Periodontal Disease and Lipid Profile in Systemic Sclerosis: an EUSTAR Cohort Experience

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Dental pathology is commonly described among patients with systemic sclerosis (SSc), a multisystem autoimmune disorder, and assumed to be multifactorial. We aimed to evaluate the periodontal status and to identify potential relation with SSc-specific parameters as well as serum lipid profile in a cross-sectional study on consecutive SSc. Standard assessments comprised dual, rheumatologic (disease subtype, clinical spectrum, inflammatory, immunological, lipid metabolism - total cholesterol and fractions, triglycerides), and dental evaluation (plaque index, bleeding on probing, pocket depth, clinical attachment level). 70.96% SSc developed oral manifestations, 51.61% periodontal disease, while one third severe aggressive periodontitis, particularly in diffuse SSc ($p<0.05$). Abnormal lipid pattern (low serum HDL- and high LDL-cholesterol, increased serum triglycerides, without significant modification in total cholesterol level) significantly correlated with diffuse SSc and skin involvement, disease duration, anti-topoisomerase 1 positivity, SSc activity and severity, as well as periodontitis ($p<0.05$). Our results clearly define an association between the presence and severity of periodontal disease and lipid anomalies in SSc, suggesting a potential link with early atherosclerosis via gingival inflammation and altered lipid metabolism.

Keywords: systemic sclerosis, periodontal disease, oral pathology, lipid metabolism abnormalities

Systemic Sclerosis (SSc) is a complex multisystem disease characterized by a broad spectrum of clinical findings as a result of vascular dysfunction, excessive and extensive cutaneous and visceral fibrosis (e.g., digestive tract, lungs, heart, kidneys), with subsequent organ damage, as well as dysregulated immune activation occurring in a genetically predisposed host [1-3].

It belongs to the so called orphan autoimmune rheumatic disorders and is generally classified as either diffuse or limited pattern, with different clinical, immunological, therapeutic and prognostic implications [1, 2].

Orofacial manifestations are commonly described among SSc patients (more than two thirds of cases) and, apparently, multifactorial [1-6]. Recent studies focused on severe impaired oral health indicating several SSc-related specific factors such as decreased oral aperture (microstomia) (43% to 80% cases) with abnormal inter-incisal distance (mean inter-incisal distance for people with SSc being about 33 mm), excessive dry mouth (decreased salivary flow secondary to concomitant Sjogren's syndrome) (up to 60% cases), gastroesophageal reflux disease, reduced manual dexterity (hand deformity, contractures) to maintain optimal oral hygiene, defective vascularity and alterations of the microcirculation of the gingival tissues with subsequent gingival inflammation [1-9]. Moreover, immunosuppressant drugs and symptomatic medication e.g. calcium channel blockers may influence the risk of developing gingival hyperplasia in SSc [9, 10].

It is widely accepted that dental pathology comprises more missing teeth, tooth decay and more periodontal disease in SSc as compared to age- and sex-matched healthy controls [1-9]. Furthermore, patients are at increased risk for dental plaque, gingival hyperplasia, gingival inflammation and, even, gingival bleeding (about 60%) [9 - 11].

Although the orofacial manifestations are typically reported in SSc, only few studies have adequately addressed the issue of oral health-related quality of life and derived dental pathology in such pathobiological settings [1-11].

The main aims of our study were to evaluate periodontal status in SSc and to identify potential relation with different disease specific characteristics (clinical, serological, inflammatory tests), as well as serum lipid profile.

Experimental part

Material and method

Cross-sectional observational study conducted in 31 consecutive SSc patients (fulfilling the 1980 American College of Rheumatology diagnostic criteria), with a history of disease of more than 12 months, attending at least once the Rheumatology Department (EUSTAR 162 center, Iasi, Romania).

Patients with concomitant diabetes mellitus as well as current or past smokers were excluded owing potential overlap with periodontal disease; only partial (minimum 8 evaluable teeth excluding the 3rd molar) or fully dentate patients were admitted.

A dual rheumatologic and periodontal assessment was done in all cases according to a standard protocol. All

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parameters were collected as a single point data, comprising:

- *general data about SSc* - disease subtype meaning limited or diffuse cutaneous SSc based on their skin extent (LeRoy classification criteria); disease duration; clinical spectrum; inflammatory (erythrocyte sedimentation rate, C reactive protein), immunological (anti-topoisomerase-1 and anti-centromere antibodies) and lipid metabolism profile (total cholesterol, TC; low- and high-density lipoprotein cholesterol, LDL-C and HDL-C; triglycerides, TG; the atherogenic plasma index, AI);

- *dental evaluation* - plaque index, PI; gingival index, GI; bleeding on probing, BOP; pocket depth, PD; and clinical attachment level, CAL.

Clinical measurements were done at four sites on all teeth, including mesiobuccal, distobuccal, mesiolingual and distolingual; a Williams probe was used for measurements of PD and CAL.

No periodontal therapy or invasive dental procedures (professional scaling and prophylaxis) were permitted before the dental evaluation during the study, and all participants were instructed not to change their oral hygiene routines.

All participants have signed a written informed consent before their enrollment and the study received Ethics Committee approval.

Statistical analysis was done in IBM SPSS-19 software, $p<0.05$, with a subgroup analysis based on skin extent and the presence of periodontitis. Multivariable regression analysis was done to evaluate association between SSc, periodontal disease and lipid metabolism parameters.

Results and discussions

SSc-related parameters

We enrolled 31 SSc, predominantly women (83.87%), with a mean age of 42.9 years (ranging between 23 and 58), and a mean disease duration of 6.3 years (from 1.2 to a maximum of 10.7 years); the majority of patients enrolled had a diffuse SSc subtype (67.74%) and only one third were diagnosed with a limited disease. To note, all men in our study developed extensive severe diffuse SSc.

Musculoskeletal involvement with potential impact on oral hygiene in SSc revealed non-erosive arthritis in 67.74% cases, with major functional impact on hand dexterity in up to one third of patients (32.25%) and significant impaired quality of life as demonstrated by an average HAQ (Health Assessment Questionnaire) of 2.1 (1.5-3). Only 12.90% of SSc had myositis, with decreased muscle endurance and influence on the ability to perform routine daily activities. Patients with hand deformity and contractures were typically classified in the diffuse SSc subset.

Limited oral aperture (microstomia) with decreased inter-incisal distance was demonstrated in 58% cases.

An average high ESR as well as CRP level were registered, while immunological abnormalities account for about one out of five anti-centromere antibody positivity and more than half SSc with anti-topoisomerase-1 specificity.

General data about SSc-related characteristics are summarized in table 1.

Periodontal disease in SSc

35.48% of all participants were regular attendees of dental practice.

Overall, up to 70.96 % of SSc developed oral manifestations and had reduced oral health-related quality of life. We demonstrated a low resting salivary flow rate and PH (25.80% cases), a reduced maximal mouth opening (54.83% cases) and a small inter-incisal distance (32.5 mm). 64.51% of SSc experienced one or more caries and more than half of patients (51.61%) presented with periodontal disease.

Key clinical manifestation of periodontal disease featured in SSc included gingival inflammation in 81.25% cases, 50% patients displaying sites with detectable plaque, 53.75% with bleeding on probing, 31.25% with periodontal pockets (classic pocket depth >3 mm), while clinical attachment level ≥ 5.5 mm in 18.75% SSc of patients with periodontitis. Severe aggressive periodontitis was described in one third of SSc patients with periodontal disease (table 2). Subgroup analysis based on skin extent and periodontal status showed that patients with diffuse SSc presented more frequently with periodontitis than those with limited disease ($p<0.05$); besides, they developed more aggressive periodontal disease ($p<0.05$).

A routine orthopantomogram was done in all patients demonstrating a wide periodontal ligament space (0.37 mm in average).

Lipid profile in SSc

A detailed analysis of the lipid metabolism parameters demonstrated a mean total cholesterol level of 173.91 (ranging from 118 to 278) mg/dL, mean HDL-cholesterol of 43.18 (34-71) mg/dL, mean LDL-cholesterol of 132 (120-

General SSc data	
Demographics	
Age (years)	42.9 (23-58)
Gender (%); F: M ratio	83.87% F; 26 F : 5 M
Disease-related	
Disease duration (years)	6.3 (1.2-10.7)
Disease subset	
• Diffuse cutaneous SSc (%)	67.74
• Limited cutaneous SSc (%)	32.25
Disease activity (MEDSGER)	1.25 (0-2)
Disease severity	4.5 (3-6)
Skin score (modified RODNAN, mRSS)	17 (10-37)
Pulmonary fibrosis (computer tomography) (%)	70.96
Pulmonary hypertension (%)	
Raynaud phenomenon (%)	22.58
Digital ulcers ever (%)	100
Myositis (%)	64.51
Non-erosive arthritis (%)	12.90
Renal involvement (%)	67.74
Calcinosis (%)	6.45
	9.67

Table 1
GENERAL SSC DATA IN STUDIED PATIENTS

Table 2
ORAL MANIFESTATIONS IN STUDIED SSC PATIENTS

Overall dental pathology (%)	70.96
Decreased saliva production (%)	25.80
Microstomia (%)	54.83
Inter-incisal distance (mm)	32.5
Caries (one or more) (%)	64.51
Periodontal disease (%)	51.61
• Gingival inflammation (%)	81.25
• Sites with dental plaques (%)	50
• POB (%)	43.75
• PD (%)	31.25
• CAL (%)	18.75

192) mg/dL, and mean serum triglycerides of 151.4 (117-231) (table 3).

Overall, we detected an abnormal lipid pattern in SSc, characterized by low HDL-cholesterol and high LDL-cholesterol fractions, although no significant anomalies of total cholesterol and triglycerides. Lipid levels of risk determined in accordance with latest NCEP and AHA/ACC recommendations.

Subgroup analysis based on disease subsets revealed significant differences with more important dyslipidemia in patients with a diffuse SSc as compared with those with limited disease (CREST syndrome): lover serum HDL-cholesterol (61.90% versus 30%, $p<0.05$), higher LDL-cholesterol (52.38% versus 30%, $p<0.05$), as well as slightly higher triglycerides (42.85 versus 2%, $p<0.05$).

Correlation between lipid metabolism, periodontal disease and SSc-related parameters

Dyslipidemia (elevated LDL-cholesterol, decreased HDL-cholesterol fractions, and increased serum triglycerides, without significant modification in total cholesterol level) was observed in all SSc with periodontal disease, especially in those with severe periodontitis; significant correlation between lipid metabolism changes and periodontitis ($p<0.05$) was demonstrated.

Moreover, lipid abnormalities were related to high skin involvement (mRSS) ($p<0.05$), disease duration ($p<0.05$), anti-topoisomerase 1 positivity ($p<0.05$), SSc activity (EUSTAR score) ($p<0.05$) and severity (MEDSGER severity scale) ($p<0.05$).

We assumed that patients with SSc are at risk to develop impaired oral health, including periodontal disease, based on multiple either general or disease-specific predisposing factors; we further assessed the prevalence of periodontitis in a sample of consecutive SSc patients and potential relation with various SSc-related characteristics and lipid metabolism abnormalities.

Overall, we demonstrated an excess of oral pathology in SSc, with oral manifestations detected in up to 71% of SSc, while an abnormal periodontal status was demonstrated about half of our cases, irrespective of the SSc subset.

Typically monitored periodontal manifestations were also reported in our cohort, comprising gingival inflammation, plaques and bleeding [3, 4, 9, 13]; up to one third of cases displayed periodontal pockets, and one out of five significant clinical attachment loss and, even alveolar bone loss. Although periodontitis was reported in both diffuse and limited SSc patients, aggressive oral impairment was associated with diffuse SSc settings.

Moreover, no significant association with age, disease duration or functional impairment of the hand was reported. Interestingly, recently published data from the Canadian Systemic Sclerosis Oral Health Study III, in the Canadian Scleroderma Research Group cohort suggested that a diminished inter-incisal distance correlated with overall disease severity, decreased saliva production related to concomitant Sjögren's syndrome, and the association of tooth loss with poor upper extremity function, gastroesophageal reflux, and decreased saliva [3, 4].

Finally, local defective vascularity and alteration of gingival microcirculation as a result of SSc vasculopathy may also account for high prevalence of oral abnormalities in SSc patients [9, 10].

Furthermore, we demonstrated abnormal serum lipids in our SSc cohort, particularly in diffuse form and patients with severe aggressive periodontal disease: elevated LDL-cholesterol along with decreased HDL-cholesterol fraction were usually detected.

Although we have previously reported an impaired lipid profile in different SSc settings [14-19], available data on total cholesterol and its fractions, low-density and high-density lipoprotein cholesterol, triglycerides and lipoproteins (A, B) in SSc subsets is controversial [20-25]. Thus, decreased HDL-cholesterol was detected in patients with limited cutaneous disease, while abnormal values in other studies performed in SSc [20-25]. Also, increased lipoprotein concentrations without further differences in detailed lipid profile in comparison with healthy controls were found in both limited and diffuse SSc [20-26].

On the other hand, it is widely recognized that periodontal disease may be associated with various lipid metabolism abnormalities [13, 27]. Periodontitis shifts the lipoproteins to a proatherogenic profile comprising increased LDL-cholesterol and triglycerides, as well as impaired HDL-cholesterol [13], predisposing to early accelerated atherosclerosis [13, 26].

A closer look to lipid changes in patients with chronic periodontal inflammation shows raised LDL-C and triacylglycerol's levels, with smaller lipoprotein particles and also higher dense LDLs particularly in those developing

Table 3
IMMUNE PROFILE, INFLAMMATORY SYNDROME AND LIPID METABOLISM IN STUDIED SSC PATIENTS

Lab parameters	
Antibodies positivity	
Anti-centromere, ACA (%)	22.58
Anti-topoisomerase 1 positivity, anti-SCL70 (%)	58.06
Total anti-nuclear antibodies, ANA (%)	87.09
Inflammatory syndrome	
CRP (mg/dL)	6.2 (1-14)
ESR (mm/hour)	29 (15-64)
Cholesterol (mg/dL)	173.91 (118-278)
HDL-cholesterol (mg/dL)	43.18 (34-71)
LDL-cholesterol (mg/dL)	132 (120-192)
Triglycerides (mg/dL)	151.4 (117-231)

aggressive periodontitis [13]. It is more than obvious that the relationship between altered lipid metabolism and gingival inflammation influence the pathobiology of atherosclerosis in a genetic predisposed background [13, 26, 27].

In recent years, several studies demonstrated the benefits of periodontal therapy on lipoproteins as well as lipoprotein metabolism. It seems that periodontal treatment has special deleterious effects on circulating inflammatory mediators, with subsequent influence cholesterol fractions (both LDL and HDL), and, thus, on subclinical atherosclerosis [9, 13]. LDL-cholesterol is usually reduced after periodontal therapy, while HDL-cholesterol replaced by a more anti-atherogenic fraction [13].

Our results clearly suggest a link between the presence and severity of periodontal disease and lipid anomalies in SSc patients. Interestingly, patients with SSc are prone to develop periodontal disease along with changes in lipoprotein profile, suggesting a potential link between SSc and (subclinical) atherosclerosis via gingival inflammation and lipid metabolism [13, 28].

Further research is necessary in order to assess the true prevalence of clinically manifest or subclinical premature atherosclerosis in SSc with or without concomitant periodontal disease.

Conclusions

Patients with SSc are at risk to develop excessive impaired oral health, particularly related to chronic periodontal disease, as well as abnormal lipid profile, with low serum HDL-cholesterol and high LDL-cholesterol levels. The link between gingival inflammation, periodontal destruction and changes in lipid metabolism might represent one pathobiological pathway for atherosclerosis in SSc.

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