5 mm thickness). Measurements were performed on teeth (665 in SSc patients and 707 in controls; except third molars) without significant metal restoration, signs of occlusal trauma or periapical lesion using ImageJ software (version 1.53). The external (PDL–alveolar bone interface) and internal (PDL–cementum interface) limits of PDL were drawn, and two areas were calculated: the internal area corresponding to the root surface, and the external area corresponding to the root and the PDL surfaces (Figure S1). Two values were calculated: PDL surface (external area − internal area) and the ratio (PDL surface divided by internal surface) to normalize the data on the root surface. Two measurements were performed per tooth (middle and apical third).

2.7 | GCF collection

GCF samples were collected at six sites with the deepest PPD. The sample sites were first air-dried and isolated with cotton rolls. Paper points were inserted into the gingival sulcus or the periodontal pocket, maintained for 30 s and immediately stored at −20°C. After thawing, extraction of the samples from the paper points was performed in 0.2 mL of phosphate-buffered saline with 30-min agitation. After centrifugation (3000*g*, 4°C for 5 min), the paper points were removed and the supernatants were kept frozen at −80°C until assayed.

2.8 | Enzyme-linked immunosorbent assay

The concentrations of IL-6, CXCL-4 and MMP-9 in the GCF were determined in a blind fashion using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (human IL6 high-sensitivity [catalogue #ab46042], human PF4 [CXCL-4] [catalogue #ab100628] and human MMP-9 [catalogue #ab100610] ELISA kits; Abcam, Cambridge, UK) following the manufacturer's instructions. GCF samples were used undiluted for IL-6 and CXCL-4 and diluted to a ratio of 1:300 in the assay buffer for MMP-9. The absorbance values were read at 450 nm. The concentrations were calculated using standard curves.

2.9 | Calibration

Three examiners (SJ, MG and OH) were calibrated using a representative sample of subjects (inter-incisal distance, PI, GI, PPD, CAL, DMFT, Saxon test) and CBCT (PDL surface measurements). The inter-observer reliability reached kappa values >.85.

2.10 | Sample size calculation analysis

The sample size was calculated considering PDL width as the primary outcome variable (Leung et al., 2011) to demonstrate a difference of 0.03 mm with an α level of .05 and a power of 90%. The sample size was estimated based on an effect size (Cohen's *d*) of 0.5, corresponding to a medium effect size and assuming a correlation coefficient of .5 between cases and controls. Forty-five subjects per group were needed to achieve this goal.

2.11 | Statistical analyses

Continuous variables are presented as mean with standard deviation, and categorical variables are presented as counts and percentages. To account for individual matching between cases and controls, comparisons between the two groups were performed using paired tests. Continuous variables were compared using the Wilcoxon signed rank test, and categorical variables were compared using the McNemar or Bapkhar tests. Comparisons between independent groups were performed with the Wilcoxon rank sum test for continuous variables and Pearson's Chi-squared test or Fisher's exact test for categorical variables. Correlations were assessed using Spearman's rank correlation

TABLE 1 Socio-demographic characteristics of SSc patients and controls.

Characteristics	SSc patients ($n = 39$)	Controls ($n = 39$)	p-Value
Gender, *n* (%)			1.00
Female	35 (89.7%)	35 (89.7%)	
Male	4 (10.3%)	4 (10.3%)	
Age (years), mean ± SD	51.7 ± 15.3	51.1 ± 15.6	.24
Ethnicity, *n* (%)			.45
Caucasian	33 (84.6%)	30 (76.9)	
African (North Africa)	2 (5.1%)	6 (15.4%)	
African (Black)	2 (5.1%)	2 (5.1%)	
Hispanic	0 (0%)	0 (0%)	
Asian	1 (2.6%)	1 (2.6%)	
Other	1 (2.6%)	0 (0%)	
Occupational status, *n* (%)			**.02**
Working/studying	17 (43.6%)	26 (66.7%)	
Unemployed	9 (23.1%)	2 (5.1%)	
Retired	10 (25.6%)	11 (28.2%)	
Work stoppage/disability	3 (7.7%)	0 (0%)	
Smoking status, *n* (%)			.38
Never smoker	27 (69.2%)	27 (69.2%)	
Current smoker (<10/day)	7 (18.0%)	3 (7.7%)	
Former smoker	5 (12.8%)	9 (23.1%)	

Note: Proportions were compared using the McNemar or Bapkhar test, and continuous variables were assessed using Wilcoxon signed rank test. Significant p-values are in bold.
Abbreviations: SD, standard deviation; SSc, systemic sclerosis.

coefficient (Spearman's ρ). The effects of the covariates of interest on the different outcomes were assessed using univariable and multivariable models. Continuous outcomes including PDL surface, HAQ, MHISS, inter-incisal distance and periodontal parameters were analysed using linear regression models. Results are presented as differences (β coefficients) with their 95% confidence intervals (CIs). The normality of the residuals was assessed graphically using histograms and the Q–Q plot (quantile–quantile plot). Results are presented as relative risk (RR) with their 95% CIs. A p-value <.05 was considered statistically significant. All analyses were performed with the R software version 4.1.1.

3 | RESULTS

3.1 | Subjects and disease characteristics

Seventy-eight patients met the inclusion criteria and were included: 39 SSc patients and 39 sex-matched controls with a mean age of 51.7 ± 15.3 years and 51.1 ± 15.6 years, respectively (Table 1). The female-to-male ratio was 8.75:1 (Table 1). In all, 71.8% of the patients were affected by SSc for more than 2 years (Table 2), 53.8% has lcSSc and 46.2% had dcSSc with a mean mRSS of 5.19 ± 4.83 and 20.17 ± 8.08, respectively. Complications were 2 times more common in patients with dcSSc (66.7% vs. 33.3% in lcSSc patients, $p = .04$), with a higher frequency of cardiac manifestations. As described, anti-centromere antibodies were more frequently detected in patients with lcSSc, whereas anti-Scl70 antibodies were mainly found in dcSSc patients (Table 2). Of the total, 77.8% of dcSSc patients and 28.6% of lcSSc patients received disease-modifying anti-rheumatic drugs (DMARDs) (Table S1).

3.2 | Oral hygiene habits

In the patient group, 79.5% of SSc patients had a regular dental follow-up. Nearly all SSc patients (97.4%) and all controls performed daily toothbrushing. No significant differences were observed in terms of frequency of use of interdental devices between SSc patients and controls, nor between the lcSSc and dcSSc subgroups (Table S2).

3.3 | PDL surface

A significant increase of both the PDL surface and PDL ratio was found in SSc patients compared with controls (Figure 1a, Table 3). When considering disease severity subgroups, the differences observed with the control group remained statistically significant (Table 3). However, no statistically significant difference between lcSSc and dcSSc patients (Table 3) or between early- and late-stage

TABLE 2 Clinical and biological characteristics of SSc patients.

Characteristics	SSc patients ($n = 39$)	lcSSc ($n = 21$)	dcSSc ($n = 18$)	p-Value dcSSc vs. lcSSc
Age at onset of Raynaud's phenomenon (years), mean ± SD	35.5 ± 15.9 ($n = 38$)	36.1 ± 13.7 ($n = 20$)	34.8 ± 18.5	.81
First manifestation of Raynaud's phenomenon, *n* (%)	$n = 38/39$	$n = 20/21$		.08
Sclerodactyly	12 (31.58%)	7 (35%)	5 (27.78%)	
Gastroesophageal reflux	7 (18.42%)	6 (30%)	1 (5.56%)	
Scleredema	5 (13.16%)	3 (15%)	2 (11.11%)	
Skin sclerosis	4 (10.53%)	0 (0%)	4 (22.22%)	
Others	10 (26.32%)	4 (20%)	6 (33.33%)	
Disease duration[a] (years), mean ± SD	9.91 ± 11.99 ($n = 36$)	10.03 ± 13.72 ($n = 19$)	9.79 ± 10.12 ($n = 17$)	.93
Stage, *n* (%)				.76
Early stage (<2 years)	11 (28.21%)	5 (23.81%)	6 (33.3%)	
Late stage (≥2 years)	28 (71.79%)	16 (76.19%)	12 (66.67%)	
Age at diagnosis (years), mean ± SD	42.7 ± 17.3 ($n = 38$)	46.6 ± 16.3 ($n = 20$)	38.5 ± 17.7	.13
Clinical manifestations, *n* (%)				
Gastroesophageal reflux	29 (74.36%)	15 (71.43%)	14 (77.78%)	.93
Telangiectasias	25 (64.10%)	13 (61.90%)	12 (66.67%)	1
Digital ulcers	13 (33.3%)	4 (19.05%)	9 (50%)	.09
Calcinosis	8 (20.51%)	4 (19.05%)	4 (22.22%)	1
At least one complication, *n* (%)	19 (48.72%)	**7 (33.33%)**	**12 (66.67%)**	**.04**
Type of complication, *n* (%)				
ILD	9 (23.08%)	2 (9.52%)	7 (38.89%)	.06
Pulmonary fibrosis	2 (5.12%)	0 (0%)	2 (11.11%)	.21
PHTN	2 (5.12%)	2 (9.52%)	0 (0%)	.49
Cardiac involvement	4 (10.26%)	0 (0%)	4 (22.22%)	**.04**
Renal involvement	0 (0%)	0 (0%)	0 (0%)	1
Others	5 (12.82%)	3 (14.29%)	2 (11.11%)	1
mRSS, mean ± SD	12.10 ± 9.94	5.19 ± 4.83	20.17 ± 8.08	**<.001**
HAQ, mean ± SD	0.87 ± 0.75 ($n = 34$)	0.42 ± 0.53 ($n = 19$)	1.43 ± 0.59 ($n = 15$)	**<.001**
Autoantibodies, *n* (%)	38 (97.44)	20 (95.24%)	18 (100%)	1
Antinuclear antibodies, *n* (%)	32 (82.05%)	18 (85.71%)	14 (77.78%)	.82
Titre, mean ± SD	1156 ± 328.2 ($n = 30/32$)	1145.9 ± 307.6 ($n = 17/18$)	1169.2 ± 365.9 ($n = 13/14$)	.63
Pattern, *n* (%)	$n = 29/32$	$n = 18/18$	$n = 11/14$	**.02**
Homogeneous (H-ANA)	1 (3.45%)	0 (0%)	1 (9.09%)	
Speckled (S-ANA)	7 (24.14%)	4 (22.22%)	3 (27.27%)	
Nucleolar (N-ANA)	4 (13.79%)	1 (5.55%)	3 (27.27%)	
Centromere (Cent-ANA)	9 (31.03%)	9 (50%)	0 (0%)	
Cytoplasmic (C-ANA)	0 (0%)	0 (0%)	0 (0%)	
Others	8 (27.59%)	4 (22.22%)	4 (36.36%)	
Specificity, *n* (%)				
Anti-centromere (ACA)	13 (33.33%)	**12 (57.14%)**	1 (5.56%)	**<.001**
Anti-Scl-70	14 (35.90%)	2 (9.52%)	**12 (66.67%)**	**<.001**
Anti-RNA polymerase III	4 (10.26%)	1 (4.76%)	3 (16.67%)	0.32
Others	6 (15.38%)	2 (9.52%)	4 (22.22%)	0.39

Note: Proportions were compared using Pearson's chi-squared test or Fisher's exact test, and continuous variables were assessed using Wilcoxon rank sum test. Significant p-values are in bold.

Abbreviations: ACA, anticentromere antibodies; ANA, antinuclear antibodies; anti-Scl-70, anti-topoisomerase 1 antibody; dcSSc, diffuse cutaneous SSc; HAQ, Health Assessment Questionnaire; ILD, interstitial lung disease; lcSSc, limited cutaneous SSc; mRSS, modified Rodnan skin score; PHTN, pulmonary hypertension; SD, standard deviation; SSc, systemic sclerosis.

[a]Period between disease onset (first manifestation out of Raynaud's phenomenon) and patient's inclusion.

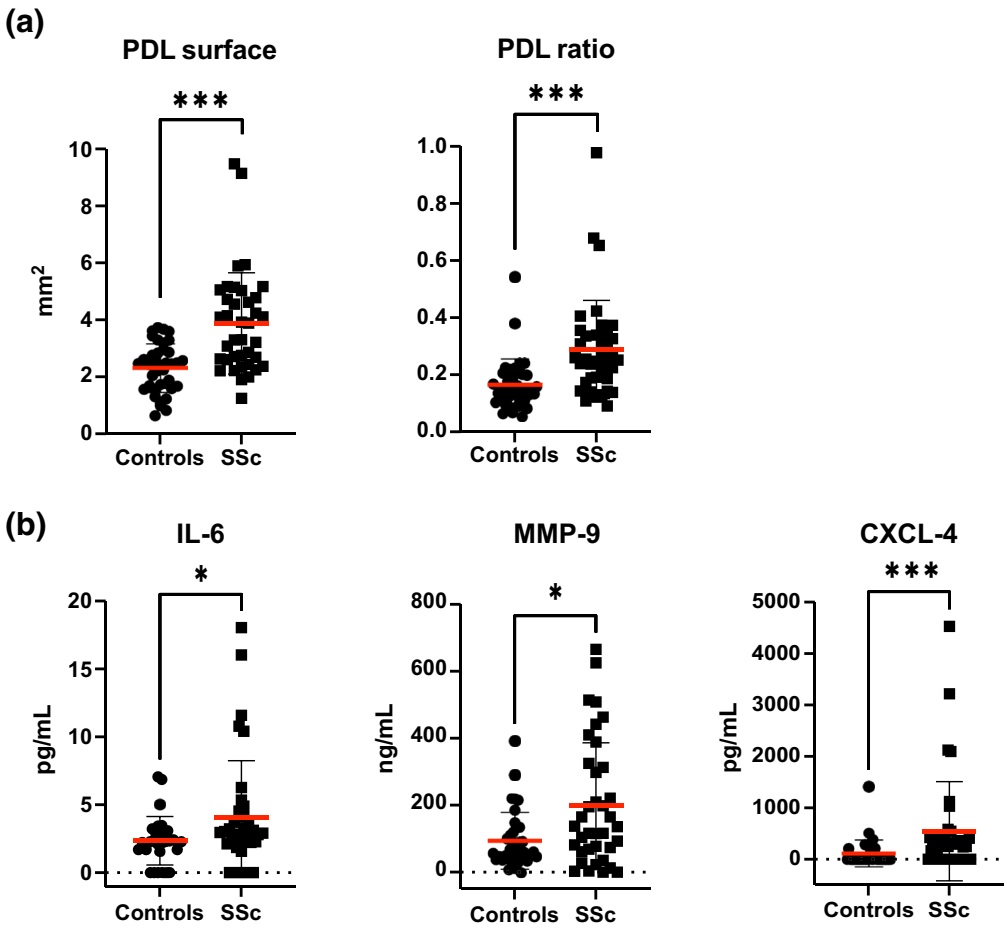

FIGURE 1 Periodontal ligament (PDL) surface and biomarker levels in the gingival crevicular fluid (GCF) of systemic sclerosis (SSc) patients and matched healthy controls. (a) PDL surfaces were measured (in square millimetre) on cone-beam computed tomography (CBCT) axial sections. The PDL ratio represents the normalization of the PDL surface on the root surface. (b) Concentrations of interleukin-6 (IL-6; in picograms per millilitre), matrix metalloproteinase 9 (MMP-9; in nanograms per millilitre) and chemokine (C-X-C motif) ligand 4 (CXCL-4; in picograms per millilitre) were measured by enzyme-linked immunosorbent assay in the GCF of SSc patients (black circles) and controls (black squares). The red bars represent the mean concentrations and the black bars standard deviations. Significant results of the Wilcoxon signed ranked test are indicated are indicated (*$p < .05$; ***$p < .001$).

disease was observed (PDL surface: 3.285 ± 1.144 vs. 4.114 ± 1.949, $p = .09$; PDL ratio: 0.243 ± 0.085 vs. 0.307 ± 0.195, $p = .16$). A negative association between enlarged PDL (surface and ratio) and maximum mouth opening, as well as between enlarged PDL and PI, was observed, but no correlation was found with disease duration, mRSS skin score, number of missing teeth, DMFT index, GI, PPD and CAL (Table 4).

3.4 | Oral features

Maximum mouth opening was significantly reduced in patients with dcSSc compared with controls, but not in patients with lcSSc. Number of missing teeth and DMFT index were higher in SSc patients, but this difference was not statistically significant when considering disease subgroups (i.e., lcSSc and dcSSc vs. controls). No difference in terms of unstimulated saliva production or in periodontal diagnosis between SSc patients and controls was detected (Table 3). Regarding periodontal parameters, SSc patients showed significantly higher PI, GI, PPD and CAL. When considering disease subgroups, the differences observed with the control group remained statistically significant in lcSSc and dcSSc for PI and PPD, but only in lcSSc for GI (Table 3). However, we found no difference in oral variables between early- and late-stage SSc.

No correlation between skin thickness score (mRSS) and oral features (number of missing teeth, DMFT, periodontal parameters), except an expected negative association with maximum mouth opening (Spearman's $\rho = -.54$, $p < .001$), was observed. However, both PI and PPD were significantly correlated with reduced mouth opening (Spearman's $\rho = -.32$, $p = .04$). In addition, PPD was associated with increased PI (Spearman's $\rho = 1$, $p < .001$), GI (Spearman's $\rho = .43$, $p = .01$) and CAL (Spearman's $\rho = .32$, $p = .04$).

3.5 | Biomarkers in the GCF

Levels of IL-6, MMP-9 and CXCL-4 were significantly elevated in the GCF of SSc patients compared with the control group (Figure 1b). The differences observed in CXCL-4 levels between SSc patients and controls remained statistically significant regardless of the disease subgroup (i.e., lcSSc/dcSSc) and duration (i.e., early-stage/late-stage disease) (Table 5). Interestingly, the differences in MMP-9 levels remained statistically significant only in patients with early-stage disease (Table 5). Although MMP-9 and CXCL-4 levels did not correlate with other disease characteristics such as the existence of complications, or with mRSS skin score, a statistically significant positive correlation with periodontal parameters including CAL, PPD and GI was observed (Table 6). No correlation was detected between IL-6 levels

TABLE 3 Oral status of SSc patients and controls.

Characteristics	Controls ($n = 39$)	SSc patients ($n = 39$)	lcSSc ($n = 21$)	dcSSc ($n = 18$)	*p*-Value SSc vs. control	*p*-Value lcSSc vs. dcSSc	*p*-Value lcSSc vs. controls	*p*-Value dcSSc vs. controls
Maximum mouth opening (mm)	46.2 ± 7.6	36.1 ± 10.7	42.4 ± 9.4	28.7 ± 6.8	**<.001**	**<.001**	.12	**<.001**
No. of missing teeth[a]	3.0 ± 3.3	4.6 ± 4.3	3.7 ± 3.2	5.6 ± 5.2	**.03**	.62	.62	.23
DMFT	11.9 ± 7.8 [3]	15.5 ± 6.3 [1]	15.8 ± 6.5 [1]	15.2 ± 6.3	**.01**	.69	.29	.37
Periodontal measurements								
PI	0.3 ± 0.3	0.9 ± 0.5	0.8 ± 0.5	0.9 ± 0.5	**<.001**	.41	**<.001**	**<.001**
GI	0.5 ± 0.4	0.8 ± 0.5	0.9 ± 0.4	0.7 ± 0.5	**.01**	.41	**.01**	.41
PPD (mm)	1.7 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	2.1 ± 0.5	**.01**	.68	**.02**	**.02**
CAL (mm)	2.2 ± 0.7	2.7 ± 0.9	2.6 ± 0.8	2.8 ± 1.0	**.01**	.52	.16	.07
Periodontal diagnosis, *n* (%)								
Healthy	5 (12.8%)	6 (15.4%)	1 (4.8%)	5 (27.8%)	.97	.054	.45	.40
Gingivitis	14 (35.9%)	13 (33.3%)	9 (42.9%)	4 (22.2%)				
Periodontitis stage I–II	8 (20.5%)	7 (18.0%)	2 (9.5%)	5 (27.8%)				
Periodontitis stage III–IV	12 (30.8%)	13 (33.3%)	9 (42.9%)	4 (22.2%)				
Unstimulated saliva production (mg/min)	1146 ± 830	938 ± 618	962 ± 682	909 ± 553	0.37	1	1	1
MHISS								
Total score	2.6 ± 3.8 [1]	18.9 ± 12.9 [1]	11.4 ± 8.7	28.2 ± 11.3 [1]	**<.001**	**<.001**	**<.001**	**<.001**
Score for the handicap related to reduced salivary secretion	1.4 ± 1.8 [1]	7.3 ± 5.1 [1]	4.9 ± 3.9	10.4 ± 4.8 [1]	**<.001**	**<.001**	**<.001**	**<.001**
PDL								
PDL surface (mm^2)	2.308 ± 0.836 [1]	3.904 ± 1.794 [1]	3.625 ± 1.299 [1]	4.150 ± 2.203	**<.001**	.198	**<.001**	**<.001**
PDL ratio	0.166 ± 0.088 [1]	0.288 ± 0.175 [1]	0.294 ± 1.183 [1]	0.282 ± 0.164	**<.001**	.823	**<.001**	**<.001**

Note: Values are presented as mean ± SD except for periodontal diagnosis that is presented as *n* (%). Number of missing values in indicated into brackets. Proportions were compared using Pearson's chi-squared test or Fisher's exact test and continuous variables were assessed using Wilcoxon rank sum test. Significant *p*-values are highlighted in bold. The PDL ratio represents the normalisation of the PDL surface on the root surface.

Abbreviations: CAL, clinical attachment level; dcSSc, diffuse cutaneous SSc; DMFT, Decayed, Missing, and Filled Teeth Index; GI, gingival index; lcSSc, limited cutaneous SSc; MHISS, mouth handicap in systemic sclerosis; No, number; PDL, periodontal ligament; PI, plaque index; PPD, periodontal probing depth; SD, standard deviation; SSc, systemic sclerosis.

[a]Excluding wisdom teeth.

TABLE 4 Correlations with disease and periodontal parameters.

Parameters	PDL surface (mm^2)		PDL ratio		HAQ		MHISS	
	Correlation coefficient (95% CI)	*p*-Value	Correlation coefficient (95% CI)	*p*-Value	Correlation coefficient (95% CI)	*p*-Value	Correlation coefficient (95% CI)	*p*-Value
mRSS	−.07 (−0.38; 0.25)	.68	−.13 (−0.42; 0;19)	.44	.67 (0.43; 0.82)	**<.001**	.54 (0.26; 0.73)	**<.001**
Maximum mouth opening (mm)	−.29 (−0.48; −0.05)	**.01**	−.32 (−0.51; −0.09)	**<.001**	−.59 (−0.78; −0.32)	**<.001**	−.44 (−0.67; −0.14)	**.01**
No. of missing teeth[a]	−.03 (−0.25; 0.20)	.82	.14 (−0.09; 0.36)	.14	.23 (−0.11; 0.53)	.18	.32 (0.00; 0.58)	**.05**
DMFT	.04 (−0.19; 0.27)	.76	.15 (−0.10; 0.38)	.21	−.04 (−0.37; 0.31)	.87	.12 (−0.21; 0.43)	.49
Periodontal parameters								
PI	.40 (0.18;0.58)	**<.001**	.38 (0.16; 0.58)	**<.001**	.23 (−0.12; 0.52)	.20	.38 (0.07; 0.62)	**.02**
GI	.10 (−0.14; 0.33)	.41	.10 (−0.13; 0.34)	.37	−.25 (−0.54; 0.10)	.16	−.05 (−0.36; 0.27)	.76
PPD (mm)	.14 (−0.10; 0.38)	.21	.22 (−0.03; 0.46)	.06	.03 (−0.31; 0.36)	.87	.28 (−0.04; 0.55)	.09
CAL (mm)	.14 (−0.10; 0.36)	.23	.17 (−0.08; 0.41)	.14	.04 (−0.30; 0.37)	.83	.25 (−0.08; 0.53)	.13

Note: Values are presented as correlation coefficient (95% confidence interval [CI]). The PDL ratio represents the normalization of the PDL surface on the root surface. Correlations were assessed using Spearman's rank correlation coefficient. Significant *p*-values are in bold.
Abbreviations: CAL, clinical attachment level; DMFT, Decayed, Missing, and Filled Teeth Index; GI, gingival index; HAQ, Health Assessment Questionnaire; MHISS, mouth handicap in systemic sclerosis; mRSS, modified Rodnan skin score; PDL, periodontal ligament; PI, plaque index; PPD, periodontal probing depth; SD, standard deviation.
[a]Excluding wisdom teeth.

TABLE 5 Biomarkers levels in the GCF of SSc patients and controls.

Biomarkers levels	Controls ($n = 37$)	lcSSc ($n = 21$)	dcSSc ($n = 16$)	*p*-Value lcSSc vs. dcSSc	*p*-Value lcSSc vs. controls	*p*-Value dcSSc vs. controls
IL-6 (pg/mL)	2.4 ± 1.8	4.1 ± 4.4	4.0 ± 4.0	.66	.18	.28
MMP-9 (ng/mL)	94.0 ± 83.4	201.4 ± 184.2	197.7 ± 195.8	.90	.14	.14
CXCL-4 (pg/mL)	115.7 ± 258.6	589.1 ± 1083.9	485.6 ± 810.3	.91	**.007**	**.02**

Biomarkers levels	Controls ($n = 37$)	Early stage <2 years ($n = 10$)	Late stage ≥2 years ($n = 27$)	*p*-Value Late vs. early stage	*p*-Value Early stage vs. controls	*p*-Value Late stage vs. controls
IL-6 (pg/mL)	2.4 ± 1.8	3.8 ± 3.0	4.2 ± 4.6	.48	.13	.24
MMP-9 (ng/mL)	94.0 ± 83.4	243.7 ± 198.8	183.5 ± 183.1	.28	**.005**	.28
CXCL-4 (pg/mL)	115.7 ± 258.6	931.0 ± 1124.6	401.1 ± 877.3	.10	**.002**	**.02**

Note: Values are presented as mean ± SD. Proportions were compared using Pearson's chi-squared test or Fisher's exact test. Significant *p*-values are in bold.
Abbreviations: CXCL-4, chemokine (C-X-C motif) ligand 4; dcSSc, diffuse cutaneous SSc; GCF, gingival crevicular fluid; IL-6, interleukin-6; lcSSc, limited cutaneous SSc; MMP-9, matrix metalloproteinase-9; SSc, systemic sclerosis.

in GCF and SSc clinical parameters or periodontal parameters, but a positive correlation between MMP-9 and CXCL-4 was observed in patients with dcSSc (coefficient = .73, $p < .001$ and .49, $p < .02$ in lcSSc).

3.6 | Quality of life

HAQ (Table 2) and MHISS (Table 3) QoL scores were higher in dcSSc patients than in lcSSc patients (HAQ: 1.43 ± 0.59 vs. 0.42 ± 0.53, $p < .001$; MHISS: 28.2 ± 11.3 vs. 11.4 ± 8.7, $p < .001$) as well as in patients who developed organ complications (HAQ: 1.2 ± 0.8 vs. 0.5 ± 0.5, $p = .003$; MHISS: 24.6 ± 13.2 vs. 13.8 ± 10.5, $p < .001$). When considering the items specifically assessing the handicap related to mouth dryness in the MHISS scale (domain 2), SSc patients, in particular those with dcSSc, had significantly higher scores than controls, suggesting that xerostomia is a prominent symptom associated with SSc (Table 3).

Both HAQ and MHISS QoL scores correlated positively with mRSS (Spearman's $\rho = .67$ and .54 respectively, $p < .001$) and

TABLE 6 Correlations between biomarkers levels in the GCF and periodontal parameters.

	IL-6		MMP-9		CXCL-4	
Periodontal parameters	Correlation coefficient (95% CI)	*p*-Value	Correlation coefficient (95% CI)	*p*-Value	Correlation coefficient (95% CI)	*p*-Value
PI	−.22 (−0.51; 0.11)	.20	.05 (−0.28; 0.37)	.78	.11 (−0.22; 0.42)	.50
GI	−.05 (−0.22; 0.28)	.76	.34 (0.01; 0.60)	**.04**	.43 (0.13; 0.66)	**.01**
PPD (mm)	.02 (−0.31; 0.34)	.92	.61 (0.36; 0.78)	**<.001**	.64 (0.39; 0.80)	**<.001**
CAL (mm)	.08 (−0.039; 0.25)	.64	.52 (0.23; 0.72)	**<.001**	.48 (0.18; 0.69)	**<.001**

Note: Values are presented as correlation coefficient (95% confidence interval [CI]). Correlations were assessed using Spearman's rank correlation coefficient. Significant *p*-values are in bold.

Abbreviations: CAL, clinical attachment level; CXCL-4, chemokine (C-X-C motif) ligand 4; GCF, gingival crevicular fluid; GI, gingival index; IL-6, interleukin-6; MMP-9, matrix metalloproteinase-9; PPD, periodontal probing depth; PI, plaque index; SD, standard deviation.

negatively with maximum mouth opening (Spearman's $\rho = -.59$, $p < .001$ and $-.44$, $p = .01$ respectively). MHISS had also an association with PI (Spearman's $\rho = .38$, $p = .02$) and the number of missing teeth (Spearman's $\rho = .32$, $p = .05$) (Table 4).

3.7 | Regression analyses

Univariate analysis revealed that HAQ as well as MHISS score were correlated with skin thickness assessed by higher mRSS score (MHISS: $\beta = .54$ [0.15–0.92], $p = .006$), diffuse form of the disease (MHISS: $\beta = 17$ [10–23], $p < .001$) and the existence of complications (MHISS: $\beta = 11$ [3.3–18], $p = .005$). Inter-incisal distance was inversely associated with higher mRSS score ($\beta = -.49$ [−0.80 to −0.18], $p = .002$) and dcSSc ($\beta = -14$ [−19 to −8.5], $p < .001$), and the number of missing teeth was correlated with the existence of complications (incidence rate ratio [IRR] = 1.41 [1.05–1.91], $p = .022$) as well as dcSSc (IRR = 1.50 [1.11–2.02], $p = .007$). In multivariable analyses, only the association between HAQ ($\beta = .81$ [0.16–1.5], $p = .021$), MHISS ($\beta = 17$ [7.4–27], $p = .002$), inter-incisal distance ($\beta = -15$ [−25 to −6.4], $p = .002$), number of missing teeth ($\beta = 1.87$ [1.14–3.07], $p = .013$) and the diffuse form of the disease remained statistically significant. None of these parameters was correlated with disease duration either in univariate or multivariate models. Neither PDL surface and ratio nor the periodontal parameters were related to disease characteristics in univariate or multivariate analyses.

4 | DISCUSSION

The results of the current investigation showed that SSc is associated with impaired oral health with increased PDL surface, higher number of missing teeth and DMFT score, and worsened periodontal parameters, along with higher levels of IL-6, CXCL-4 and MMP-9 in the GCF.

PDL widening has been shown to be one of the most common radiological findings in SSc, affecting more than one-third of the patients (Dagenais et al., 2015; Iordache et al., 2019). However, only a few studies have presented objective PDL measurements (Dagenais et al., 2015; Iordache et al., 2019; Leung et al., 2011; Wood & Lee, 1988). Recently, Iordache et al. assessed PDL enlargement using a three-dimensional CBCT approach by evaluating PDL width at different points (Iordache et al., 2019). Here, we showed that both the PDL surface and ratio were increased in SSc patients compared with matched controls. However, unlike Baron et al., no significant association between PLS widening and disease severity or shorter disease duration (i.e., early stage disease) was observed (Baron et al., 2016).

Various hypotheses have been suggested, including occlusal trauma, to explain PDL widening in SSc. Indeed, in SSc patients, the masticatory muscles may become bulkier secondary to fibrosis, leading to increased occlusal forces and subsequent PLS widening, in particular around posterior teeth (Auluck, 2007). However, occlusal trauma induces angular bone defects and tooth mobility, which are usually not observed in teeth with enlarged PDL during SSc (Jagadish et al., 2012; Mehra, 2008). In addition, the lamina dura is intact in most cases (Anbiaee & Tafakhori, 2011). PDL widening may therefore reflect increased collagen deposition and the fibrotic process observed in SSc (Baron et al., 2015). Further studies are needed to assess whether this radiographic sign could be used as a potential diagnostic marker. To our knowledge, there are no clinical consequences of PLS widening, and the affected teeth require no intervention. Indeed, similar to Baron et al., we did not find any correlation between thickening of the PLS and periodontal parameters or the number of missing teeth (Baron et al., 2015). However, lack of awareness of this specific radiographic feature can lead to diagnosis and treatment misconducts, thereby increasing the mouth handicap.

In this study, the reduction of mouth opening was found only in dcSSc patients, reflecting the more extensive fibrosis associated with this disease subset. However, although worsened periodontal parameters were observed in both lcSSc and dcSSc patients, GI was significantly increased only in lcSSc patients. On similar lines, Pischon et al. (2016) reported a distinctive pattern of periodontitis in SSc patients with higher periodontal attachment loss but lower gingival inflammation scores (gingival and bleeding indices). Fibrosis of the gingival tissue may mask the signs of acute inflammation, making the diagnosis of periodontal disease more difficult. However, the underlying mechanisms are unknown, and more sensitive tests are required to determine the molecular aspect of the inflammation in SSc patients. Previous studies have shown that microvascular alterations, a major

hallmark of SSc, also involve the periodontium (Scardina et al., 2005). Defective vascularization may play a role in the pathogenesis of periodontal diseases associated with SSc, impairing the immune response against periodontal pathogens and decreasing healing capacities. Gingival inflammation is therefore not a constant clinical feature associated with periodontal disease in dcSSc patients, highlighting the importance of regular and thorough periodontal examinations.

Levels of IL-6, MMP-9 and CXCL-4 were elevated in GCF samples from SSc patients. Besides a positive correlation between MMP-9 and CXCL-4 concentrations, the latter also correlated with periodontal parameters including CAL and PPD. It was shown that TNF-α levels were higher in SSc patients than in healthy individuals (Elimelech et al., 2015; Mayer et al., 2013) but no correlation was detected between TNF-α levels and periodontal or SSc clinical parameters, except higher mRSS (Elimelech et al., 2015). SSc has also been associated with a dysregulation of MMP-9 activity (Kobayashi et al., 2014), with increased MMP-9 levels in the serum of SSc patients (Kim et al., 2005). Interestingly, we observed that MMP-9 levels in GCF were significantly elevated only in the early stage, suggesting that MMP-9 could potentially represent an early predictive biomarker of SSc. CXCL-4 is an important serum biomarker in the context of SSc, with elevated levels correlating with severe complications such as lung fibrosis and pulmonary arterial hypertension (van Bon et al., 2014). However, only a few studies have investigated CXCL-4 in the context of periodontitis. It has been shown that the expression of this chemokine is increased in the gingival tissue in a rat model of periodontitis (Coimbra et al., 2014) as well as in the GCF of patients with severe periodontitis (Brousseau-Nault et al., 2017).

No correlation between periodontal parameters and disease parameters was observed as previously described (Baron et al., 2015). However, multivariable analyses showed that not only increased number of missing teeth and OHRQoL score, but also reduced mouth opening, were significantly correlated with dcSSc. Interestingly, MHISS scores were almost 2.5 times higher in patients with dcSSc than in patients with lcSSc, highlighting the stronger impact of dcSSc on the OHRQoL.

Salivary secretion of SSc patients was assessed in different studies, with heterogenous results (Andonopoulos et al., 1989; Baron et al., 2014; Chu et al., 2011; Gomes da Silva et al., 2019, 2020; Nagy et al., 1994). In SSc, reduced salivary production is mainly the consequence of the fibrotic process that develops around the capillaries and excretory ducts of the salivary glands. Sjögren syndrome can however be associated with SSc in up to 30% of the cases, in particular with lcSSc (Avouac et al., 2006; Scherlinger et al., 2021). Despite varying results regarding the salivary flow, xerostomia appears to be a common symptom reported by SSc patients (Avouac et al., 2006; Chu et al., 2011; Kobak et al., 2013; Salliot et al., 2007). When we considered the section of the MHISS questionnaire assessing the handicap related to mouth dryness, we observed that SSc patients had significantly higher scores than controls.

The present study has some limitations, including its cross-sectional design. Unfortunately, due to the COVID-19 epidemic restrictions, the calculated sample size was not reached. However, it still allowed us to highlight significant differences between the groups. Regarding biomarker analyses, neither the volume nor total protein concentration of GCF was measured. Since GCF production increases in response to periodontal inflammation, this represents a limitation. Indeed, this may have introduced a bias in terms of interpretation, as the biomarker concentrations could appear higher in the healthy state. Future studies with prospective design, focusing on the oral phenotype and the GCF levels of various biomarkers in newly diagnosed and untreated patients, are needed to further investigate the impact of SSc on the oral cavity and to validate potential predictive biomarkers. Interventional studies aiming at evaluating the response to periodontal therapy, and also the effect of implementation of adapted oral hygiene measures, are also warranted.

5 | CONCLUSION

In conclusion, SSc patients showed increased PDL surface, worsened periodontal parameters, higher number of missing teeth as well as higher levels of IL-6, MMP-9 and CXCL-4 in the GCF, with an impaired OHRQoL. Our data highlight the importance of developing targeted interventions to improve oral health and OHRQoL in SSc patients.

AUTHOR CONTRIBUTIONS

Conceptualization of the study: Sophie Jung, Thierry Martin and Olivier Huck. *Funding acquisition*: Sophie Jung and Olivier Huck. *Patient inclusions*: Sophie Jung, Emmanuel Chatelus, Thierry Martin and Olivier Huck. *Data analysis*: Sophie Jung, Marianna Gavriiloglou, François Séverac, Lucille Haumesser, Amira Sayeh and Olivier Huck. *Writing-original manuscript*: Sophie Jung and Olivier Huck. *Figure and tables preparation*: Sophie Jung; *Writing-review and editing*: Sophie Jung, Marianna Gavriiloglou, François Séverac, Amira Sayeh, Emmanuel Chatelus, Thierry Martin and Olivier Huck. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This case–control study (ClinicalTrials.gov identifier: NCT02371005) was conducted in the University Hospital of Strasbourg in accordance with the Declaration of Helsinki and approved by the Ethical Committee ('Comité de Protection des Personnes Est IV', March 2015, no. 015/09). Written informed consent was obtained from all participants before enrolment to the study.

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SUPPORTING INFORMATION

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