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# LESIONS AND CONDITIONS ASSOCIATED WITH ORAL FIBROSIS - A NARRATIVE REVIEW

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## Abstract

**Background**: Fibrosis is an abnormal accumulation of excessive connective tissue (mainly collagen) in an organ or tissue, leading to scarring and stiffening. It is a reparative response to injury, inflammation, or chronic disease. **Aim**: The aim of this narrative review is to classify and discuss the lesions and conditions associated with oral fibrosis. **Methods**: This narrative review was performed through an electronic search of data for the articles dealing with fibrosis, Oral submucous fibrosis, fibrosis of oral cavity other than OSMF from the following databases such as PubMed, Scopus, Medknow, WebMD, and IndMed. **Results**: Based on our search, we were able to retrieve the information from 18 articles and tabulated the classification of Lesions and Conditions associated with Oral Fibrosis. **Conclusion**: Although there is increasing interest in the lesions and conditions linked to oral fibrosis, to the best of our knowledge this novel review offers a comprehensive analysis of these conditions and lesions with classification.

**Keywords:** Oral Fibrosis, Classification, OSMF, Scleroderma, Radiation Induced fibrosis, Fibrosis other than OSMF

## Introduction:

Fibrosis is the abnormal accumulation of excessive connective tissue (mainly collagen) in an organ or tissue, leading to scarring and stiffening. It is a reparative response to injury, inflammation, or chronic disease, but it can disrupt normal tissue structure and function when it becomes excessive. The process of fibrosis is complex and involves a series of cellular, molecular, and tissue-level events. The steps in pathogenesis are injury or inflammation, activation of fibroblasts, excessive collagen deposition, tissue remodelling and fibrosis, chronic inflammation, and fibrosis progression and resolution or progression [1]. This narrative review deals with lesions and conditions associated with oral fibrosis. Although there is increasing interest in the lesions and conditions linked to oral fibrosis, to the best of our knowledge this novel review offers a comprehensive analysis of these conditions and lesions with classification.

## ORAL FIBROSIS:

The term "**Oral fibrosis is defined as a condition that is characterized by thickening and scarring of connective tissue as a reparative response to injury or damage**". The classification of Oral fibrosis is done based on etiology and pathogenesis

## Classification of Oral Fibrosis:

1. **Tobacco Induced Fibrosis:**
   i) Oral Submucous Fibrosis
2. **Internal /External radiation Induced:**
   i) Radiation Induced Fibrosis
3. **Autoimmune Conditions:**
   i) Scleroderma
4. **Protein Induced:**
   i) Amyloidosis
5. **Idiopathic Conditions**:
   i) Idiopathic Inflammatory Myopathies (**ref Fig: 1**)

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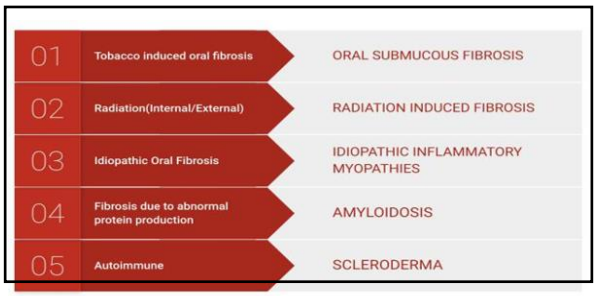


Fig 1: Classification of Oral Fibrosis

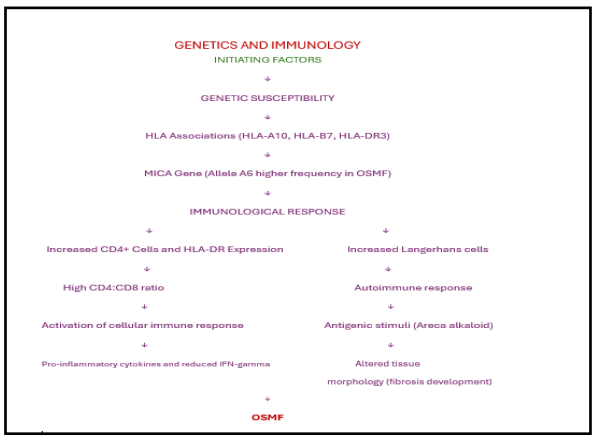


**Fig 2:** Pathogenesis of Oral Submucous Fibrosis

## ORAL SUBMUCOUS FIBROSIS

Pindborg defined OSMF as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. It is associated with juxta-inflammatory reaction followed by fibroelastic changes in the lamina propria layer, along with epithelial atrophy which leads to rigidity of the oral mucosa proceeding to trismus and difficulty in mouth opening."[4]

## PATHOGENESIS:

Many hypotheses suggest that OSMF is multifactorial in origin with etiological factors:

Arecanut, capsacin in chillies, micronutrient deficiencies of iron, zinc and essential vitamins. It is also suggested that it is an autoimmune etiological basis of disease with demonstration of various autoantibodies with a strong association with specific human leukocyte antigen (HLA). Arecanut(Betel nut) chewing is one of the most common causes of OSMF which contains tannins(11%-12%) and alkaloids such as arecoline, arecaidine, guvacine and guvacoline(0.15%-0.67%), OSMF is induced as a combined effect of tannin and arecoline by the mechanism of reducing degradation and increased production of collagen, respectively. Deficiency of iron, vitamin B complex, minerals and malnutrition are promoting factors that disturbs the healing process of inflamed oral mucosa, it leads to deranged healing and resultant scarring and fibrosis. The resulting atrophic mucosa is more susceptible to the effects of chilies, betel nuts and other irritants[3]

### Management:

1. Lifestyle and Dietary Modifications:

- Quit Betel Nut Chewing: The primary step in managing OSMF is to cease the use of betel nut or areca quid, as it is a major contributing factor to the condition.
- Balanced Diet: Improve nutritional intake, focusing on a diet rich in vitamins and minerals, particularly vitamin A, B12, and iron, which are often deficient in OSMF patients.

2. Medical Treatments:

- Topical Steroids: Corticosteroids like betamethasone can be applied for 3 months topically to reduce inflammation and fibrosis. Intralesional steroid injections may also be used in some cases.

  Intralesional steroid injection of interferon gamma (0.01-10.0 U/mL) 3 times a day for six months
- Systemic Steroids: In more severe cases, systemic corticosteroids may be prescribed to manage inflammation.
- Antioxidants like lycopene 8 mg twice a day for 2 months and Vitamins: Supplements like vitamin A, B complex, C, D, E and various antioxidants can be beneficial in managing oxidative stress and promoting mucosal healing.
- Hyoscine (Scopolamine): Some studies suggest that hyoscine, an anticholinergic agent, can help in reducing fibrosis and improving mouth opening.

3. Surgical Interventions:

- Release of Fibrosis: Surgical procedures can be considered to release the fibrotic bands and improve mouth opening. This includes procedures like mucosal or submucosal surgical release.
- Graft Placement: In some cases, grafts may be used to aid in the healing of the mucosal lining after release of fibrosis.

4. Physiotherapy:

- Mouth Opening Exercises: Regular exercises can help in maintaining or improving mouth opening and mobility. These exercises involve stretching the oral cavity and enhancing flexibility.
- Jaw Stretching Techniques: Exercises and techniques to stretch and strengthen the jaw muscles may be beneficial.

5. Supportive Measures:

- Pain Management: Analgesics or local anaesthetics may be used to manage pain and discomfort associated with OSMF.
- Regular Monitoring: OSMF patients should be regularly monitored for progression of the disease and potential malignant transformation, as OSMF has a risk of developing into oral cancer.

6. Oral Hygiene:

- Maintain Oral Health: Good oral hygiene practices are essential to prevent secondary infections and complications.

7. Counselling and Support:

- Patient Education: Educate patients about the nature of the disease, the importance of quitting betel nut, and the impact of dietary and lifestyle changes.
- Psychosocial Support: Provide support for coping with the physical and psychological effects of the disease.

### Multidisciplinary Approach

Managing OSMF often requires a multidisciplinary approach involving oral medicine specialists, dieticians, physiotherapists, and sometimes surgeons. Collaboration among healthcare professionals helps in providing comprehensive care tailored to the patient's specific needs and stage of the disease [2].

## MYOSITIS OSSIFICANS

Myositis ossificans is the most common form of heterotrophic ossification. It usually occurs within large muscles. It could mimic more aggressive pathological processes. Most cases of the myositis ossificans occur because of trauma, therefore young adults and paraplegics are more prone to it. Conditions that are similar to myositis ossificans: 1) Myositis ossificans progressive 2) Myositis ossificans circumscripta 3)Panniculitis ossificans 4) Fibro-osseous pseudotumor of the digits [6]

## PATHOGENESIS:

Myositis ossificans is the metaplasia of the intramuscular connective tissue resulting in extraosseous bone formation without any inflammation.

In the first month- Granulation and early repair: The tissue injury forms granulation tissue with fibroblastic and osteoblastic differentiation and osteoid formation.

In the second month- Mineralization and immature bone formation: Mineralized osteoid matrix develops with immature lamellar bone.

In the third month-Maturation of bone: Immature bone progresses into mature lamellar cortical and trabecular bone [5].

### RADIOGRAPHIC FEATURE:

The radiographic appearance of myositis ossificans is circumferential calcification with a lucent centre and a radiolucent cleft. The cleft separates the lesion from the cortex of the adjacent bone [5].

### TREATMENT AND PROGNOSIS:

Myositis ossificans is benign and there is no evidence of malignant transformation.

Treatment is done for symptomatic lesions and surgical resection is usually curative [5].

## AMYLOIDOSIS

Amyloidosis is a heterogeneous disease that results from the deposition of toxic insoluble beta-sheet fibrillar protein aggregates in various tissues. This disease can be localized or systemic with amyloid accumulating in the spleen, liver, kidney, blood vessels and nerves.

It causes different clinical syndromes including cardiomyopathy, hepatomegaly, proteinuria, macroglossia, autonomic dysfunction, ecchymoses, neuropathy, renal failure, hypertension and corneal and various abnormalities [8].

## PATHOGENESIS:

**Protein Misfolding**: Normally, proteins fold into specific three-dimensional structures necessary for their function. In amyloidosis, certain proteins misfold and acquire an abnormal configuration that predisposes them to form amyloid fibrils.

**Amyloid Fibril Formation**: The misfolded proteins aggregate into insoluble fibrils with a characteristic beta-pleated sheet structure. These fibrils are resistant to proteolysis, which means they are not easily broken down by the body's normal mechanisms.

1. **Deposition**: The amyloid fibrils deposit in extracellular spaces of tissues and organs. These deposits can accumulate in various tissues, including the heart, kidneys, liver, and nervous system, depending on the type of amyloidosis.
2. **Tissue Damage**: The accumulation of amyloid fibrils disrupts normal tissue architecture and function. This can lead to organ dysfunction and clinical symptoms depending on the organs affected. The presence of amyloid deposits can also trigger inflammatory responses that further contribute to tissue damage.
3. **Organ Dysfunction**: As amyloid deposits build up, they impair the function of the affected organs. For example, in cardiac amyloidosis, the amyloid deposits in the heart muscle can lead to restrictive cardiomyopathy. In renal amyloidosis, kidney function can be compromised, leading to nephrotic syndrome.

Amyloidosis can be classified into several types based on the type of protein involved and the associated underlying conditions. The main types include:

- **AL Amyloidosis (Primary Amyloidosis)**: Caused by light chains produced by abnormal plasma cells, often associated with multiple myeloma or other monoclonal gammopathies.
- **AA Amyloidosis (Secondary Amyloidosis)**: Results from chronic inflammatory conditions or infections, where the precursor protein is serum amyloid A (SAA).
- **Hereditary Amyloidosis**: Associated with genetic mutations that lead to the production of abnormal proteins, such as transthyretin (TTR) in familial amyloid polyneuropathy.
- **Age-Related Amyloidosis**: Typically involves the deposition of wild-type transthyretin (TTR) and is commonly observed in elderly individuals [8].

## EVALUATION:

Clinical suspicion, family history, and tissue biopsy establish the diagnosis.

### Tissue biopsy:

• The subcutaneous abdominal fat aspirate will stain Congo red positive with apple-green birefringence and has an 81% diagnostic sensitivity in AL amyloidosis.

• Biopsy of minor salivary glands can establish systemic amyloidosis diagnosis 60% of the times when fat aspirates are negative.

• Biopsy of the liver should be done by the transjugular route, since an amyloid-loaded liver may result in fatal bleeding.

### Plasma cell clone identification:

Serum and urine electrophoresis with immunofixation and free light chains (FLC) should be done to eliminate plasma cell dyscrasia.

Bone marrow biopsy can help establish the diagnosis by immunohistochemical staining. Immunofluorescence in situ hybridization (FISH) should be done along with a Skeletal survey.

When plasma cell dyscrasia is ruled out, other types of amyloidosis should be considered. Tissue typing is done by mass spectrometry, immune electron microscopy or immunohistochemistry.

Transthyretin can be detected by isoelectric focusing on the serum which separates wild-type or formerly known senile cardiac amyloidosis and variant transthyretin.

## Gene sequencing:

Should be done when hereditary amyloidosis has to be eliminated on clinical grounds.

When transthyretin has not been identified, and patients have macroglossia and other typical organ involvement, AL should still be suspected despite plasma cell dyscrasia absence.

ATTRwt (wild type) is diagnosed by cardiac biopsy showing positivity to antibodies against normal transthyretin.

Cardiac Scintigraphy with bone tracers can help differentiate AL amyloidosis which shows mild or no uptake from transthyretin amyloidosis which has strong uptake. This could potentially spare cardiac biopsy.

AA amyloidosis is considered when transthyretin and AL have been ruled out, and there are kidney involvement and neuropathy. Immunohistochemistry aids in the diagnosis of AA.

Organ involvement and staging of the disease should be established to design the treatment plan. For cardiac function, evaluation should include an echocardiogram with an assessment of strain, NT-proBNP, troponins, ECG, Holter ECG, and cardiac MRI should be done. For kidney function, evaluation of 24-hour urinary protein and eGFR are needed. Liver function tests and imaging (ultrasound, MRI, or CT scan) can help with hepatic function assessment [8].

# MANAGEMENT:

**1. Diagnosis**

- Confirm type of amyloidosis (e.g., AL, AA, ATTR) through biopsy and special staining techniques.

**2. Supportive Care**

- **Symptomatic Treatment:** Manage symptoms based on affected organs (e.g., diuretics for heart failure, pain management).
- **Lifestyle Modifications:** Dietary adjustments, physical therapy, and regular monitoring.

**3. Specific Treatment Approaches**

**AL Amyloidosis (Primary Amyloidosis)**

- **Chemotherapy:** Use of agents like dexamethasone, cyclophosphamide, or bortezomib to reduce plasma cell production.
- **Stem Cell Transplant:** Consider for eligible patients to achieve deeper remission.
- **Monoclonal Antibodies:** Emerging therapies like daratumumab.

**AA Amyloidosis (Secondary Amyloidosis)**

- **Treat Underlying Condition:** Focus on controlling chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease).
- **Anti-Inflammatory Medications:** NSAIDs or corticosteroids as needed.

**ATTR Amyloidosis (Hereditary or Wild-Type)**

- **Disease-Modifying Therapies:** Tafamidis or diflunisal to stabilize transthyretin and reduce amyloid deposition.
- **Supportive Care:** Management of cardiac symptoms, neuropathy, and other complications.

**4. Monitoring and Follow-Up**

- Regular assessment of organ function (e.g., heart, kidneys, liver).
- Monitor for disease progression and treatment efficacy.

**5. Multidisciplinary Approach**

- Collaboration with specialists (e.g., cardiologists, nephrologists, hematologists) for comprehensive care.

**6. Patient Education and Support**

- Educate patients about the disease, treatment options, and support resources (e.g., support groups) [7].

## IDIOPATHIC INFLAMMATORY MYOPATHIES

Idiopathic inflammatory myopathies (IIMs) are a heterogeneous group of complex muscle diseases of unknown etiology. IIMs will lead to progressive weakness and damage of the muscles involving the other organ systems. Lymphocytes and auto antibodies play an important role in the damage and weakness of the muscle [12].

## PATHOGENESIS:

Genetic and environmental factors together contribute to determine the susceptibility of IIM. The HLA alleles on chromosome 6 (HLA-DQA1*0501 and HLA-DRB1*0301) is associated with IIM. The TNFα-308A, which is the 59,60 polymorphism of TNFα, which will cause a longer course of disease, increased severity of disease.

The macrophage- activating complex (MAC), if activated, deposits on the surface of endothelium and is defined as an antigenic target which will cause necrosis and ischemia of capillary. This activated MAC triggers the secretion of pro-inflammatory cytokines that leads to B-cell, $CD4^+$ T-cell and plasmacytoid dendritic cell infiltration. In case of polymyositis and inclusion body myositis antigen response will lead to infiltration of $CD8^+$ T- cells [10]

## MANAGEMENT:

**1. Diagnosis**

- Confirm diagnosis through clinical evaluation, muscle strength testing, electromyography (EMG), muscle biopsy, and laboratory tests (e.g., creatine kinase levels, autoantibodies).

**2. Medication Management**

**a. Corticosteroids**

- **Prednisone:** First-line treatment to reduce inflammation and improve muscle strength.
- **Tapering:** Gradual reduction to minimize side effects.

**b. Immunosuppressants**

- **Azathioprine, Methotrexate, Mycophenolate Mofetil:** Often used as steroid-sparing agents.
- **IVIG (Intravenous Immunoglobulin):** Considered in cases resistant to conventional therapies.

**c. Biologic Therapies**

- **Rituximab:** Particularly in refractory cases or associated with anti-Jo-1 antibodies.
- **Other agents:** Emerging options based on individual patient profiles.

**3. Rehabilitation**

- **Physical Therapy:** Tailored exercise programs to improve strength and function, prevent contractures, and maintain mobility.
- **Occupational Therapy:** Assistance with daily activities and adaptations to improve quality of life.

**4. Management of Associated Symptoms**

- **Skin Involvement:** Topical treatments or systemic agents for dermatomyositis.
- **Fatigue Management:** Addressing sleep, nutrition, and psychological support.

**5. Monitoring and Follow-Up**

- Regular assessments to monitor muscle strength, function, and side effects of medications.
- Periodic laboratory tests to evaluate muscle enzyme levels and monitor for complications.

**6. Patient Education and Support**

- Informing patients about the disease, treatment options, and the importance of adherence to therapy.
- Encouragement to join support groups for shared experiences and coping strategies.

**7. Multidisciplinary Approach**

- Collaboration among rheumatologists, neurologists, physical therapists, and other healthcare providers for comprehensive care [11].

## RADIATION INDUCED FIBROSIS

Radiation-induced fibrosis (RIF) is a persistent complication of external beam radiation therapy for cancer treatment. Cancer patients are treated with external beam ionising radiation either alone or in combination with surgery and/or chemotherapy.

Ionising radiation damages both normal and cancer cells. Major complications occur based on the radiation dose, fraction size and volume treated.

RIF is a significant complication that leads to morbidity of the patient. RIF can occur in tissues that are exposed to irr. Radiation injury causes inflammation and causes fibroblasts to differentiate into myofibroblasts. Myofibroblasts produce more collagen and other extracellular matrix components, which is compounded by a reduction in remodelling enzymes [14].

## PATHOGENESIS:

The mechanism is the same as that of any chronic wound healing process. Radiation injury results from two primary mechanisms: damaging DNA directly and the production of reactive oxygen species. The production of reactive oxygen species is more prominent in RF and involves reaction of ionizing radiation with water molecules to produce free radicals, including superoxide, hydrogen peroxide and hydroxyl radical, the last of which accounts for 60-70% of the total damage.

Neutrophils are the primary cells that reach the injured site.

**Radiation Exposure**

- Ionizing radiation affects tissues.

**Cellular Damage**

- DNA damage in epithelial and endothelial cells.
- Induction of apoptosis and necrosis.

**Inflammatory Response**

- Release of pro-inflammatory cytokines (e.g., TNF-α, IL-1).
- Recruitment of immune cells (e.g., macrophages, lymphocytes).

**Fibroblast Activation**

- Activation of fibroblasts by cytokines and growth factors.
- Fibroblast proliferation.

**Extracellular Matrix (ECM) Deposition**

- Increased production of collagen and other ECM components.
- Alterations in ECM remodeling.

**Tissue Remodeling**

- Accumulation of fibrous tissue.
- Loss of tissue elasticity and function.

**Clinical Manifestations**

- Symptoms such as skin thickening, stiffness, and organ dysfunction.

**Chronic Phase**

- Persistence of fibrosis and potential progression to severe complications [13]

## MANAGEMENT:

Radiation-induced fibrosis (RIF) can be treated with a combination of physical therapy, massage, and medications:

**Physical therapy and massage**: Can help improve range of motion, pain, and skin induration.

**Medications**: Treatments include:

**Anti-inflammatory treatment**: Corticosteroids like prednisone 1-2mg/kg/day for 3-12 weeks or interferon gamma can help with moderate RIF.

**Vascular therapy**: Pentoxifylline 400 mg twice daily for 2 months or hyperbaric oxygen can help with moderate RIF.

**Antioxidant treatment**: Superoxide dismutase, tocopherol (vitamin E), or a combination of PTX(800mg/d) and vitamin E(1000 IU/d) for 6 months can help with moderate RIF.

**Pirfenidone**: An antiproliferative and antifibrotic agent that can help improve range of motion. [13]

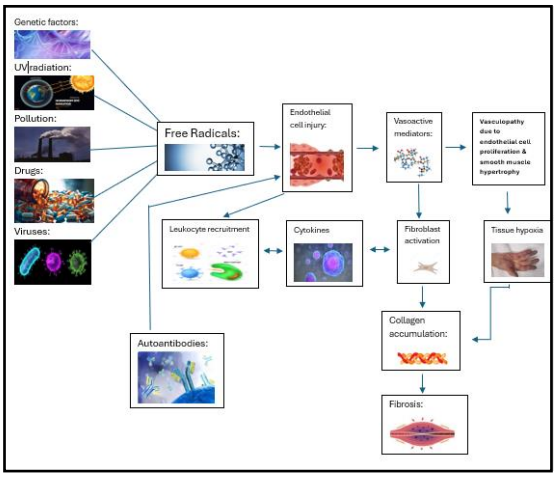


Fig 3: Pathogenesis of Radiation Induced Fibrosis

## SCLERODERMA

Systemic sclerosis or scleroderma is a rare connective tissue disorder with an unknown and complex pathogenesis [17]. Scleroderma can be divided into 2 primary forms

1.localized scleroderma

2. systemic sclerosis.

Systemic sclerosis is a chronic, multisystem connective tissue disease characterized by microangiopathy leading to inflammation and fibrosis involving skin and internal organs [17].

**Etiology:**

Various genetic, infectious and environmental factors have been implicated; vascular injury, fibrosis and immune activation are involved in the pathogenesis [16].

## MANAGEMENT:

1. Diagnosis

- Confirm diagnosis through clinical evaluation, history, laboratory tests (e.g., autoantibody testing), and imaging studies as needed.

2. Symptomatic Management

- Skin Involvement:
  - Moisturizers: To alleviate dryness and improve skin texture.
  - Topical corticosteroids: For localized inflammation.
- Raynaud's Phenomenon:
  - Calcium channel blockers (e.g., nifedipine): To improve blood flow.
  - Lifestyle modifications: Keeping warm, avoiding triggers.

3. Organ-Specific Treatments

a. Pulmonary Involvement:

- Interstitial Lung Disease:
  - Immunosuppressants: (e.g., mycophenolate mofetil, cyclophosphamide) for progressive disease.
  - Pulmonary fibrosis treatments: Newer agents like nintedanib or pirfenidone may be considered.
- Pulmonary Hypertension:
  - Vasodilators: (e.g., endothelin receptor antagonists, phosphodiesterase-5 inhibitors) to manage pulmonary arterial hypertension.

b. Gastrointestinal Involvement:

- Proton Pump Inhibitors (PPIs): For gastroesophageal reflux.
- Motility agents: (e.g., prokinetic agents) for dysmotility.
- Dietary modifications: Small, frequent meals and high-fiber diet.

c. Renal Involvement:

- Blood Pressure Management: ACE inhibitors for scleroderma renal crisis.
- Close monitoring: Regular checks on renal function.

4. Immunosuppressive Therapy

- For patients with significant organ involvement, consider agents such as:
  - Methotrexate
  - Azathioprine
  - Rituximab in selected cases.

5. Physical Therapy and Rehabilitation

- Tailored exercise programs to maintain joint mobility and prevent contractures.
- Occupational therapy for daily activities.

6. Patient Education and Support

- Inform patients about scleroderma, treatment options, and the importance of regular monitoring.
- Encourage participation in support groups.

7. Multidisciplinary Approach

- Collaboration with rheumatologists, pulmonologists, gastroenterologists, cardiologists, and dermatologists for comprehensive care.

8. Regular Follow-Up

- Ongoing assessment of disease progression, treatment efficacy, and management of complications [17]

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