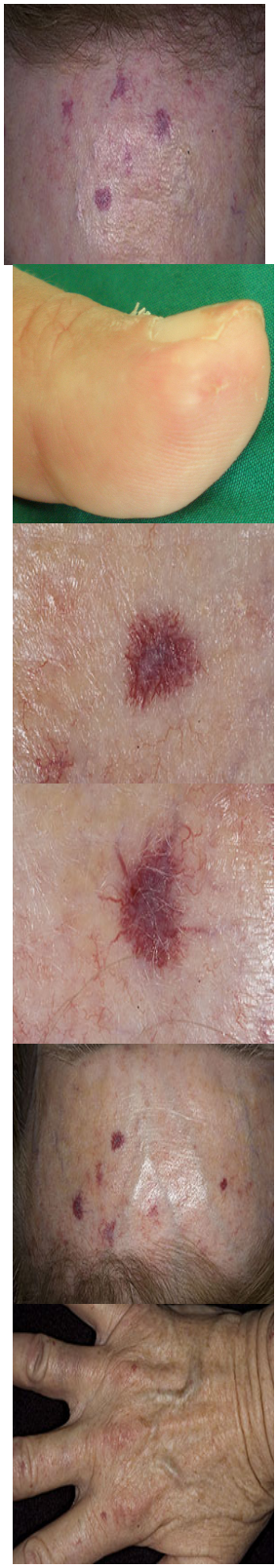

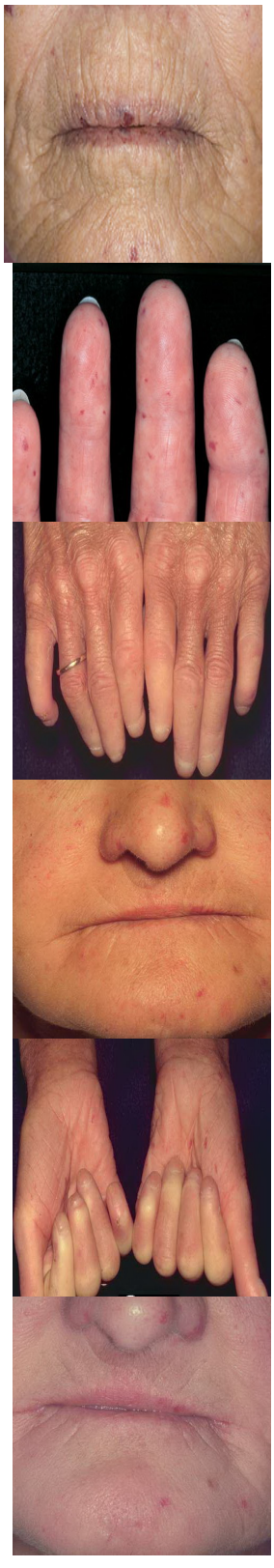

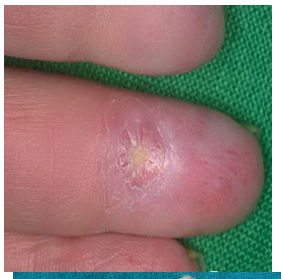

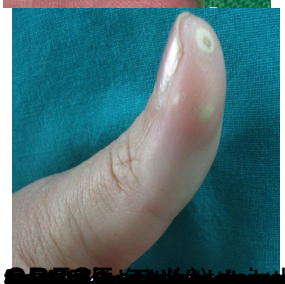

Pathophysiology

Three primary pathologic features are found in scleroderma and include increased collagen deposition, perivascular mononuclear cell infiltration, and vascular abnormalities.

The pathologic hallmark of scleroderma is progressive fibrosis of tissues. Collagen (types I, III, IV, and VII), fibronectin, glycosaminoglycans, and proteoglycans are deposited in the interstitium and in the intima of small arteries.[15] Fibrosis is found in clinically affected and unaffected tissue.

Skin fibroblasts in patients with scleroderma act as if they are persistently activated. Higher levels of *COL1A2* mRNA (gene encoding alpha-2 chain of type I procollagen) are found in the dermis of scleroderma patients compared with patients without scleroderma, and down-regulation of fibroblast collagen synthesis by collagen amino-terminal peptides is impaired.

Mononuclear infiltration probably precedes fibrosis of tissues. Histologic specimens from patients with disease duration of less than 2 years show mononuclear infiltration near blood vessels and dermal appendages. While this inflammatory infiltrate can accompany fibrosis in tissues, it can also be present without fibrosis, suggesting that it is an early event in the pathogenesis of scleroderma.

CD4 lymphocytes predominate in the inflammatory infiltrate. Suppressor T cells are diminished in number. Macrophages are present in higher numbers, as are eosinophils, basophils, mast cells, and B cells. These cells secrete a variety of cytokines, the balance of which is important in the pathogenesis of fibrosis.

Several cytokines have been implicated in the development of fibrosis. Transforming growth factor-beta (TGF-beta) stimulates collagen synthesis, and plasma levels of this cytokine are elevated in scleroderma patients (both limited and diffuse scleroderma). Fibroblasts from the skin of scleroderma patients express increased amounts of mRNA for TGF-beta and secrete higher levels of TGF-beta. Furthermore, these fibroblasts are not as sensitive as normal fibroblasts to stimulation by exogenous TGF-beta, suggesting that they are already maximally stimulated. TGF-beta3 in particular has been suggested as having a major role in the pathogenesis of the calcinosis often seen in persons with systemic sclerosis.[16]

Sera from patients with systemic scleroderma contain enhanced concentrations of granulocyte macrophage colony-stimulating factor (GM-CSF). Incubating GM-CSF with dermal fibroblasts from systemic scleroderma patients decreases type I collagen mRNA levels and collagen synthesis while increasing the production of other extracellular matrix proteins such as fibronectin and tenascin.[17]

Interleukin 4, a potent stimulator of collagen synthesis, is overexpressed in scleroderma skin. Scleroderma patients have normal or reduced levels of interferon-gamma (IFN-gamma), an inhibitor of collagen synthesis, in the skin. Interleukin 4 is produced by T helper-2 (TH2) cells, and IFN-gamma is produced by T helper-1 (TH1) cells. Scleroderma fibroblasts may be responding to an imbalance in these usual regulatory cytokines as a result of a predominance of TH2 cell activity.

Other cytokine perturbations have been demonstrated. Scleroderma fibroblasts secrete a higher basal level of connective tissue growth factor (CTGF) than normal fibroblasts. Scleroderma fibroblasts are less responsive to tumor necrosis factor-alpha, which normally acts to suppress CTGF expression.

Serum tissue inhibitor of metalloproteinase-1 (TIMP-1) levels are elevated in scleroderma patients compared with normal controls. This may allow progressive fibrosis to result because of a relative lack of collagenase activity. TIMP-1 may behave as an autocrine growth factor in the fibrotic process of scleroderma.[18] Recently, the protease nexin-1 gene (*PN1*) has been found to

be overexpressed in systemic sclerosis fibroblasts.

PN1

plays an important role in the regulation of cell growth, differentiation, and cell death by modulating proteolytic activity; in vitro evidence suggests it inhibits metalloproteinase activation.[19]

Vascular abnormalities are also likely to be an early contributor to the pathogenesis of scleroderma. Pericytes, the smooth muscle–like mural cells of capillaries and venules, synthesize matrix components and fibroblast-activating cytokines; thus, they are potential mediators of pathological changes in scleroderma. Pericyte density is increased in the microvasculature of the peripheral zones of active disease.[20] Clinically, microvascular changes are apparent in the nailfold capillaries as larger tufted capillaries and areas of dropout. The vasospastic phenomenon of Raynaud is present in most scleroderma patients.

Endothelial cell injury and dysfunction, intimal proliferation, thrombocytosis, elevated factor VIII-von Willebrand factor levels, and vasospasm are found in scleroderma patients and result in vascular compromise. Elevated levels of platelet-derived growth factor (PDGF) and increased expression of PDGF type-B receptors are found in the skin of scleroderma patients.[21,22] Ischemi a is an important contributor to end organ damage in scleroderma patients.

Animal models of scleroderma may help identify abnormalities in human scleroderma. The tight skin mouse model of scleroderma (Tsk1) is characterized by increased collagen deposition in the skin and some internal organs, as well as antinuclear antibody (ANA) production. The defect is a heterozygous mutation in the fibrillin-1 gene. A 1996 haplotype analysis of Choctaw Native Americans (who have a 50-fold increase in the prevalence of scleroderma) has demonstrated linkage between the fibrillin gene locus and the scleroderma phenotype. How a defect in fibrillin, an extracellular matrix component, may be involved in the pathogenesis of scleroderma is unclear.

An avian model, the UCD-200 chicken, develops fibrosis of the skin and internal organs and the presence of ANAs. Affected chickens develop vascular occlusion and severe perivascular lymphocytic infiltration of the skin and internal organs. These studies suggest that early pathogenetic events in scleroderma are endothelial abnormalities. Antiendothelial cell antibodies trigger both apoptosis and increased adhesion molecule expression on endothelial cells, resulting in perivascular accumulation of mononuclear cells.

In summary, while the primary trigger for CREST syndrome is not known, a reasonable speculation is that vascular endothelial cell abnormalities incite mononuclear infiltration, and the resulting perturbations in TH1 and/or TH2 cell and cytokine balance result in abnormal fibroblast activity and increased collagen deposition.

Nelson[23] has suggested the role of microchimerism in the pathogenesis of scleroderma, because of the similarity of scleroderma to chronic graft versus host disease and the frequent onset of scleroderma in women after their childbearing years. Microchimerism indeed occurs to a greater degree in persons with scleroderma or other autoimmune disorders than in healthy patients. A causal linkage between microchimerism and autoimmune disorders has not been demonstrated.

In the typical course of limited scleroderma, the patient first notices Raynaud phenomenon. Over time (usually years), fingers become puffy, then the skin thickens slowly. Internal organ manifestations are delayed for many years.

- Calcinosis is the pathologic calcification of soft tissues.
- The calcific deposits can be subclinical. When symptomatic, they can be tender and painful. They can ulcerate, drain a white chalky substance, and become secondarily infected.

- Inflammatory reactions intermittently occur at the site of calcinosis.
- Paraspinal calcifications rarely occur, causing local pain, radiculopathy, and diffuse weakness.

- Maurice Raynaud defined Raynaud phenomenon in 1862. He observed episodes of pallor, cyanosis, and/or rubor on the hands bilaterally in response to cold or emotional stress, in the setting of normal proximal arterial pulsations, and without gangrene.
- Patients occasionally describe color changes proximally as far as the wrist. Less frequently, the feet are involved. Rarely, the nose and ears can be affected.
- Involved skin is cool during the attack, but the proximal skin is warm.
- Color changes are often accompanied by symptoms that can include pain and paresthesias.
- The phenomenon lasts minutes to hours, and the patient is symptom-free between episodes.

- While the entire intestine can be involved in scleroderma, esophageal involvement is most common and most often clinically relevant.

- According to Akesson and Wollheim from 1989,[34] dysmotility is common. Cine-esophagram and radionuclide transit time studies demonstrate hypomotility in as many as 75-86% of patients with CREST syndrome. All patients have normal motility of the proximal esophagus, which primarily is striated muscle.

- In 1987, Zamost et al[35] correlated esophageal symptoms with anatomic and physiologic measurements in 53 patients with scleroderma. The prevalence of esophagitis and strictures (41%) in this patient population is higher than in otherwise healthy patients with gastroesophageal reflux disease. Abnormal motility was a significant predictor of erosive esophagitis; 70% of patients with dysmotility had gross or microscopic evidence of erosive esophagitis. No patients with normal motility had erosive esophagitis. Symptoms of heartburn and dysphagia were more common in patients with erosive esophagitis. Heartburn alone did not predict esophagitis; half the patients without this complication still experienced heartburn. Additionally, dysphagia did not predict the presence of stricture.
- Barrett esophagitis, a complication of gastroesophageal reflux, has been found in scleroderma patients, perhaps at a higher rate (37% in patients with scleroderma vs 4-13% in patients without scleroderma). Esophageal adenocarcinoma, a malignant transformation of Barrett esophagitis, has also been documented in scleroderma patients.
- Another potential complication of esophageal dysmotility and gastroesophageal reflux is occult aspiration and pulmonary disease. In 1989, Johnson et al [36] examined 13 patients with systemic sclerosis using endoscopy, laryngoscopy, esophageal manometry, 24-hour esophageal pH monitoring, pulmonary function testing, and aspiration scanning. All 13 patients had endoscopic evidence of reflux. Twelve patients had abnormal laryngeal examination findings suggestive of aspiration; however, in this group, 1 patient had no evidence of proximal reflux by pH monitoring and 2 patients had normal aspiration scan results. Nonetheless, an inverse relationship was found between diffusing capacity of lung for carbon dioxide and esophageal reflux scores, indicating that gastroesophageal reflux potentially contributes to diminished pulmonary function.

- Sclerodactyly means thickening of the skin of the digits of the hands and feet. Three phases of skin changes are seen in scleroderma: the edematous phase, indurative phase, and atrophic phase.
- Patients with early scleroderma present with puffy edema in the fingers and may report morning stiffness or arthralgias. The edematous phase is usually short (ie, months, but occasionally years).
- In the indurative phase, the skin becomes thickened. Patients may report pruritus. The skin appears shiny and tight. Skin creases are lost. Erythema may be present. In limited scleroderma, this process continues slowly for many years.
- Late in the course of scleroderma, the skin becomes fragile and lax as it enters the atrophic phase.
- Patients with limited scleroderma find that the advancement of skin disease occurs slowly, over many years. By definition, skin involvement remains distal to the elbows and knees, although it can involve the face and neck.

- Telangiectases are lesions formed by collections of dilated blood vessels.
- In scleroderma patients, telangiectases occur on the face, upper trunk, and hands.
- They also occur on mucosal surfaces (eg, lips) and throughout the GI tract and may be symptomatic. These were the most common cause of bleeding in a series of 144 patients with scleroderma (diffuse and limited disease). Telangiectases were associated with recurrent GI bleeding in 7 patients in this group. This bleeding can be chronic and cause anemia. [37]

- Other manifestations
- Arthralgias are common (90% of patients), but erosive arthritis is rare. Proximal muscle weakness can occur.
- Pulmonary hypertension most often occurs in the absence of interstitial fibrosis in approximately 3-14% of CREST syndrome patients. It is a very late event and the prognosis is poor, with a mortality rate of 50% after 2 years. [38] Symptoms heralding this phenomenon include dyspnea on exertion and cough.

- Myocardial involvement is rare in patients with limited scleroderma; however, patchy fibrosis in the myocardium can occur and typically is asymptomatic. Significant myocardial involvement manifests as dyspnea on exertion, fatigue, and palpitations. Arrhythmias and conduction abnormalities can occur.
- Primary biliary cirrhosis may be associated with CREST syndrome.[39,40]
- Renal crises rarely occur in persons with limited scleroderma (1%); they manifest accelerated hypertension, renal failure, and microangiopathic hemolytic anemia.
- Entrapment neurologic syndromes (eg, carpal tunnel syndrome) occur. Autonomic dysfunction of the GI tract also occurs.
- Sicca symptoms are present in approximately 35% of patients. Of patients with sicca symptoms, half have anti-Ro (SSA) or anti-La (SSB) antibodies.
- Scleroderma is associated with an increased risk of cancer, in particular lung cancer.[41]

Physical

- Calcinosis
- In scleroderma, calcific deposits are found predominantly in the extremities, around joints, and around bony prominences.
- Deposits typically are found in the flexor surfaces of the hands and the extensor surfaces of the forearms and knees.
- The deposits rest in the dermis but can be found in deeper periarticular tissues.

- Raynaud phenomenon
- Triphasic color changes of pallor, cyanosis, and erythema represent phases of

vasoconstriction, slow blood flow, and reperfusion, respectively.

- Color changes extend proximally from the tips of digits to various levels, with a well-demarcated border.

- Esophageal dysmotility
- The earliest change in the distal esophagus (primarily smooth muscle) is an uncoordinated disorganized pattern of contractions resulting in low amplitude or absent peristalsis.
- Lower esophageal sphincter (LES) pressure typically is lower than in healthy controls, and incomplete relaxation of the LES occurs. [42]

- Sclerodactyly
- The process typically begins in the distal fingers and advances proximally.
- The process also may occur on the face, over the forehead, and around the mouth. Facial involvement can lead to a *mauskopf* (mouse head) appearance. Lips become thinner, and radial furrowing develops around the mouth. The oral aperture is reduced in size (microstomia). Wrinkles over the forehead diminish

The cause of limited scleroderma is yet to be determined. Studies of genetic factors show only rare occasions of multicase families. HLA associations are present but are not strong. These include HLA-DRB*01, HLADRB*11, HLA-A*30, and HLA-A*32 showing increased susceptibility to scleroderma and HLA-DRB*07, HLA-B*57, and HLA-Cw*14 being protective.[43]

The predominance of cases occurring in women after their childbearing years and the similar clinical presentation of scleroderma to graft versus host disease has suggested the importance of fetal/maternal microchimerism in the etiology of scleroderma.

Environmental factors also are likely important. Some similarities in clinical presentation occur with L-tryptophan and rapeseed oil exposure. Certain occupations have been linked to an increased risk to systemic sclerosis, including female teachers, female textile workers, and construction workers. Exposure to silica, synthetic adhesives, solvents (including chlorinated solvents, aromatic solvents, white spirit, toluene, trichloroethylene, formaldehyde, vinyl chloride,

and cleaning products) have been implicated in a higher risk of developing systemic sclerosis. Interestingly, the use of vibrating tools was also found to increase the risk of systemic sclerosis. [44,45]

The pathogenesis of calcinosis, Raynaud phenomenon, esophageal dysmotility, and sclerodactyly are described in more detail.

- Calcinosis
- Ultrastructural study of calcifications from patients with CREST syndrome demonstrates calcium apatite crystals. Serum calcium, phosphorus, and alkaline phosphatase levels typically are normal; therefore, the calcifications are considered dystrophic.
- Elevated levels of gamma-carboxyglutamic acid (Gla), a calcium-binding amino acid found in vitamin K–dependent clotting factors, are present in the urine and the involved tissues of patients with calcinosis. Gla and other calcium-binding proteins may be deposited abnormally in soft tissues during clotting. The occurrence of calcinosis at sites of repeated trauma appears to support this idea.

- Raynaud phenomenon
- Microvascular abnormalities and dysfunction are central to the pathogenesis of scleroderma-associated Raynaud phenomenon.
- Endothelial injury is believed to result in intimal hyperplasia and fibrosis, concentric narrowing of digital arteries by as much as 75-80%, and occlusion by intravascular thrombi.

- Resting blood flow in fingers was lower in scleroderma patients compared with normal controls as measured by laser Doppler flowmeter. Arteries from scleroderma patients have significantly increased sensitivity to alpha2-adenoreceptor–mediated vasoconstriction. Whether this is a consequence or cause of endothelial cell injury and dysfunction is unclear.
- Endothelin, a naturally occurring peptide, has been implicated as a pathologic mediator of vasoconstriction, fibrosis, vascular hypertrophy, and inflammation in patients with Raynaud syndrome. [46]

- Esophageal dysmotility
- The earliest abnormality in the involved gut of scleroderma patients is dysmotility secondary to nerve injury, perhaps resulting from arteriolar changes in the vasa nervorum or compressive nerve damage via collagen deposits. Smooth muscle atrophy occurs later (and often marks the beginning of symptoms).
- The predilection for smooth muscle rather than striated muscle atrophy explains the distribution of anatomic involvement. The proximal esophagus primarily is striated muscle and remains essentially uninvolved. The esophagus typically is weakly responsive to prokinetic therapy, until, according to Sjogren, [42] the final stage of the disease (fibrotic infiltration of muscle) halts the response to medications.

- The consequences of esophageal dysmotility are reflux and its complications. The reduced LES pressure in patients with scleroderma likely allows acid reflux, which is exacerbated by delayed clearance of acid from the esophagus because of abnormal distal motility. This creates an environment in which stricture, Barrett esophagus, adenocarcinoma, [47]
or aspiration may supervene.

- The relationship of Raynaud phenomenon to esophageal dysmotility is interesting. Cold-induced vasospasm of the hands also results in esophageal dysmotility, and reversal of this vasospasm with reserpine reverses both peripheral Raynaud phenomenon and abnormalities in esophageal motility (as reported by Sjogren [42] in 1994); however, patients with primary Raynaud phenomenon do not tend to have esophageal dysmotility. Therefore, the significance of these observations remains to be determined.

- Sclerodactyly
- The development of sclerodactyly begins with a perivascular inflammatory infiltrate in the dermis. The trigger for this inflammatory process is not known.
- The edematous phase of skin involvement results from mucopolysaccharide, glycoprotein, and collagen (types I and III) deposition in the dermis.
- As collagen deposition continues, the dermis becomes more sclerotic than edematous. Meanwhile, a similar process occurs in small arteries. Mucinous deposition occurs in the intima. The adventitia is infiltrated first with inflammatory cells, and then it becomes fibrotic. This process results in narrowing of the artery and then arterial collapse or thrombosis. The tissue then becomes ischemic.
- Years after the onset of skin changes, fibrosis usually subsides, leaving atrophic skin.

Other Problems to Be Considered

Sclerodermalike disorders
Diffuse scleroderma
Limited scleroderma

Morphea
Mixed connective-tissue disease
Vinyl chloride disease
Silica exposure
Amyloidosis
Eosinophilic fasciitis
Eosinophilia-myalgia syndrome
Toxic oil syndrome
Type 1 diabetes mellitus
Carcinoid syndrome
Myeloma
Paraproteinemia
Scleromyxedema
Chronic graft versus host disease
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes)
Porphyria cutanea tarda
Phenylketonuria

Raynaud phenomenon
Primary Raynaud phenomenon

Secondary Raynaud phenomenon
Livedo reticularis
Acrocyanosis
Diffuse systemic sclerosis
Limited systemic sclerosis
Systemic lupus erythematosus
Dermatomyositis
Rheumatoid arthritis
Sjögren syndrome
Systemic vasculitis
Cryoglobulinemia
Macroglobulinemia
Cold agglutinins
Beta-adrenergic blockers
Nicotine
Ergotamine
Vinyl chloride exposure
Thoracic outlet syndrome
Atherosclerotic disease
Thromboangiitis obliterans (Buerger disease)
Frostbite
Vibratory tool use
Reflex sympathetic dystrophy
Carpal tunnel syndrome
Diabetes mellitus

Calcinosis
Dystrophic (normal calcium/phosphorus)
Dermatomyositis
Systemic lupus erythematosus
Scleroderma
Panniculitis
Porphyria cutanea tarda
Ehlers-Danlos syndrome
Pseudoxanthoma elasticum
Werner syndrome
Cutaneous neoplasms
Infections
Trauma

Metastatic calcinosis
Chronic renal failure
Hypervitaminosis D
Milk-alkali syndrome
Neoplasms
Sarcoidosis
Pseudoxanthoma elasticum

Idiopathic calcinosis
Tumoral calcinosis
Subepidermal calcified nodule
Idiopathic calcinosis cutis in Down syndrome
Idiopathic calcification of the scrotum

Iatrogenic calcinosis

Primary telangiectasia
Ataxia telangiectasia
Generalized essential telangiectasia
Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome)
Spider angiomas
Unilateral nevoid telangiectasia syndrome

Secondary telangiectasia
Actinically damaged skin
Postlaser or electrosurgery
Postcryosurgery
Basal cell carcinoma
Collagen-vascular disease
Dermatomyositis
Lupus erythematosus
Scleroderma

Cushing syndrome
Estrogen excess
Cirrhosis
Oral contraceptives
Pregnancy
Poikiloderma
Metastatic carcinoma
Necrobiosis lipoidica diabeticorum
Pseudoxanthoma elasticum
Radiation therapy injury
Rosacea
Generalized cutaneous mastocytosis
Topical steroid induced
Xeroderma pigmentosa

Laboratory Studies

- ANAs: Limited scleroderma is associated with an early rise in ANA levels, particularly of the immunoglobulin G3 subclass. The overall sensitivity of ANA in systemic sclerosis is 85%, while the specificity is approximately 54%. Serial testing of ANAs to monitor the progress of disease is not currently recommended. [48]
- Anticentromere antibodies are found in approximately 50-90% of patients with limited forms of scleroderma; Anticentromere antibodies are present in 82-96% of patients with the CREST variant. The specificity of this test is 95%. [49]

- Anti-Scl-70 (anti-topoisomerase I) antibody is associated with diffuse scleroderma, early internal organ involvement, and a worse prognosis. Perform this laboratory test early in the course of the patient's presentation to determine if the patient is at risk for this course of scleroderma.
- Nonspecific indicators of inflammation (eg, mild leukocytosis, normocytic-normochromic anemia, thrombocytosis, elevated erythrocyte sedimentation rate, elevated C-reactive protein) are rare but may be present in persons with limited scleroderma.

- Calcinosis: Evaluate serum calcium and phosphorus levels to exclude a metabolic disturbance; however, calcinosis resulting from limited scleroderma is not associated with calcium or phosphorus abnormalities.
- Raynaud phenomenon: The presence of ANA predicts the development of connective-tissue disease. The positive and negative predictive values of ANA values by immunofluorescence are 65% and 93%, respectively.
- Esophageal dysmotility: Patients who are positive for ANAs and anticentromere antibodies while also being negative for anti-Scl70 antibody appear to have more esophageal involvement. [50]

- Sclerodactyly: A thyrotropin level may help exclude the presence of thyroid disease as another potential cause of edematous or thickened skin.
- Telangiectasia: No laboratory data are necessary.

Imaging Studies

- Calcinosis
- The diagnosis of calcinosis (suspected based on physical examination finding of palpable, hard, subcutaneous nodules) is confirmed with plain radiographs demonstrating dermal or subcutaneous radiodense deposits.
- Computed tomography and bone scanning (skeletal scintigraphy with diphosphate compounds) are more sensitive for identifying calcinosis when plain radiography findings are normal. [51]
- Videodermatoscopy may also be a useful tool for diagnosing dystrophic calcifications such as those resulting from CREST syndrome; however, it is not yet widely used. [52]

- Raynaud phenomenon: Digital ischemia and/or infarction secondary to Raynaud disease may prompt Doppler ultrasonography or angiography to identify anatomic occlusive disease, which may be amenable to angioplasty or bypass surgery.
- Esophageal dysmotility: Multiple modalities are available to evaluate esophageal dysmotility.
- The least invasive evaluation involves radiologic barium studies with attention to the esophagus (cine-esophagram). Findings include dilatation with decreased or absent peristalsis in the distal esophagus, indicating advanced disease. Esophageal stricture and ulcerations indicate late findings of erosive esophagitis. The best use of a barium swallow is to exclude a stricture when the patient reports dysphagia.

- Esophageal transit time can be demonstrated by fluoroscopy, but this is not clinically useful. Radionuclide scanning is specific for gastroesophageal reflux and pulmonary aspiration, but it is expensive and is not sensitive.

- Sclerodactyly: No imaging studies are necessary.
- Telangiectasia: No imaging studies are necessary for cutaneous telangiectasia.
- Cough or fatigue: If patients have cough or fatigue, perform transthoracic echocardiography to look for pulmonary hypertension. More advanced pulmonary hypertension may demonstrate signs of right-sided heart enlargement on chest radiographs.

Other Tests

- Raynaud phenomenon: Research tools, such as strain plethysmography, laser Doppler flowmetry, thermography, or finger systolic blood pressure, are not useful clinically for diagnosis, monitoring disease progression, or monitoring response to treatment.
- Esophageal dysmotility: Esophageal manometry is highly sensitive for abnormal motility.

- Findings include diminished or absent distal peristalsis.
- LES pressure often is diminished.
- Manometry is fairly simple and inexpensive; abnormal results predict the development of erosive esophagitis, and findings are more likely to be positive in CREST syndrome patients. [53]

- Twenty-four–hour pH monitoring is greater than 90% sensitive for the presence of gastroesophageal reflux; however, this test is more cumbersome and expensive.
- Esophagogastroduodenoscopy can identify the gross or histologic presence of esophagitis and the complications of esophagitis (eg, ulcers, stricture, Barrett esophagitis, adenocarcinoma). A biopsy is required to make the diagnosis of Barrett esophagitis or adenocarcinoma.

Medical Care

- Globally
- The diagnosis of CREST syndrome carries with it both physical and psychological consequences, so a holistic approach to patient care should be taken. An evaluation of organ involvement, patient education regarding the clinical course, patient and family support, and treatment based on disease severity and organ involvement are necessary. [54,55]
- A pilot study of multidisciplinary patient education for persons with systemic sclerosis showed that patients may benefit from meeting others with the disease, may learn more about the disease, and may actually experience some pain relief. [56]

- Depression affects approximately 45% of patients with systemic sclerosis and 64% also develop anxiety; thus, early assessment and treatment of these psychological issues is recommended. [57,58]
- European investigators have been conducting phase I and II studies on the use of hematopoietic stem cell transplantation for severe systemic sclerosis, and randomized trials are proceeding. Only further research and time will tell if this is a useful therapy for severe scleroderma in the future. [59]
- Tamoxifen has been studied for use in patients with scleroderma and CREST syndrome, but it was not shown to be efficacious. [60]

- Calcinosis
- No large, prospective, placebo-controlled trials have been performed to study the treatment of calcinosis. The literature predominantly consists of reports and series. Therefore, keep in mind that calcinosis has resolved spontaneously in as many as 55% of patients in some series, as noted by Fink and Cook in 1986. [61]
- Treatment with oral corticosteroids is not usually considered effective, but, according to Hazen et al, [62] intralesional corticosteroid therapy has been associated with improvement of calcinosis.
- Several case reports have demonstrated the efficacy of probenecid.
- Early case reports suggested that diltiazem was associated with regression of calcific deposits and improvement of symptoms. A 1998 case series of 12 patients by Vayssairat et al [63]

did not confirm these findings.

- A 1987 small randomized placebo-controlled trial by Berger et al[64] using low-dose warfarin reduced urinary levels of Gla protein and reduced extraskeletal uptake on bone scans in 2 of 3 patients after 18 months of follow-up care. No changes in plain radiographs or clinical assessment were noted in these patients. Cukierman et al [65]

used low-dose dose warfarin on 3 patients with systemic sclerosis, and 2 of the patients, who had newly diagnosed, diffuse, and relatively small calcinotic lesions, responded to warfarin treatment, with complete resolution of the calcinosis. As reported in 1998, Lassoued et al [66]

used warfarin in patients with extensive calcinosis and saw no benefit. Low-dose warfarin may be helpful in selected patients with early or mild disease.

- Several case reports have shown that aluminum hydroxide may be useful for calcinosis.[67]

- Bisphosphonate treatment has had only limited success. Etidronate appeared to help calcinosis in one patient with scleroderma; however, another study reported failure. Alendronate was used successfully in one patient with calcinosis associated with juvenile dermatomyositis. The other bisphosphonates, pamidronate, risedronate, zoledronate, and ibandronate, have not been studied for calcinosis. [67,68,69,70]
- In one case series, 8 of 9 patients with limited systemic sclerosis had a good response to low-dose minocycline. [71]

- Suppression of intermittent local inflammatory reactions can be achieved by low-dose colchicine. [72]
- Kalajian et al found intravenous immunoglobulin therapy to be unreliable.[73]
- In summary, no consistently reliable pharmacological treatment seems to be available to prevent or eliminate calcinosis. One or a combination of the above treatments may be tried on a case-by-case basis; however, larger randomized trials are needed to prove efficacy.

- Raynaud phenomenon
- Advise all patients with Raynaud phenomenon to use good hand and body warming techniques. Goodfield et al [74] have shown that according to laser Doppler flowmetry, secondary Raynaud phenomenon patients respond appropriately to simple warming techniques compared with controls. Reinforce the wearing of gloves, a hat, and a coat outdoors and, if necessary, indoors. The importance of keeping the core body and hand temperature elevated cannot be overemphasized.
- Behavior therapy, including temperature biofeedback and autogenic training, has been evaluated in the treatment of scleroderma-associated Raynaud phenomenon. In 1989, Freedman [75] demonstrated an improvement of finger blood flow and elevation of finger temperature with biofeedback training. A large, randomized, controlled trial, however, showed no clinical benefit with temperature biofeedback; however, this has been criticized because the patients may not have been adequately trained in the technique. [76] These researchers [76] claim that thermal biofeedback is efficacious if proper hand warming technique is used.

- Calcium channel blockers are the mainstay of medical therapy for Raynaud phenomenon. Short-acting calcium channel blockers have been effective, yet they are frequently associated with adverse effects (eg, headache, flushing, dizziness, edema). In a recent study by the Raynaud's Treatment Study Investigators, sustained-release nifedipine reduced attack frequency by approximately 60% and was well tolerated. Some literature has suggested that calcium channel blockers are less effective in scleroderma-associated Raynaud phenomenon than in primary Raynaud disease, but Meyrick Thomas et al [77] demonstrated the effectiveness of nifedipine in this group in a longer-duration trial. A 2005 meta-analysis of calcium channel blocker therapy for Raynaud phenomenon by Thompson et al [78] showed a small benefit in reducing the severity and frequency of ischemic attacks (an average of 2.8-5 fewer attacks/wk and a 33% reduction in severity).

- Topical nitroglycerin and topical glyceryl trinitrate have been used in patients with Raynaud phenomenon. Several studies have shown that they both increase blood flow at the application site and they may help with symptomatic management of vasospasms. [79,80,81]
- Prostaglandin E1, prostacyclin I2, and iloprost (a prostacyclin-I2 analogue) have been evaluated for treatment of Raynaud phenomenon. Prostaglandins may be beneficial because of their vasodilatory and antiplatelet effects. None of these treatments is approved by the US Food and Drug Administration for the treatment of Raynaud phenomenon. Use of these agents should be reserved for patients whose Raynaud phenomenon has resulted in severe ischemia

or nonhealing ulcers.

- Intravenous infusions of prostacyclin I2 (epoprostenol) in patients with severe Raynaud phenomenon demonstrated substantial clinical improvement. The frequency and duration of attacks were reduced, and significant healing of digital ulcers occurred.
- Intravenous prostaglandin E1 (alprostadil) has been beneficial in some small studies, particularly in patients with sepsis or necrosis.
- Oral iloprost therapy showed a trend toward improvement of the severity and duration of attacks in patients with scleroderma. Intravenous iloprost reduced the severity, frequency, and duration of Raynaud attacks; helped with ulcer healing [82] ; and showed an increase in quality of life. [83]

- Antiplatelet therapy has had mixed results. Ticlopidine showed benefit in one case and was ineffective in another study. [84] Clopidogrel has not been studied in Raynaud phenomenon. Cilostazol has shown some benefit in open-label trials, and a recent double-blinded randomized trial showed that it significantly increased the mean brachial artery diameter; however, the patient's subjective symptoms did not appear to improve. [85,86]

Recombinant tissue plasminogen activator produces only transient improvement in blood flow in patients with digital ischemia and is not recommended for Raynaud phenomenon. [87]

- A 2000 pilot study by Denton et al[88] suggests that low molecular heparin may be beneficial for severe Raynaud phenomenon; however, further evaluation is necessary.

- Some evidence has shown that plasma exchange may help with the symptoms of Raynaud phenomenon; however, it is unlikely to affect the disease course. [89,90,91]
- Losartan, an ACE inhibitor, has been shown in 2 trials to reduce the frequency and severity of vasospastic episodes. [92,93] A review of the literature[94] concluded that ACE inhibitors and angiotensin II receptor blockers may provide minor relief for Raynaud phenomenon; however, the benefit is not proven to be any better than the current treatment of choice, which is calcium channel blockers.

- Case reports[95,96] have suggested that the phosphodiesterase V inhibitors, sildenafil and tadalafil, may also be effective. An open-label pilot trial of vardenafil [97] also showed promise.

- Alpha-adrenergic antagonists have received some interest recently as a new treatment for Raynaud phenomenon. An experimental selective alpha(2C)-adrenergic receptor blocker was well tolerated and improved digital skin perfusion during recovery from cooling in patients with Raynaud phenomenon associated with scleroderma. [98] One case report describes a patient who paradoxically experienced worsening of Raynaud phenomenon while using the alpha-2 adrenergic antagonist yohimbine. [99]

Further research is needed before the efficacy and safety of this class of drugs can be established for use in this disease.

- Bosentan, an orally active competitive endothelin-1 antagonist that blocks the endothelin receptors, is being used for systemic sclerosis-associated pulmonary arterial hypertension, and this agent may also help alleviate vasospasm and prevent digital ulceration; however, clinical trials need to be performed first. [100]
- A pilot study with fluoxetine and a case report on paroxetine suggest that the selective serotonin reuptake inhibitors might be effective as novel treatments for Raynaud phenomenon. [101,102]

- The following therapeutic ladder is suggested for the treatment of patients with Raynaud phenomenon:
- Reduce and remove risk factors and triggers. Stop smoking, avoid beta-blockers, and avoid any remediable underlying cause (eg, use of vibratory equipment). [103]
- Teach hand and body warming activities.
- Administer long-acting formulations of calcium channel blockers.
- Add topical nitroglycerin paste to this regimen if required.

- Esophageal dysmotility
- The treatment of esophageal dysmotility and gastroesophageal reflux in scleroderma patients is the same as in patients without scleroderma. Systemic immunosuppressants are not helpful.
- Emphasize behavior changes (eg, weight loss; elevating head of bed; reduction of caffeine, tobacco, alcohol, chocolate intake and avoidance prior to recumbency; eating small meals; waiting 3-4 h after eating before lying down).
- Administration of H2 blockers (eg, ranitidine, famotidine, nizatidine) may help symptoms, but use of a proton-pump inhibitor should be instituted if erosive esophagitis is present. Motility-promoting agents may help with symptoms. Cisapride has been shown to increase lower esophageal pressure and the amplitude of esophageal contractions in healthy patients and to stimulate esophageal motility with resultant symptomatic improvement in one patient with progressive systemic sclerosis. [104]
- Esophageal dilatation can help when significant dysphagia or regurgitation occur in the presence of an esophageal stricture.

- Sclerodactyly
- Various treatment regimens including corticosteroids, nonsteroidal anti-inflammatory drugs, D-penicillamine, IFN-gamma, cyclosporine, and cytostatic drugs have been used with limited success in scleroderma.
- An open-label study of calcitriol had promising results; however, a recent double-blinded, placebo-controlled trial was too small to draw any conclusions. [105]
- After retrospective data showed the benefits of D-penicillamine for scleroderma skin changes, Clements et al [106] performed the first randomized controlled trial of D-penicillamine in scleroderma. This trial compared high-dose D-penicillamine (750-1000 mg/d)

to low-dose D-penicillamine (125 mg qod) in patients with early diffuse cutaneous scleroderma. The mean skin thickness score improved over 2 years of treatment in both groups, and no advantage was seen to using the higher dose of D-penicillamine.
[106]

This study had no placebo group and the authors concluded later that they were not able to tell whether either dose was effective or ineffective.

- D-penicillamine cannot, therefore, be recommended until placebo-controlled trials are conducted to show effectiveness.

- The natural course of diffuse dermal sclerosis involves skin softening after 4-5 years; therefore, placebo-controlled trials are essential for determining an effective therapy. Skin involvement in limited scleroderma typically is not severe; therefore, attempts are not usually made to treat skin involvement.

- Telangiectasia: Pulsed-dye laser treatment has been shown to be effective for the treatment of facial telangiectasia, but this has not been specifically studied in CREST patients.
[107]

Many treatment modalities have been used with success to treat symptomatic GI telangiectasia (eg, medical treatment with estrogen-progesterone or desmopressin, laser ablation, sclerotherapy).

Surgical Care

- Calcinosis: Surgical excision of localized painful large deposits can relieve symptoms; recurrence is rare. Saddic et al report a case of painful fingertip calcinosis treated with surgical debridement. [108] If calcinosis is diffuse, recurrence is more common. Overzealous debridement to remove all calcinosis is apt to compromise digital viability and should be avoided. [109] Successful palliation and significant remission of calcinosis using a carbon dioxide laser has been shown in 2 case reports with a total of 7 patients.
[110,111]

- Raynaud phenomenon: Cervical sympathectomy is less beneficial for scleroderma patients than for patients with Raynaud phenomenon secondary to peripheral vascular disease. Newer surgical approaches include digital sympathectomy, with or without revision of surgically correctable vascular disease. In the event of nonhealing digital ulcers, amputation, unfortunately, sometimes is unavoidable.
- Esophageal dysmotility: Surgical therapy may help gastroesophageal reflux in general. Common techniques use complete or partial surgical wraps around the gastroesophageal junction to increase LES pressure and reduce reflux. The degree of tightness of the wrap inversely correlates with the reduction of reflux; however, the scleroderma cohort of patients

may not tolerate a tight wrap. They are more likely to experience abdominal discomfort and dysphagia as a result. Therefore, avoid surgery for reflux in scleroderma patients except in the most severe refractory cases.

- Sclerodactyly: If sclerodactyly is causing extensive contractures, a carefully planned and precisely performed operative treatment has been shown to have good success with a high level of patient satisfaction. [109]
- Telangiectasia: Bowel resection for uncontrollable GI bleeding from telangiectasia is rarely necessary

Calcium channel blockers

These agents are used as part of therapy for Raynaud phenomenon.

Nicardipine (Cardene)

Used for vasodilatation and possible antiplatelet effects. Start with lowest dose available. Extended-dose preparations and agents with fewer negative inotropic effects are preferred.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

20 mg PO tid

Pediatric

Not recommended

- Dosing
- Interactions
- Contraindications
- Precautions

Fentanyl and alcohol may increase hypotensive effects; calcium channel blocker may increase cyclosporine levels; H2 blockers (cimetidine), erythromycin, nafcillin, and azole antifungals may increase toxicity (avoid combination or monitor closely); carbamazepine may reduce bioavailability (avoid this combination); rifampin may decrease levels (monitor and adjust dose of calcium channel blocker)

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Adjust dose in renal/hepatic impairment; may cause lower extremity edema; allergic hepatitis has occurred but is rare

Nifedipine (Procardia)

Relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery; adverse reactions occur predominantly with short-acting formulations and include peripheral edema, headache, dizziness, and tachycardia; calcium channel blockers may worsen gastroesophageal reflux; SR formulations are associated with fewer adverse effects.

- Dosing

- Interactions
- Contraindications
- Precautions

Adult

IR: 10 mg PO tid initially; increase to 10-30 mg PO tid/qid
SR: 30-60 mg PO qd initially; increase prn to 30-90 mg PO qd; may be administered bid

Pediatric

IR: 0.6-0.9 mg/kg/24h divided tid/qid

- Dosing
- Interactions
- Contraindications
- Precautions

Caution with coadministration of any agent that can lower BP, including beta-blockers and opioids (H2 blockers may increase toxicity)

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; symptomatic hypotension; persistent dermatologic reactions

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may

use if benefits outweigh risk to fetus

Precautions

May cause lower extremity edema; allergic hepatitis has occurred rarely

Prostaglandins

Agents included as part of therapy for Raynaud phenomenon.

Alprostadil (Prostaglandin E1)

Strong vasodilator of all vascular beds.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

6-10 ng/kg/min IV for up to 72 h

Pediatric

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Coadministration with anticoagulants may increase bleeding risk because of shared effects on platelet aggregation

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Initiation of alprostadil requires experienced personnel and physiologic monitoring; bradycardia, hypotension, and/or postural hypotension, fever, headache, and flushing can occur

Antidepressants

For treatment of Raynaud phenomenon.

Fluoxetine (Prozac)

Selectively inhibits presynaptic serotonin reuptake with minimal or no effect in reuptake of norepinephrine or dopamine.
May cause more adverse GI effects than other SSRIs now currently available, which is the reason it is not recommended as a first choice. May be given as a liquid and a cap.
May give as 1 dose or divided doses. Presence of food does not appreciably alter levels.
Because of long half-life (72 h), may take up to 4-6 wk to achieve steady state levels.
Long half-life is an advantage and a drawback. If it works well, an occasional missed dose is not a problem; if problems occur, eliminating all active metabolites takes a long time. The choice depends on adverse effects and drug interactions. Adverse effects of SSRIs seem to be quite idiosyncratic; thus, relatively few reasons exist to prefer one to another at this point if dosing is

started at a conservative level and advanced as tolerated.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

20 mg/d PO

Pediatric

Not established

- Dosing
- Interactions
- Contraindications
- Precautions

Inhibits CYP450 isoenzymes 2C9, 2C19, 2D6, and 3A4; increases toxicity of diazepam and trazodone by decreasing clearance; also increases toxicity of MAOIs and highly protein-bound drugs; serotonin syndrome (ie, myoclonus, rigidity, confusion, nausea, hyperthermia, autonomic instability, coma, eventual death) occurs with simultaneous use of other serotonergic agents (eg, anorectic agents, tramadol, buspirone, trazodone, clomipramine, nefazodone, tryptophan), so discontinue other serotonergic agents at least 2 wk prior to beginning SSRIs

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; concurrently taking MAOIs or took them in the last 2 wk; coadministration with thioridazine

- Dosing

- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Known or suspected history of mania or hypomania; caution in hepatic impairment and history of seizures; MAOIs should be discontinued at least 14 d before initiating therapy

Phosphodiesterase enzyme inhibitors

For Raynaud phenomenon.

Cilostazol (Pletal)

Affects vascular beds and cardiovascular function. May improve blood flow by altering rheology of red blood cells. Produces nonhomogenous dilation of vascular beds, with more dilation in femoral beds than in vertebral, carotid, or superior mesenteric arteries.
Cilostazol and its metabolites are inhibitors of phosphodiesterase III and, as a result, cyclic AMP is increased, which leads to inhibition of platelet aggregation and vasodilation.

- Dosing
- Interactions
- Contraindications
- Precautions

Adult

100 mg PO bid

Pediatric

<12 years: Not established

>12 years: Administer as in adults

- Dosing
- Interactions
- Contraindications
- Precautions

Diltiazem, erythromycin, grapefruit juice, itraconazole, ketoconazole, macrolide antibiotics, and omeprazole may increase levels

- Dosing
- Interactions
- Contraindications
- Precautions

Documented hypersensitivity; CHF; coadministration with grapefruit juice

- Dosing
- Interactions
- Contraindications
- Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in renal impairment; do not prescribe or administer without thoroughly reading complete prescribing information

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