Scleroderma and Oral Submucous Fibrosis: A Narrative Review of Comparative Insights into Pathogenesis, Clinical Features and Comprehensive Management Strategies

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Abstract: Fibrotic lesions play a key role in conditions involving connective tissue such as Scleroderma and Oral Submucous Fibrosis (OSF), leading to the development of tissue similar to scars that limit function and raise the risk of complications. This review contrasts Scleroderma, an autoimmune disorder resulting in systemic fibrosis in various organs, with OSF, a condition mainly triggered by prolonged irritation and inflammation of the oral mucosa, commonly related to areca nut consumption. Both conditions are defined by gradual fibrosis, resulting in notable limitations in functionality and a substantial decline in quality of life for patients. Scleroderma's development includes a complicated combination of autoimmunity, genetic elements, and environmental factors, resulting in broad systemic impacts. On the other hand, the development of OSF is primarily centered around the oral cavity due to environmental factors, genetic susceptibility, and nutritional deficiencies. In terms of epidemiology, Scleroderma is more prevalent among women in their middle age around the world, whereas OSF mainly impacts younger men in South Asia. In clinical terms, Scleroderma is characterized by thickened skin and fibrosis of organs, while OSF is identified by trismus, mucosal blanching, and a risk of turning malignant. The review emphasizes the significance of recognizing the unique and common features of these conditions to enhance diagnostic precision and direct individualized treatment plans. The aim of this analysis is to improve treatment results and patient care for individuals with Scleroderma and OSF.

Key words:-Autoimmunity, Collagen, Fibrosis, Malignant Transformation, Systemic Sclerosis, Oral Submucous Fibrosis, Trismus

Introduction

Oral Submucous Fibrosis (OSF) and Scleroderma are two different but related disorders that affect connective tissues in a major way, yet they have different pathophysiological causes. Scleroderma is characterized by systemic fibrosis brought

on by autoimmune mechanisms that impact various organs, whereas OSF is predominantly caused by persistent irritation and inflammation that is restricted to the oral mucosa. Both diseases have significant morbidity, which emphasizes the necessity for efficient care techniques. Progressive fibrosis and functional impairments are the hallmarks of both disorders. Comprehending their relative etiology and clinical characteristics not only improves the precision of diagnosis but also provides guidance for customized treatment strategies that can enhance patient outcomes and quality of life.

Systemic sclerosis, (referred to as scleroderma), is a chronic autoimmune illness that affects the skin and internal organs and is marked by extensive fibrosis and vascular anomalies. The illness causes progressive tissue scarring because of an excess of collagen and other extracellular matrix components being produced.[1,2] Scleroderma can present with a wide range of clinical symptoms, from severe multi-organ involvement to localized skin thickening.[3] Scleroderma's complex and diverse appearance makes it difficult to manage even with advances in treatment.[4]

Oral Submucous Fibrosis (OSF) is a condition that primarily affects the oral mucosa and has the potential to be malignant. Chewing areca nuts is frequently linked to it, as it causes long-term inflammation and fibrosis in the oral tissues.[5] In its severe phases, this disorder causes substantial tissue rigidity, pain, and restricted mouth opening.[6] Collagen deposition is a key factor in the development of OSF, which is caused by a combination of genetic susceptibility, dietary inadequacies, and environmental irritants.[7]

Improving patient outcomes and developing new therapeutic approaches depend on an understanding of the parallels and differences in their pathophysiology, clinical characteristics, and management. Comparing scleroderma and OSF sheds light on both conditions' distinctive and common characteristics. Significant fibrosis is present in both disorders, but there are notable differences in the underlying causes and systemic effects. For example, OSF is more localized and associated with environmental and lifestyle variables, whereas scleroderma is largely an autoimmune condition with systemic involvement.[8-11] Comprehending these distinctions is vital in customizing suitable management approaches. The present review aims to elucidate the pathogenesis, clinical features, and management of scleroderma and OSF, highlighting their similarities and differences. This comparative analysis will help in understanding the clinical relevance of these conditions and improve patient care through better-targeted therapies. By integrating current research and clinical practices, this review seeks to enhance our approach to managing these complex conditions and optimizing patient outcomes.

Pathogenesis

Scleroderma, also called systemic sclerosis, is a complicated autoimmune condition marked by extensive fibrosis and vascular irregularities throughout different

organs. The cause of scleroderma is a mixture of genetic vulnerability, environmental factors, and an abnormal immune reaction. Research involving genetics has discovered various genetic markers that make individuals more prone to developing the disease, while exposure to silica dust and certain infections have also been linked to the onset of the illness.[1] The development of scleroderma is mainly focused on the excessive accumulation of collagen and changes in the remodeling of the extracellular matrix. Abnormal activation of fibroblasts and myofibroblasts drives this process, causing fibrosis in the skin, lungs, heart, and gastrointestinal tract.[2] The disease is characterized by the production of autoantibodies like anti-topoisomerase I and anti-centromere antibodies, which are linked to different clinical subtypes of scleroderma through molecular mechanisms.[4] It is believed that these autoantibodies contribute to starting and maintaining the inflammatory and fibrotic processes by impacting fibroblast activation and causing vascular damage. The development of scleroderma includes an early damage to the endothelial cells, followed by immune cell activation, and then gradual fibrosis. This sequence ultimately leads to dysfunction of the organs and important clinical symptoms.[11,12,13] Understanding these mechanisms is essential to create specific treatments that can reduce the disease's effects and enhance patient results.

Oral Submucous Fibrosis (OSF) is a long-lasting lesion that mainly impacts the mucosa of the oral cavity, marked by the slow growth of fibrosis and limited mouth opening. The cause of OSF is strongly connected to the regular chewing of areca nut, a common habit in numerous Asian nations. This behavior causes cancer-causing chemicals to trigger a fibrotic reaction in the tissues of the mouth.[8] Moreover, genetic predisposition is also a major factor, as specific genetic variations could potentially elevate the likelihood of developing OSF.[14] Deficiencies in nutrients like iron, vitamin B12, and folic acid are believed to play a role in the development of OSF, making the condition worse by hindering the healing of mucosal tissues.[5] At a molecular level, OSF is identified by the over activation of fibroblasts and myofibroblasts, resulting in excessive collagen buildup in the connective tissue.[7] Cytokines like TGF-β drive this process, playing a vital role in stimulating the growth of fibroblasts and the production of collagen.[15] The progressive buildup of fibrous tissue in OSF is caused by an imbalance in collagen production and degradation, leading to clinical manifestations.The pathophysiological mechanisms in OSF entail a gradual fibrotic reaction that impacts the mouth's inner lining, causing symptoms like thickened mucosa, decreased mouth movement, and limited jaw opening.[9] As time passes, this fibrosis hinders the regular operation of the oral tissues, causing eating, talking, and oral hygiene to become more challenging. Recognizing the fundamental workings of OSF is essential for creating successful treatment plans and preventive actions to lessen the effects of this disabling condition.[16,17]

Common pathways: Both OSF and scleroderma are chronic conditions that result in excessive collagen buildup and tissue scarring. In oral submucous fibrosis (OSF), fibroblasts and myofibroblasts become active, leading to increased production of collagen and extracellular matrix components.[7] In the same way, in scleroderma, an abnormal fibroblast activation leads to elevated collagen production and fibrosis in various organs.[2,3] Both diseases also involve a significant immune reaction, in which cytokines like transforming growth factor-beta (TGF-β) are crucial in the development of fibrosis. TGF-β plays a crucial role in OSF by promoting fibroblast growth and collagen build-up, as seen in scleroderma where it contributes to fibrosis and immune function changes.

Direct mechanisms: Significant differences exist in the causes and molecular processes of OSF and scleroderma. OSF is primarily associated with habitual areca nut chewing, which leads to carcinogen-induced fibrosis in the oral mucosa.[8] On the other hand, scleroderma's development is intricate, as it combines autoimmunity and genetic predisposition, with certain autoantibodies and environmental elements playing a role in systemic fibrosis.[11] Distinct molecular mechanisms in OSF involve the impact of malnutrition and genetic predisposition on intensifying fibrosis, while scleroderma is characterized by widespread systemic inflammation and autoimmunity affecting several organs.Moreover, although fibrosis occurs in both conditions, the clinical symptoms vary. OSF mainly impacts the oral mucosa, causing issues like limited mouth opening and thickening of the mucosal lining, while scleroderma is characterized by extensive fibrosis that affects the skin, lungs, and internal organs, resulting in systemic symptoms. (Table 1)

Epidemiology and Demographics

Distinguishing between Scleroderma and Oral Submucous Fibrosis (OSF), two independent but occasionally overlapping disorders, requires an understanding of their epidemiological and clinical characteristics. A thorough comparison of important parameters, such as age of onset, gender distribution, socioeconomic and regional determinants, and clinical manifestations, is given in this table. (Table 2) By looking at these factors, we can learn more about the frequency, societal trends, and management difficulties related to each ailment, which will ultimately improve diagnosis precision and therapeutic strategies.

Cinical Features

Scleroderma or Systemic sclerosis, is defined by a range of systemic and oral symptoms. The disease is characterized by skin thickening caused by an overabundance of collagen deposition, leading to tight and shiny skin, especially impacting the extremities and face.[2,11] Raynaud's phenomenon, a main characteristic of scleroderma, includes intermittent alterations in finger and toe colors due to cold or stress triggers.[3]

Internal organs can be significantly affected, such as with pulmonary fibrosis leading to interstitial lung disease, renal complications resulting in renal crisis, and gastrointestinal problems causing motility disorders.[4,20] Scleroderma in the oral cavity causes microstomia, xerostomia, and a higher risk of periodontal disease due to changes in oral conditions.[21,22] Different types of the illness are categorized, such as limited cutaneous scleroderma, impacting the skin of the limbs and face, and diffuse cutaneous scleroderma, leading to widespread skin alterations and initial organ fibrosis.[11]

The main characteristics of oral submucous fibrosis (OSF) are limited mouth opening (trismus) and a burning feeling in the oral mucosa, as noted by Rajendran (1994)[5] and Shih et al. (2019)[8]. The situation results in whitening of the mouth lining caused by scarring and gradual decrease in mouth opening, which greatly affects the patient's ability to eat and talk easily.[7,16] OSF goes through various stages, beginning with initial signs such as slight mucosal alterations and trismus.[5,23] Progression of the illness leads to increased fibrosis, causing worse trismus and reduced functional ability.[9,24] In advanced stages, significant fibrotic changes result in severe restrictions in mouth opening and substantial limitations in oral function.[6,25](Table 3)

Histopathological Features(Table 4)

Diagnostic Markers and Laboratory Investigations

Laboratory results and diagnostic markers are essential for distinguishing OSMF from other diseases. Reduced levels of hemoglobin, serum iron, serum protein, vitamin B12, folic acid, copper, zinc, albumin, and mucoproteins are commonly observed in laboratory tests, accompanied by elevated erythrocyte sedimentation rate (ESR) and normal eosinophil count. Increased serum levels of the immunoglobulins IgA, IgD, and IgE, as well as Beta-2-microglobulin and particular HLA types (A10, B7, and DR3), are indicated by immunological markers. Hyalinization, collagen fibrosis, and sub-epithelial inflammatory infiltrates are among the histopathological observations in OSMF. Reduced antioxidants and micronutrients, along with changed salivary indicators such as higher S-100A7, peroxidases, and lactic acid dehydrogenases, are indicative of a possible malignant risk, according to cytogenetic studies.[7,8]

Certain laboratory and serological markers are associated with scleroderma, also known as systemic sclerosis. Anti-Scl-70 (topoisomerase I), anticentromere antibodies (ACA), and anti-nuclear factor antibodies are important serological indicators. Elevated levels of transaminases (ALT, AST), cholestasis markers (γ-GT, ALP), lactate dehydrogenase (LDH), creatinine, and aldolase may be observed in laboratory examinations. Renal impairment may be indicated by high creatinine values in advanced stages. Edematous endothelial cells, thicker blood vessel walls, and widespread collagen deposition are among the histopathological observations. Localized scleroderma can be distinguished from other types by autoimmune markers

such as reduced anti-phospholipid antibodies and elevated procollagen type III serum levels.[2,3,4,11,20,26](Table 5)

Management (Table 6)

The treatment of scleroderma requires a comprehensive method that combines medication, alternative therapies, and researching new treatment options. The focus of pharmacological treatments is on immunosuppressants like methotrexate, which work to decrease autoimmune reactions and inflammation.[2]Nintedanib, an antifibrotic agent, is used to combat the fibrosis commonly seen in scleroderma according to Thoreau et al., 2021.[13] Vasodilators, such as endothelin receptor antagonists, are employed for treating Raynaud's phenomenon and enhancing blood circulation to the extremities.[3] Non-medication methods are crucial, including physical therapy to preserve joint movement and function, skin care to combat dryness and prevent issues, and specific tactics for handling Raynaud's phenomenon like staying out of the cold and wearing thermal gloves.[4] Novel treatments like biologics and targeted therapies that target specific pathways involved in scleroderma's development are receiving increased interest, providing optimism for more personalized and efficient treatment choices.[11,13,27,28]

Treating oral submucous fibrosis (OSF) requires a mixture of medications, surgeries, and changes in lifestyle. Corticosteroids and hyaluronidase are medications used to treat OSF by reducing inflammation and fibrosis, and breaking down fibrous tissue, respectively. Antioxidants are employed to counter oxidative stress and may help delay the advancement of the disease.[15] Surgery is an option for treating advanced cases of OSF, such as fibrotomy to release fibrous bands and grafting to improve mouth function and opening.[6] It is important to make lifestyle changes, such as quitting areca nut and tobacco, as they are main causes of OSF, and offering nutritional assistance to address issues with eating and mouth changes from trismus.[18,24,29,30,31] This thorough strategy targets managing symptoms, enhancing functionality, and halting disease advancement.

Comparative analysis

Treatment goals: According to Rosendahl et al. (2022)[2] and van den Hoogen et al. (2013)[3], the main goals of treating scleroderma are to decrease fibrosis, manage symptoms such as Raynaud's phenomenon, and enhance overall quality of life by non-pharmacological and pharmacological approaches. By means of a mix of medication, surgery, and lifestyle changes, the objectives for OSF, on the other hand, are to lessen fibrosis, relieve symptoms like trismus and mouth discomfort, and enhance functional outcomes.[5,6]

Therapeutic challenges: Both conditions face significant challenges. In scleroderma, adherence to treatment can be problematic due to the side effects of medications and

the variability in treatment efficacy.[11] Emerging therapies, while promising, are often costly and their long-term safety remains uncertain.[13] For OSF, the main challenges include managing side effects of corticosteroids, achieving consistent results with hyaluronidase, and ensuring patient adherence to lifestyle modifications.[8,18] Surgical interventions, although effective, come with risks of recurrence and complications.[6]

Clinical Implications

Early detection: For both scleroderma and oral submucous fibrosis (OSF), early detection is essential to stopping the disease's progression and enhancing long-term results. Early detection in scleroderma can have a major effect on how systemic problems are managed and can avert serious internal organ damage.[2] Early detection of OSF can stop the condition from getting worse and necessitate more intrusive treatments.[14]

Diagnostic tools: Diagnosis of Scleroderma typically involves a combination of imaging techniques and serological tests. Imaging modalities such as high-resolution chest CT scans are crucial for assessing pulmonary involvement, while serological tests help identify autoantibodies associated with scleroderma.[3] These tools are integral in diagnosing and monitoring disease progression and response to treatment.[2] The diagnosis of OSF frequently depends on clinical staging and biopsies. Histopathological confirmation of fibrosis is provided by biopsy, and clinical staging aids in determining the degree and character of the illness.[5] These techniques are necessary for making an accurate diagnosis and choosing the best course of action.[15]

Multidisciplinary approach: A multidisciplinary team approach is crucial for managing both conditions effectively. In scleroderma, a team including rheumatologists, dermatologists, and other specialists is necessary to address the multi-systemic nature of the disease.[11] Similarly, OSF management benefits from a team involving oral surgeons, dentists, and general practitioners to address various aspects of the disease, from surgical intervention to dietary modifications.[14]

Patient education: An important part of managing both OSF and scleroderma is patient education. To improve quality of life and treatment compliance, individuals with scleroderma must be educated on the disease's course and self-care techniques.[2] In patients with OSF, teaching them about the significance of abstaining from tobacco and areca nut usage, together with the necessity of dietary modifications, can assist to improve treatment outcomes and delay the progression of the disease.[5,7]

Conclusion

This review emphasizes the crucial need to distinguish between oral submucous fibrosis (OSMF) and scleroderma, considering their unique causes, symptoms, and outcomes. This paper is important because it focuses on the frequently neglected

difficulties in diagnosing these conditions, which, despite having similar fibrotic traits, need distinct treatment methods. It is essential for clinicians to identify the key diagnostic distinctions between OSMF and scleroderma. OSMF, mostly associated with betel nut consumption, is characterized by limited mouth opening, fibrous bands in the oral mucosa, and a high likelihood of developing cancer. On the other hand, scleroderma is an autoimmune condition that presents with widespread symptoms like tightening of the skin, Raynaud's phenomenon, and possible effects on various organs, but oral issues are considered less significant. Future studies should focus on improving diagnostic criteria by possibly including new biomarkers and imaging methods to improve early detection and differentiation. Furthermore, targeted therapeutic strategies need to be developed to address the specific pathophysiological mechanisms of each condition. By enhancing our knowledge and control of these illnesses, we can enhance patient results and lessen the impact of misdiagnosis and improper treatment.

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Table 1: Comparative Analysis of Pathogenesis in OSF and Scleroderma

Characteristics/Features	OSF (Oral Submucous Fibrosis)	Scleroderma (Systemic Sclerosis)
Primary Etiology	Chewing areca nuts regularly releases carcinogens that cause localized fibrosis.[8]	Systemic fibrosis is caused by autoimmune processes that are influenced by environmental and genetic factors.[11]
Key Molecular Events	- Activation of fibroblasts and myofibroblasts. - Excessive collagen deposition driven by cytokines.[5]	- Dysregulated fibroblast activation leading to widespread collagen deposition. - Systemic inflammation and autoimmunity.[2]
Role of Cytokines	TGF-β is a key mediator that encourages the production of collagen and fibroblasts.[15]	TGF-β is essential for fibrosis and for modifying immune responses.[1]
Genetic Susceptibility	Although individual genes are less well-defined, genetic factors may contribute to the course of disease.[5]	Certain autoantibodies and genetic mutations are components of genetic predisposition.[3]
Nutritional Factors	Nutritional deficiencies (e.g., vitamin B complex) exacerbate fibrosis.[5]	Nutritional factors are less prominently involved; however, nutritional management may impact disease progression.[11]
Immune Response	Local inflammation and immune response to carcinogens.[8]	Systemic autoimmunity with production of autoantibodies.[4]

Table 2: Comparison of the various epidemiological and demographical features

Characteristic	Scleroderma	Oral Submucous Fibrosis (OSF)
Age of Onset	Typically, onset in middle adulthood (30-50 years)[4]	Commonly affects young adults (15-30 years).[7]
Gender Distribution	Higher prevalence in females (2-4 times more common).[3]	Higher prevalence in males, particularly in regions with high areca nut consumption.[18]
Ethnicity and Region	Variations by ethnicity and region; higher incidence in Caucasian populations.[11]	More prevalent in South Asia, especially in regions where areca nut chewing is widespread.[19]
Geographic Distribution	Global; variable incidence with notable higher rates in Europe and North America.[2]	Predominantly South Asia; rare in Western countries.[18]
Socioeconomic Factors	Socioeconomic status influences access to treatment and outcomes.[2]	Socioeconomic factors influence prevalence and management; lower access in rural areas.[15]
Areas Affected	Systemic involvement including skin, lungs, kidneys, and gastrointestinal tract.[3]	Mainly impacts the oral cavity but can extend to the pharynx and larynx.[5]
Primary Etiological Agents	Autoimmune response, genetic predisposition, environmental factors.[3]	Chewing areca nut, genetic susceptibility, nutritional deficiencies.[15]
Histopathological Features	Skin fibrosis, collagen deposition, vascular damage, and autoantibody presence.[3]	Dense fibrous bands, atrophy of oral mucosa, and decreased vascularity.[5]
Chief Complaints	Skin thickening, Raynaud's phenomenon, organ dysfunction.[4]	Trismus, burning sensation, restricted mouth opening.[9]
Clinical Presentation	Skin fibrosis, digital ulcers, gastrointestinal symptoms, pulmonary fibrosis.[11]	Blanching of oral mucosa, fibrous bands, loss of oral mobility.[9]
Incidence	Rare, estimated at 3-10 cases per 100,000 population.[3]	Prevalence varies by region; reported as high as 1.2% in some South Asian populations.[18]
Prevalence	Less common compared to other autoimmune diseases.[3]	High prevalence in areas with areca nut consumption.[19]

Malignant Transformation Risk	Low risk of malignancy; primary focus is on organ fibrosis and functional impairment.[4]	Risk of oral cancer; malignant transformation reported in 7-10% of cases.[7]
Management Challenges	Difficulty in managing systemic symptoms and organ fibrosis; high cost of treatment.[4]	Difficulty in stopping areca nut use; mixed outcomes with surgical interventions.[9]
Impact on Quality of Life	Significant impact due to systemic involvement and chronic symptoms.[11]	Major impact on oral function and daily activities.[9]

Table 3: Clinical Features of Scleroderma and OSF

Characteristics/Features	Scleroderma (Systemic Sclerosis)	Oral Submucous Fibrosis (OSF)
Systemic Manifestations	- **Skin Thickening**: Marked by skin fibrosis and induration, resulting in a tight, shiny appearance. - **Raynaud's Phenomenon**: Episodes of finger and toe color changes triggered by cold or stress. - **Organ Involvement**: Involves fibrosis of internal organs, including the lungs (interstitial lung disease), kidneys (renal crisis), and gastrointestinal tract (motility disorders).[10]	- **Oral Manifestations**: OSF primarily affects the oral cavity, causing symptoms like trismus (restricted mouth opening), burning sensations in the oral mucosa, and mucosal blanching.[5,9]
Oral Manifestations	- **Microstomia**: Reduced mouth opening due to skin tightening. - **Xerostomia**: Dry mouth due to salivary gland involvement. - **Periodontal Disease**: Increased risk of	- **Trismus**: Difficulty opening the mouth caused by fibrosis. - **Burning Sensation**: Persistent discomfort in the oral mucosa. - **Blanching of the Oral Mucosa**: Whitening of the

	periodontal issues due to altered oral environment.[21]	mucosa due to fibrotic changes. - **Reduced Mouth Opening**: Progressive limitation in mouth opening.[7,11]
Disease Subtypes	- **Limited Cutaneous Scleroderma**: Fibrosis primarily affects the skin and underlying tissues of the extremities and face. - **Diffuse Cutaneous Scleroderma**: Extensive skin involvement and early visceral organ fibrosis.[3]	- **Initial Stage**: Early symptoms include mucosal changes and mild trismus. - **Moderate Stage**: Progressive fibrosis with significant trismus and functional impairment. - **Severe Stage**: Extensive mucosal fibrosis leading to marked trismus and impaired oral functions.[9,24]

Table 4: Histopathological Comparison of Scleroderma and Oral Submucous Fibrosis (OSF)

Characteristic	Scleroderma	Oral Submucous Fibrosis (OSF)
Sub-Epithelial Reaction	- Perivascular inflammation - Hyalinization with muscle atrophy	- Perivascular inflammation - Hyalinization, mainly in submucosa
Extracellular Matrix	- Excess matrix - Thickened vessels - Loss of papillary structures - Extensive fibrosis	- Submucosal hyalinization - Thickened vessels - Severe submucosal sclerosis
Histological Stages	Inflammation; Hyalinization; Fibrosis; Potential malignancy	Inflammation; Vasculopathy; Fibrosis/Sclerosis; Possible malignancy
Epithelium	- Atrophic with dysplasia in late stages	- Normal or atrophic superficial layer

	- Loss of rete ridges	- Loss of rete ridges - Nodular lymphocyte collections
Connective Tissue Stroma	- Granulation and degeneration - Collagen hyalinization - Obliterated vessels - Dense collagen - Potential malignancy	- Edematous endothelial cells - Submucosal hyalinization - Disappearing fat - Thickened collagen - Atrophic adnexal structures

Table 5: Comparative Laboratory Investigations in Oral Submucous Fibrosis (OSF) and Scleroderma

Parameter	OSMF	Scleroderma (SSc)
Hemoglobin	↓	Normal
Serum Iron	↓	Normal
Serum Protein	↓	Normal
Vitamin B12	↓	Normal
Folic Acid	↓	Normal
Erythrocyte Sedimentation Rate (ESR)	↑	↑
Copper (Cu)	↓	Normal
Zinc (Zn)	↓	Normal
Albumin	↓	Normal
Mucoproteins	↓	Normal
T Lymphocyte Count	↓	Normal
Eosinophils	Normal	↓
Immunological Markers	↑ IgA, IgD, IgE, Beta-2-microglobulin; Specific HLA types (A10, B7, DR3)	Anti-Scl-70 (topoisomerase I), ACA, Anti-nuclear factor, Anti-histone antibodies
Cytological Studies	↑ AgNOR, Elevated S-100A7, peroxidases, and lactic acid dehydrogenases; ↓ antioxidants	Not typically reported
Histopathological Findings	Sub-epithelial inflammation, hyalinization, collagen fibrosis	Edematous endothelial cells, thickened blood vessel walls, extensive collagen deposition

Table 6: Comparison of Management Strategies for OSF and Scleroderma

	Scleroderma	Oral Submucous Fibrosis

		(OSF)
Pharmacological Treatments		
Immunosuppressants (e.g., methotrexate)	Used to reduce autoimmune inflammation and fibrosis. Challenges include adherence issues due to side effects and uncertain long-term efficacy.[2]	**Corticosteroids**: Aimed at reducing inflammation and fibrosis. Challenges include side effects such as immunosuppression and weight gain.[5]
Antifibrotic agents (e.g., nintedanib)	Slows progression of fibrosis. Limited availability and high cost are notable challenges, along with variable patient response.[13]	**Hyaluronidase**: Works to break down fibrous tissue and improve mouth opening. Challenges include variable response and the need for multiple sessions.[8]
Vasodilators (e.g., endothelin receptor antagonists)	Manage Raynaud's phenomenon and improve blood flow. Side effects such as hypotension and potential drug interactions are key challenges.[3]	**Antioxidants**: Aim to slow disease progression and manage symptoms. Efficacy can vary and long-term compliance issues may arise.[15]
Non-Pharmacological Approaches		
Physical therapy	Maintains joint mobility and function. Challenges include patient compliance and accessibility to therapy.[4]	**Fibrotomy**: Used to release fibrous bands and improve mouth opening. Risks include recurrence and surgical complications.[6]
Skin care	Prevents skin complications and manages dryness. Requires consistent management and patient adherence.[4]	**Grafting procedures**: Aims to restore oral function and reduce trismus. Potential issues include graft failure and the need for follow-up.[6]
Management of	Reduces frequency and	**Cessation of areca nut and**

Raynaud's phenomenon	severity of episodes. Effective management often requires significant lifestyle changes.[3]	**tobacco use**: Essential for preventing disease progression and reducing symptoms. Adherence to these behavioral changes can be challenging.[18]
Emerging Therapies		
Biologics and targeted therapies	Aimed at personalized treatment and improved efficacy. Challenges include high costs and unknown long-term safety.[11,13]	**Nutritional support**: Intended to improve oral intake and overall health. Managing dietary changes and ensuring patient compliance are challenges.[24]