Periodontal Conditions and Tumor Necrosis Factor-Alpha Level in Gingival Crevicular Fluid of Scleroderma Patients

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ABSTRACT: **Background:** Systemic sclerosis (SSc) is a chronic disease with prominent vasculopathy, inflammation, production of autoantibodies, and tissue fibrosis. Periodontitis is a chronic inflammatory oral condition manifesting as microbial infection, inflammation and destruction of the alveolar bone. In both conditions tumor necrosis factor-alpha (TNFα) and other pro-inflammatory cytokines play an important role in pathogenesis.
Objectives: To assess the periodontal status in SSc patients and compare these parameters to TNFα level in gingival crevicular fluid (GCF) of SSc patients and healthy controls.
Methods: Twenty SSc patients and 20 controls underwent periodontal examination, including probing depth (PD), plaque index (PI), gingival index (GI), bleeding on probing (BOP), and measurement of TNFα levels in collected GCF.
Results: SSc patients had a greater PD (3.74 ± 0.32 mm vs. 3.35 ± 0.31 mm, $P > 0.003$), GI (1.53 ± 0.34 vs. 1.12 ± 0.54, $P > 0.049$), and non-significantly higher BOP than controls. TNFα levels in GCF were higher in SSc patients (1.63 ± 0.36 vs. 1.15 ± 0.34 pg/ml, $P = 0.001$). Periodontitis parameters correlated with several SSc variables; PI in particular was higher in patients with longer disease duration, sclerodactyly, more severe skin involvement, and SSc activity score.
Conclusions: Patients with SSc have higher indices of periodontal inflammation and higher TNFα level in GCF than did healthy individuals. These changes probably reflect the complexity of factors that influence oral health in SSc. Common pathologic pathways may be responsible for the association between SSc and periodontitis, which requires further study.

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KEY WORDS: gingival crevicular fluid (GCF), systemic sclerosis (SSc), periodontitis, probing depth (PD), plaque index (PI), gingival index (GI), bleeding on probing (BOP)

Systemic sclerosis (SSc) is a chronic autoimmune disease characterized by widespread obliterative vasculopathy, inflammation, production of specific autoantibodies, and extensive organ and tissue fibrosis. Vascular alterations have been found in the nail fold bed and on biopsies from skin, lungs, oral and gastrointestinal mucosal tissue, and kidney. The initial vascular damage seems to precede and provoke the inflammation and fibrosis, followed by accumulation of collagen and other extracellular matrix components in vessel walls and interstitial tissue. Among cytokines involved in SSc, transforming growth factor-beta (TGFβ), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNFα) have been implicated as playing a pivotal role [1].

Periodontitis is a chronic progressive inflammatory disease manifested by inflammation of the periodontal tissue with destruction of alveolar bone. Periodontal infection contributes to periodontitis. Treatment directed to suppress the microbial load and to restore host-microbe homeostasis may be effective in patients with periodontitis. In some patients, despite antimicrobial therapy, uncontrolled breakdown of periodontal tissue continues and ultimately leads to tooth loss. The severity of periodontitis is thought to be determined by abnormal host immune response with increased pro-inflammatory cytokine production. Release of interferon-gamma (IFNγ) and TNFα by reactive T cells, TNFα production by macrophages, and production of proteolytic enzymes such as matrix metalloproteinases (MMPs), are enhanced in periodontitis [2].

Abnormal periodontal conditions have been reported in SSc patients, among them a high prevalence of limited oral aperture and periodontal disease [3], widening of the periodontal ligament (PDL) [3-7], abnormalities in periodontal microcirculation [8], and loss of gingival attachment [9]. SSc patients often develop finger contractures and deformation (sclerodactyly) that make it almost impossible to grasp items such as a toothbrush and other oral hygiene devices, leading to longstanding poor oral hygiene and the inevitable loss of multiple teeth due to caries and periodontal disease. The combination of elevated pro-inflammatory cytokines, microvascular alterations and poor oral hygiene may enhance the development and progression of periodontitis to SSc.

The aim of this study was to evaluate the periodontal status of SSc patients, measure the levels of TNFα in the gingival crevicular fluid (GCF) and compare them to healthy controls.

PATIENTS AND METHODS

The study group included 20 consecutive SSc patients (according to classification of systemic sclerosis, 1980) attending the Shine Rheumatology Unit Outpatient Clinic at Rambam Health Care Campus in Haifa, Israel. Twenty age-matched and gender-matched healthy subjects who arrived at the periodontology department for initial periodontal examination comprised the control group. After signing a written informed consent, all patients and controls were evaluated in the Department of Periodontology at Rambam Health Care Campus. The study was approved by the Institutional Review Board (Helsinki committee study number 0416-10). Patients under 18 years old, pregnant or lactating were excluded from the study. Patients who had received antibiotic therapy within the previous 6 months or periodontal treatment in the last 12 months were also excluded from the study.

DATA COLLECTION

Patients' demographics, smoking status, clinical (skin and internal organ involvement, arthritis, sclerodactyly, calcinosis, digital ulcers) and laboratory parameters [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), autoantibodies status] were collected from medical records on the day of the visit. Patients' clinical status was assessed by two rheumatologists (A.B.G., Y.B.M.). SSc disease activity was assessed according to the European Scleroderma Disease Activity Index [10].

PERIODONTAL EXAMINATION

Full-mouth periodontal examination was performed by experienced examiners (Y.M., R.E., interobserver agreement κ = 0.93). Assessment of periodontal parameters included probing depth (PD), plaque index (PI), gingival index (GI), and bleeding on probing (BOP). Listed periodontal parameters were assessed in all teeth excluding third molars. PD was measured at six sites per tooth using a University of North Carolina probe (Hu-Friedy, Chicago, IL, USA) recorded in millimetres and presented as mean patient values. BOP was recorded as either present or absent within 30 seconds of probing at six sites per tooth, and the mean bleeding percentage for each patient was calculated. Patients with clinical signs of gingival inflammation without attachment loss were considered to exhibit gingivitis. Periodontitis patients had to exhibit two or more teeth with clinical attachment level (CAL) ≥ 6 mm and at least one site with a PD ≥ 5 mm [11].

TNFα SAMPLING AND ASSAY

GCF samples from each subject were collected from five deepest periodontal pockets that were evaluated at an early screening session. Prior to GCF sampling, supra-gingival plaque was carefully removed using Gracey's curettes, after which the sample sites were isolated with cotton rolls. Each sterile paper strip (PerioPaper, ProFlow, Amityville, NY) was inserted into the pocket for 30 seconds. Samples were wrapped in aluminium foil and stored at -20°C. Total TNFα level in GCF was determined using a quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit (Human TNF-alpha Quantikine HS ELISA, R&D Systems, Minneapolis MN, USA, catalogue # HSTA00D) as described previously by our group [12].

Briefly, filter papers were unwrapped and inserted into a sterile test tube containing 0.5 ml phosphate-buffered saline (PBS). The tubes stood at room temperature for 30 minutes and were then agitated every 5 minutes to facilitate extraction of the sample from the filter paper. A monoclonal antibody specific for TNFα was pre-coated on a microplate. Standards and samples were pipetted into the wells where the immobilized antibody binds the cytokine. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for TNFα was added to the wells. Absorbance values were determined using an ELISA reader at 450 nm. A standard curve was constructed by using standards provided in the kit, and the cytokine concentration was calculated from the standard curve. The color intensity results were obtained using the SUNRISE microplate reader (Magellan™, Tecan Group Ltd. Männedorf, Switzerland). The minimum sensitivity of the assay was 0.191 pg/ml with an assay range of 0.5–32 pg/ml.

STATISTICAL ANALYSIS

Mean ± standard deviation (SD) of the clinical and immunologic parameters was calculated. Analysis of variance (ANOVA) with Scheffe modification was used to test the differences between the clinical periodontal parameters and TNFα level between the SSc patients and the control group. Mann-Whitney U test was used for analysis of periodontal parameters and SSc clinical features. Pearson's correlation coefficient test was used to analyze correlation between TNFα level in GCF and the various periodontal parameters. Results were considered statistically significant at $P < 0.05$.

RESULTS

The demographic, clinical and laboratory status of SSc patients and healthy controls are summarized in Table 1. No statistically significant differences were found between SSc patients and controls with respect to smoking status. Table 2 demonstrates parameters of periodontal status in SSc patients and healthy controls; PD and GI were significantly higher in the SSc patients than in the healthy controls. BOP was non-significantly higher in SSc patients compared to controls while PI did not show any difference. Owing to the minimal number of smokers (n=3), its effect could not be assessed. Eleven SSc patients (55%) had clinical signs of periodontitis and gingivitis; 9 (45%) exhibited signs of gingivitis only. TNFα levels in GCF samples were significantly higher in SSc patients than in

Table 1. Demographic and clinical data of study subjects

Demographics	SSc patients (n=20)	Healthy controls (n=20)
Age (years, ± SD)	45.6 (± 10)	48.5 (± 9)
Gender (Female : Male)	18 : 2	15:5
Smoking (no. of patients, %)	3 (15)	3 (15)
Diseases duration (years, ± SD)	7.2 (± 5.6)	
Disease subset (DcSSc : LcSSc)	10 : 10	
Autoantibodies ANA (%) SCL-70 (%) ACA (%)	 20 (100) 12 (60) 4 (20)	
Modified Rodnan's skin score (mean, ± SD)	8.2 (± 7.1)	
Digital ulcers (no. of patients, %)	13 (65)	
Sclerodactyly (no. of patients, %)	8 (40)	
Calcinosis (no. of patients, %)	5 (20)	
Arthritis (no. of patients, %)	8 (40)	
Pulmonary fibrosis/pulmonary hypertension (no. of patients, %)	3 (15)	
Renal crisis (no. of patients, %)	4 (25)	
Esophageal involvement (no. of patients, %)	7 (35)	
Disease activity score (mean, SD)	3.3 (+2.7)	
Treatment (no. of patients, %) Corticosteroids Immunosuppressive drugs Calcium channel blockers Iloprost Proton pump inhibitors ACE	 11 (55) 9 (45) 11 (55) 9 (45) 18 (90) 3 (15)	

SD = standard deviation, DcSSc = diffuse cutaneous SSc, LcSSc = limited cutaneous SSc, ANA = anti-nuclear antibodies, SCL-70 = anti-topoisomerase antibodies, ACA = anti-centromere antibodies, ACE = angiotensin-converting enzyme inhibitors

Table 2. Periodontal status and TNFα levels in SSc patients and healthy controls

Clinical measurements	SSc patients	Healthy subjects	*P* value
PD (mm)	3.74 ± 0.32 3.7 (3.2–4.5)	3.35 ± 0.31 3.2 (2.8–4.2)	0.003*
No. of sites with PD › 4 mm	39.75–18.61 34.6 (31.4–45.3)	24.33–15.62 22.1 (19.8–28.5)	0.005*
PI	1.47 ± 0.40 1.5 (0.6–2.4)	1.24 ± 0.61 1.3 (0.1–2.5)	0.289
GI	1.53 ± 0.34 1.6 (0.4–2.1)	1.12 ± 0.54 2.0 (1.0–2.0)	0.049*
BOP (%)	37 ± 14.80 30 (10–70)	27 ± 90 30 (10–50)	0.06
TNFα (pg/ml)	1.63 ± 0.36 1.5 (0.8–3.0)	1.15 ± 0.34 1.1 pg/ml (0.6–3.5)	0.001*

Values are presented as mean ± SD and median (minimum–maximum). Statistical significance was considered with *P* value ‹ 0.05

All periodontal parameters were measured in all teeth excluding third molars

Table 3. Correlation between clinical and periodontal variables in SSc patients

SSc variables/periodontal status	PD	PI	GI	BOP
Disease duration	0.91	0.17	0.02*	0.03*
Disease subset	0.39	0.09	0.09	0.39
Modified Rodnan's skin score	0.38	0.002*	0.05*	0.16
Digital ulcers	0.18	0.84	0.13	0.66
Sclerodactyly	0.42	0.02*	0.001*	0.46
Calcinosis	0.26	0.51	0.48	0.66
Arthritis	0.97	0.04*	0.13	0.49
Pulmonary fibrosis/pulmonary hypertension	0.99	0.22	0.22	0.85
Renal crisis	0.32	0.12	0.54	0.89

Results are presented as *P* value using the Mann-Whitney U test

*Statistically significant (*P* ‹ 0.05)

PD = pocket depth, PI = plaque index, GI = gingival index, BOP = bleeding on probing

healthy controls: mean 1.63 ± 0.36 vs. 1.15 ± 0.34 pg/ml, *P* = 0.001; median (minimum-maximum) 1.5 pg/ml (0.8–3.0) vs. 1.1 pg/ml (0.6–3.5). No correlation could be detected between TNFα levels and various periodontal parameters in SSc patients (Pearson's correlation coefficient test, data not shown). There was no correlation between TNFα level in GCF and SSc clinical parameters, such as disease duration, subset (diffuse SSc versus limited SSc), autoantibodies, modified Rodnan's skin score (MRSS), calcinosis, arthritis, esophageal reflux, or disease activity score. Significantly higher TNFα levels in GCF samples were observed in SSc patients with active digital ulcers compared to SSc without active digital ulcers (mean 1.24 ± 0.22 vs. 1.77 ± 0.54 pg/ml, *P* = 0.007). Higher MRSS (cutoff less or more than 9) also correlated with higher levels of TNFα in GCF samples (mean 1.39 ± 0.29 vs. 1.87 ± 0.67 pg/ml, *P* = 0.02). The relationship between periodontal status parameters and main SSc features are presented in Table 3. Higher PI was observed in SSc patients with higher MRSS, presence of sclerodactyly or arthritis, and higher disease activity score. Higher GI correlated with disease duration, MRSS, presence of sclerodactyly and higher disease activity score. Higher percentage of BOP correlated with SSc disease duration. SSc patients with elevated acute-phase reactants had higher PI than those with normal acute-phase reactants [1.69 (SD ± 0.53) vs. 1.2 (SD ± 0.35), *P* = 0.02].

DISCUSSION

In this study, all assessed SSc patients had poor periodontal condition presenting as isolated gingivitis or gingivitis combined with periodontitis. Only a few studies on peri-

odontal status in SSc have been reported [4,6,13-15]. A high prevalence of periodontitis was demonstrated in SSc patients (~76%) [16], as was a high incidence of periodontal inflammation accompanied by radiographic periodontal ligament space widening, resorption of the posterior mandibular, and coronoid process destruction [4,15].

It has been suggested that chronic diseases, such as RA and periodontitis, may share similar pathogenesis pathways: relapsed inflammation, elevated levels of pro-inflammatory cytokines (IL-1β, IL-6, TNFα), and low levels of anti-inflammatory cytokines (IL-10, TGFβ) [17,18]. TNFα is one of the key mediators in diseases such as RA, PsA, and ankylosing spondylitis. TNFα blockade is an effective treatment in these inflammatory conditions. Our group previously demonstrated abnormal periodontal status in patients with RA, mainly reflected in higher indices of PD and BOP [12]. We also demonstrated significantly higher levels of TNFα in GCF in RA and PsA patients. In a subgroup of RA patients treated with TNFα inhibitors, TNFα levels in GCF were close to those in normal controls, and signs of periodontitis were milder [19].

Periodontitis and SSc have many similarities: a chronic and progressive course, elevated serum inflammatory markers (CRP and ESR), comparable pathogenesis pathways such as microvascular abnormalities, inflammation and fibrosis with major impact on soft tissues and bone (resorption), and elevated levels of pro-inflammatory cytokines such as TNFα, IL-6, IL-1 and IL-17 [20]. Both diseases significantly disturb oral health resulting in gingival microvascular damage, persistent inflammation, and bone and tooth loss. In contrast to periodontitis, microbial pathogen in SSc pathogenesis has not been identified. Despite this difference both conditions express similar profiles in a toll-like receptor repertoire. Antibodies to periodontal collagen and neutrophilic cytoplasm (ANCA) have been reported in sera from patients with periodontal diseases. Patients with SSc almost unexceptionally have positive antibodies to nuclear factor as well as specific antibodies (anti-centromere, anti-topoisomerase, anti-RNA polymerase III, etc.). Positive ANCA was demonstrated in patients with SSc/vasculitis overlap. In both conditions, SSc and periodontitis, there is a similarity in the course of the disease: early phase with prominent inflammatory process and late phase with tissues fibrosis, atrophy, and damage.

Our SSc patients had significantly more signs of periodontal inflammation than healthy controls, mainly presented as higher PD and higher GI, but also with a tendency to higher BOP. While PD reflects the active inflammatory phase of periodontitis, BOP is higher in patients with progressive gingival damage late in the disease course. Poorer oral status in our SSc patients correlated with higher levels of acute-phase reactants. As in other inflammatory diseases, we found that TNFα level in GCF was higher in SSc patients compared to controls. However, we could not find a correlation between TNFα level in GCF and any periodontal parameter. We suggest that the higher TNFα level in GCF in SSc patients is due to the periodontitis itself and mainly reflects severity of local periodontal inflammation. In our patients, higher TNFα levels in GCF correlated with higher MRSS (> 9). This finding may reflect similar processes in the skin and periodontal tissue such as inflammatory cell activation and accumulation in affected tissues.

SSc patients have multiple contributory factors that may disturb oral health: thin lips, fibrosis and atrophy of facial soft tissue that causes difficulty in closing the mouth and covering teeth, microstomia, and significant limitation in mouth opening. Reduced access to the oral cavity produces problems with oral hygiene and thereby could enhance infective and inflammatory components of the periodontium as well as significantly limit the possibility of the fabrication and prosthetic replacement of teeth. Patients with connective tissue diseases are less likely to visit a dental professional for preventive care than healthy people; this often results in advanced pathology in the oral cavity [4,16]. Prominent xerostomia and insufficient salivary flow impair the buffer balance within the oral cavity, leading to bacterial colonization and raised acidity produced by oral bacterial colonies. A blunting of the angles of the mandible, pathologic fractures of the mandible, and osteolysis of the mandible contribute to reduction in oral opening. Esophageal reflux, which is present in the majority of SSc patients, contributes to oral cavity acidity and to the development of dental corrosions [3,20-23].

PI generally reflects poor hygiene in the oral cavity. In our patients, higher PI correlated with higher levels of acute-phase reactants. The infective processes in the oral cavity may influence the production of TNFα without relation to periodontal status. The use of corticosteroids, immunosuppressive or cytotoxic drugs (cyclophosphamide, cyclosporine, methotrexate), and calcium channel blockers may have an impact on gingival health in SSc patients [3,4,9,16,20-22]. Because of the small patient sample and the combination of drugs used by our patients, we could not assess correlation between gingival status and treatments.

SSc-related vasculopathy in the oral cavity is presented as multiple telangiectasias on mucosal surfaces and tongue, and attacks of numbness and discolouration, equivalent to oral Raynaud's phenomenon. Abnormal oral cavity microcirculation was demonstrated on labial capillary microscopy [13] and electron microscopy [20]. In our SSc patients, higher levels of TNFα in GCF correlated with the presence of active digital ulcers, a characteristic feature of SSc vasculopathy. Association between periodontitis and another vasculopathy based on endothelial dysfunction, atherosclerosis, has been reported [24]. Fibrosis is a hallmark of SSc. Recently, a comparable pattern in pro-fibrotic growth factors in SSc and periodontitis was demonstrated [25].

The correlation between GI and PI and several SSc vari-

ables, mainly with disease duration (GI), higher MRSS (GI, PI), sclerodactyly (GI, PI), arthritis (PI), and disease activity score (GI, PI) are probably not sporadic. It could reflect poor oral hygiene that may be a result of significant limitation in finger function as a result of sclerodactyly, joint inflammation and contraction, and profound skin fibrosis. BOP is a prominent sign of advanced periodontitis with fibrosis and atrophy; accordingly, higher BOP reflected longer disease duration.

This study has several limitations: small number of patients, possible concentration of patients with more severe SSc (our facility is a university tertiary center), and absence of patients with early disease. These limitations could be overcome by further studies or larger population-based studies.

In summary, our results indicate that patients with SSc have higher indices of periodontal inflammation and higher TNFα level in GCF as compared to healthy individuals. These changes could not be attributed to the inflammatory component of SSc pathogenesis only, but rather reflect the complexity of factors that influence oral health in SSc. While common pathologic pathways may be responsible for the association between SSc and periodontitis, future studies are necessary to evaluate this further.

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"A man is like a fraction whose numerator is what he is and whose denominator is what he thinks of himself. The larger the denominator, the smaller the fraction"

Leo Tolstoy (1828-1910), Russian novelist and philosopher, best known for his works *War and Peace* and *Anna Karenina*. In the 1870s Tolstoy experienced a profound moral crisis and spiritual awakening. His literal interpretation of the ethical teachings of Jesus, centering on the Sermon on the Mount, caused him to become a fervent Christian anarchist and ascetic (the latter leading to the renunciation of his considerable wealth). Tolstoy's ideas on non-violent resistance, expressed in such works as *The Kingdom of God Is Within You*, were to have a profound impact on such pivotal 20th century figures as Gandhi and Martin Luther King