

The impact of systemic sclerosis on oral health

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ABSTRACT

Systemic sclerosis (SSc) is a rare connective tissue disorder characterized by a wide range of manifestations, including oral changes. The pathogenesis of SSc is complex and remains incompletely understood. In the development of SSc following mechanisms are involved: immune activation, vascular alterations, and increased accumulation of extracellular collagen matrix. Genetics plays an important role in SSc development. Oral manifestations of SSc include microstomia, xerostomia, telangiectasia, periodontitis, increased width of the periodontal ligament, and alveolar bone resorption. These manifestations are a significant cause of comorbidities and a decreased quality of life in SSc patients. Education on oral hygiene and home-based orofacial physiotherapy may improve the oral status of these patients. A multidisciplinary team should be involved in the management of SSc.

Keywords: systemic sclerosis, periodontitis, fibrosis, vasculopathy

INTRODUCTION

Systemic sclerosis (SSc) is a rare and complex autoimmune disease defined by vasculopathy, immune system alterations, and progressive fibrosis of the skin and internal organs [1]. There are two main physiopathological processes responsible for the pathogenesis of SSc: fibroproliferative vasculopathy of small vessels and excessive accumulation of collagen leading to tissue fibrosis.

Compared to rheumatoid arthritis which is estimated to affect approximately 1 in 100 people, SSc is a rare rheumatic disorder in comparison with. Also, as opposed to rheumatic diseases SSc affects more women than men, with a ratio ranging from 3:1 to 8:1 [2]. The SSc onset can occur at any age, including childhood, but most frequently it develops between the ages of 20 to 50 years [3].

SSc is a heterogeneous condition with a variety of clinical manifestations, ranging from mild fibrosis of the skin with minimal involvement of internal

organs (limited form of SSc-lcSSc) to severe skin and organ impairment (diffuse form of SSc-dcSSc). Disabling changes which occur in the severe forms are associated with a low survival rate of SSc diagnosed patients [4].

Fibrotic and vascular changes also carry a significant impact on the head and neck [5]. Patients with SSc display major facial alterations, such as reduced mouth opening, salivary glands fibrosis, decreased salivary flow (xerostomia), dental and periodontal diseases. Orofacial manifestations lead to treatment issues in these patients [6].

Pathogenesis of SSc

Several immunological vascular and proliferative abnormalities are involved in the onset of SSc which contribute to severe and complex clinical expressions of the disease [7]. Vasculopathy and fibrotic alterations are two significant pathological processes of SSc responsible for the most severe

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manifestations. However, the biological mechanism behind vasculopathy and fibrosis is still unknown. Certain genetic changes are considered to be involved in SSc pathogenesis. The major compatibility complex (MHC) II, particularly HLA-I and HLA-II complexes, was emphasized as a key player in the SSc development [8,9,10]. HLA-DRB1*01, HLA-DRB1*11, HLA-A*30 and HLA-A*32 genes are associated with an increased susceptibility towards SSc, while HLA-DRB1*07, HLA-B*57 and LA-Cw*14 genes protect against SSc [9].

Scientific studies suggest that genetic factors may indicate not only SSc susceptibility but also the predisposition towards particular clinical phenotypes as well as the presence of specific autoantibodies [11]. Additionally to MHC/HLA complex other three non-HLA genes (IRF8, SOX5 și GRB10) were found to be involved in SSc pathogenesis [11]. IRF8 regulates Toll-like receptors signaling (TLR) and mediates the crosstalk between γ -interferon and TLR. Type I and type II interferons play an important role in SSc pathogenesis through the immunomodulation of collagen production [12]. Also, a strong association between IFN8 gene, lcSSc form and positive anti-centromere antibodies (ACA) has been highlighted [11]. Specific SSc auto-antibodies are ACA and anti-topoisomerase antibodies (ATA) [13]. Most patients with lcSSc are more likely to be ACA positive while dcSSc patients were associated with positive ATA. GRB10 gene plays a potential role in apoptosis modulation. SOX5 gene is a member of the transcription factors involved in chondrogenesis regulation in the embryonic development stage and connective tissue formation [14]. Identified genes implicated in genetic predisposition to SSc are predominantly involved in immune regulation [4].

The innate immune system is a critical part of SSc pathogenesis. Variations of TLR genes, in particular TLR2 and TLR4 have been linked to SSc development [15]. A functional polymorphism of TLR2 is associated with positive ATA and enhanced IL-6 production by dendritic cells [16]. TLR4 ligands (fibronectin, hyaluronan particles and S100A proteins) activate TLR4 receptors (TLR4 expression being increased in SSc tissue and lungs) and act synergistically with transforming growth factor-beta (TGF- β) increasing fibroblast production [17]. Innate and adaptive immune cells synthesize a variety of cytokines and chemokines, such as interleukin-4, -6, -1, -13 și -17, TGF- β and platelet-derived growth factor. High concentrations of these mediators have been found in tissues prone to accumulate excessive connective tissue matrix [4].

An external trigger, such as an infection has been hypothesized to be involved in the SSc onset in patients with a susceptible genetic background. Some evidence has shown that microbiota plays an impor-

tant role in autoimmune disorders, but this a yet unexplored path in SSc [18].

SSc implications in the head and neck

Oral manifestations in SSc

Systemic sclerosis often has a negative impact on oral health due to the significant intra- and extraoral alterations [19]. Characteristic features of SSc are the thickening and hardening of the skin and lips alongside with profound facies modifications (smooth, rigid face) [20]. The paucity of facial wrinkles and the presence of vertical furrows around the mouth, periorbital connective tissue fibrosis, sharpening of the nose due to nasal alar cartilage atrophy and lips stiffening are representative features of SSc patients [21,22]. Microstomia caused by fibrosis deeply impairs the normal functioning of the dento-maxillary apparatus and hinders proper oral hygiene maintenance as well as dental treatments [23]. Jung et al. (2017) studied the oral changes in SSc and showed that SSc patients had a significantly decreased interincisal distance as compared to healthy subjects (37.7 mm vs 44.3 mm) [20]. Cutaneous telangiectasia, visible macular, dilated blood vessels caused by atypical neoangiogenesis, most commonly observed on the hands and face is one of the earliest signs of SSc [21,22].

SSc induces salivary and lacrimal glands fibrosis and subsequent xerostomia and xerophthalmia. Xerostomia is perceived as the subjective sensation of dry mouth, burning mouth syndrome, difficulties in mastication, swallowing and speech and it is objectively characterized by dry and atrophic mucosa and decreased salivary secretion. The low salivary flow and low pH levels increase the risk of tooth decay, altered taste sensation and make dentures wearing difficult for patients [20]. Oral mucosa and dental tissues may present lesions and ulcerations due to gastroesophageal reflux which is most common in SSc patients [22].

Several studies have reported bone resorption in multiple bones including maxillary bones. Maxillary bone resorption comes in the form of erosions at the level of bony muscle insertions (mandibular angle, condylar and coronoid processes and digastric fossa) and widening of the desmodontal space caused by increased desmodontal collagen deposition [6,24,25]. The hard palate is flattened, the uvula appears shortened and the fibrosis affects the fixed gingival mucosa and the taste buds from the entire tongue surface [23].

The association between periodontitis and SSc

Recent studies indicated a potential link between periodontitis and SSc due to the presence of greater probing depths and attachment loss in patients with SSc as compared to healthy individuals [5,26]. The

average attachment loss in SSc patients was 9.92 mm as opposed to 2.59 mm in non-diseased controls. Moreover, probing depth registered 4.78 mm in SSc patients and 2.81 mm in healthy subjects [5]. Previous investigations suggested that increased levels of dental plaque and bleeding indexes in SSc patients are caused by microstomia, which hinders proper oral hygiene, and extensive tissue fibrosis. These factors promote inflammation and periodontal tissue loss [5,27]. An extrinsic risk factor that links SSc to periodontitis is the low education level of SSc patients [5].

The role of periodontal pathogens in triggering auto-immune responses

Periodontitis is an inflammatory disease defined by the progressive and irreversible destruction of the periodontal supporting apparatus which in the absence of treatment eventually leads to tooth loss. The relationship between bacterial dysbiosis and the altered immune-inflammatory responses is central to periodontitis pathogenesis [28]. *Porphyromonas gingivalis*, *Bacteroides forsythus*, *Prevotella intermedia*, *Campylobacter rectus*, *Treponema denticola* and *Fusobacterium nucleatum*, are some of the most frequent pathogens contributing to the direct and indirect pathways of periodontal tissue breakdown [29].

Periodontal pathogens may act as potential triggering factors of autoimmune responses, as seen in rheumatoid arthritis [5]. The autoimmune responses can be activated by dysbiosis through several mechanisms such as TLR dysregulation, autoantigen overproduction, cytokines hyperproduction and amplified autoimmunity [30]. For instance, *Aggregatibacter actinomycetemcomitans* may stimulate the production of citrullinated antibodies in polymorphonuclear neutrophils and their presentation to Langerhans cells which in turn further sustain autoantibodies synthesis [31]. The citrullination induced by an excessive proportion of bacteria in periodontitis may support the inflammation and autoimmune pathogenetic pathways in rheumatic diseases, such as SSc [5].

Therapeutic approaches in SSc patients

Prophylactic and specialized care measures are mandatory in SSc patients. These include interdisciplinary treatment approaches provided by dentists, oral and maxillofacial surgeons and physiotherapists. Oral alterations caused by SSc have a major impact on the quality of life and require specific treatment early on. Symptoms of xerostomia can be tackled by using artificial salivary substitutes or stimulating salivary flow with sugar-free gum and maintaining adequate oral hydration [23].

Progressive microstomia is an important limitation in performing dental treatments. Its progression can be delayed and countered by physiotherapy and facial surgery, such as oral commissurotomy and commissuroplasty [32]. Recent studies recommend using botulinum toxin A which prevents muscular contraction and acts on oral muscles and fibroblasts inhibiting the progression of microstomia caused by orbicularis oris muscle fibrosis [33].

Due to vascular alterations and the risk of microangiopathy complications the use of anesthetics with adrenaline is not recommended. Mucogingival surgery is contraindicated in patients with increased fibrosis of the oral mucosa because it can cause significant postoperative complications due to impaired healing. Conventional dental treatments are allowed to be carried out in SSc patients, but wearing dental prosthesis in subjects with advanced microstomia is difficult. Moreover, prosthetic and dental implant treatments in SSc patients are not yet well documented and researched to allow for a categorical therapeutic indication [34].

The treatment of periodontal disease should include raising patients' full awareness with respect to their oral health status and the local and systemic implications of periodontitis, individualizing oral hygiene practices and performing timely specific periodontal treatments, such as scaling and root planning [35]. To ensure adequate oral health in SSc patients regular check-ups, follow-ups and monitoring are required.

DISCUSSIONS

The inflammatory, fibrotic and atrophic changes in SSc affect the internal organs and promote significant functional limitations. Oral impairment in SSc is proportional to the severity degree of the patients disability. A wide range of orofacial manifestations has been observed in these patients, including periodontitis. Although some studies support a positive association between periodontitis and SSc, mainly because of the altered clinical periodontal parameters (probing depth, attachment loss, gingival recessions) seen in SSc patients, not all studies are in agreement [5]. Not only periodontitis was associated with SSc, but gingivitis was also frequently reported in patients with diffuse forms of the disease due to the severe impairment (severe microstomia, higher Rodnan score, limited hand dexterity) [36].

Successful periodontal treatment depends primarily on the effective supra- and subgingival biofilm removal and modifying factors control. A prophylactic approach reduces the occurrence of dental and periodontal complications in these patients. Due to the fact that SSc affects the entire oral cavity as well as the facial tissues, a multidisciplinary team must work jointly to improve the pa-

tients' quality of life [37]. Detection of genetic variations associated with specific clinical SSc traits will lead to a better understanding of the pathogenesis and facilitate the development of an individualized treatment plan [4].

CONCLUSIONS

SSc is one of the most complex autoimmune systemic diseases. The pathogenetic mechanisms involve vascular alterations, excessive connective tissue deposition and immune system activation with increased autoantibodies production. Clinical manifestations of SSc are the result of the complex interaction between pathogenetic mechanisms, genetic and external triggering factors, such as infectious agents.

SSc has a significant impact on the orofacial area and is associated with severe impairment of oral

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