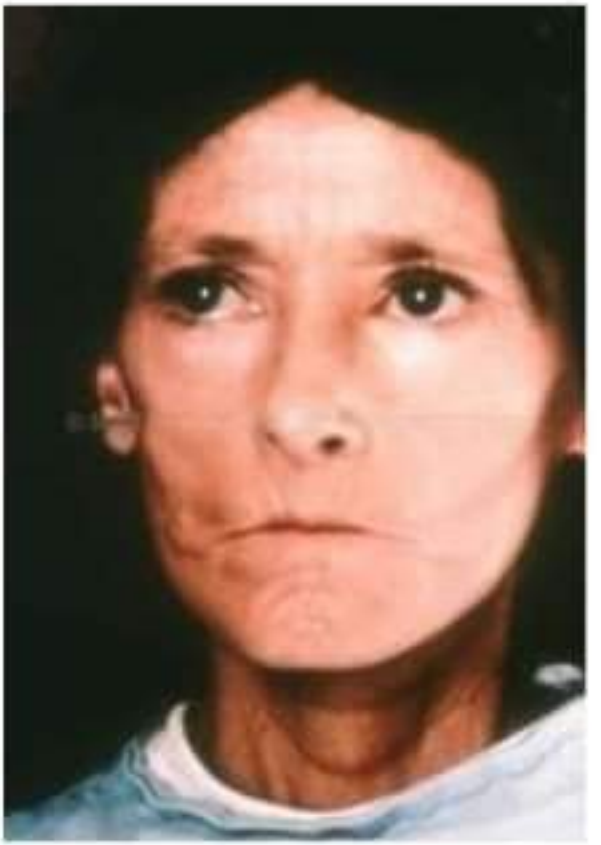
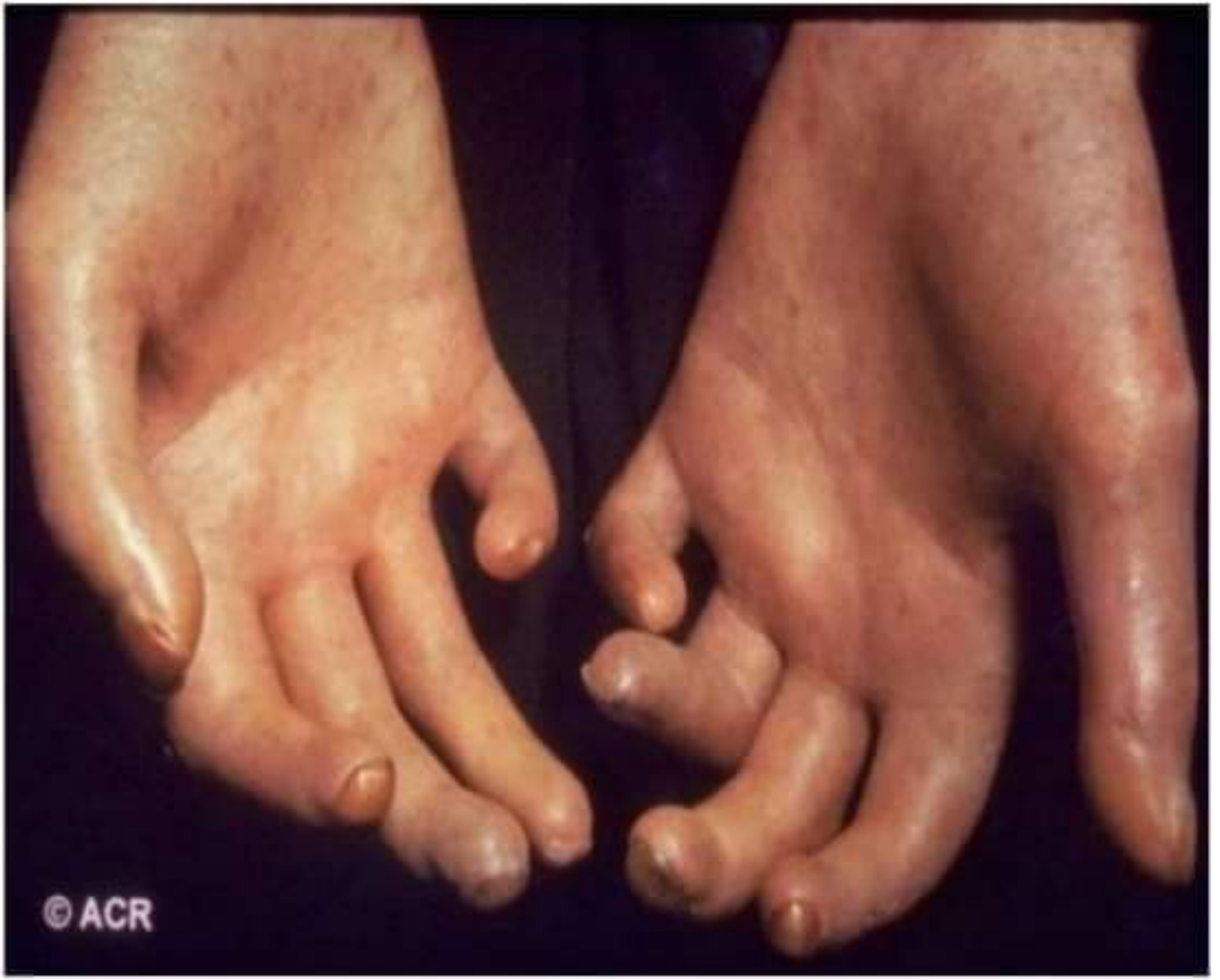
SCLERODERMA (systemic sclerosis)

Definition

Multisystem collagen vascular disease of unknown etiology characterized by

- fibrosis of the skin with
- involvement of the internal organs.

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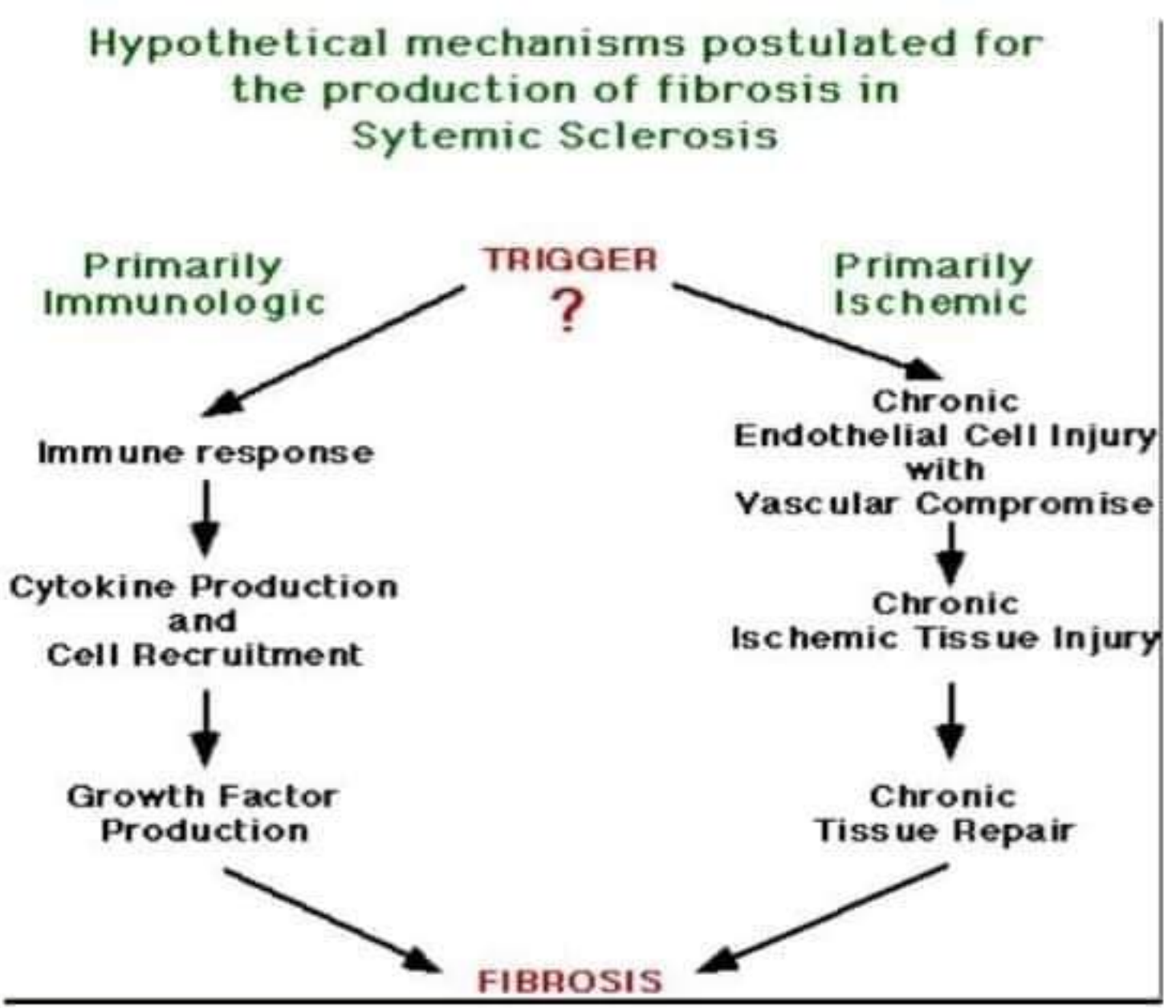

Hypothetical mechanisms postulated for the production of fibrosis in Sytemic Sclerosis
Primarily Immunologic
TRIGGER
?
Primarily Ischemic
Immune response
Cytokine Production and Cell Recruitment
Growth Factor Production
Chronic Endothelial Cell Injury with Vascular Compromise
Chronic Ischemic Tissue Injury
Chronic Tissue Repair
FIBROSIS

Pathophysiology

Vasculopathy of small artery and capillary

- Endothelial cell injury
- Adhesion and activation of platelet
- PDGF, thromboxane A2 release
- Vasoconstriction & growth of endothelial cell and fibroblast
- Narrowing or obliteration, increased permeability

Fibrosis

- Aberrant regulation of fibroblast cell growth
- Increased production of extracellular matrix (collagen, fibronectin, and glycosaminoglycan)
- Thickening of the skin & fibrosis of internal organs

Immunological mechanism

Cell mediated immunity

- Skin: cellular infiltrates in perivascular region and dermis (T cell, Langerhans cell, plasma cell, macrophages)

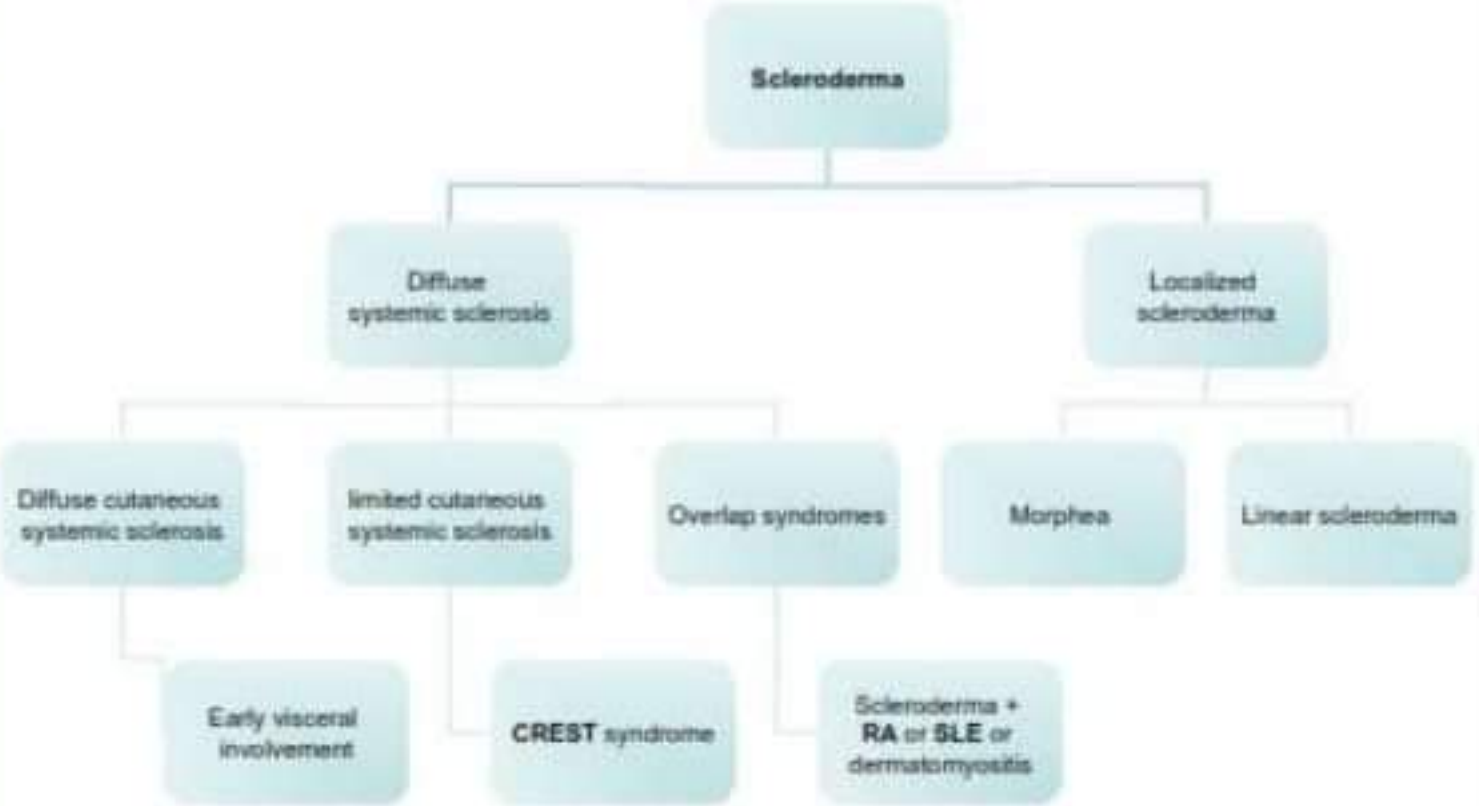
Humoral immunity

- Hypergammaglobulinemia
- Autoantibody production : Antinuclear antibody (+) >95%

Environmental factors

1. Silica dust
2. Organic solvents
3. Biogenic amines
4. Urea formaldehyde
5. Polyvinyl chloride
6. Rapeseed oil
7. Bleomycin
8. L-tryptophan
9. Silicone implant

Types of scleroderma



Systemic sclerosis

A multisystem disorder characterized by

- Functional and structural abnormalities of blood vessels
- Fibrosis of the skin and internal organs
- Immune system activation
- Autoimmunity

Diffuse cutaneous systemic sclerosis

- Proximal skin thickening - distal and proximal extremity and often the trunk and face
- Tendency to rapid progression of skin change
- Rapid onset of disease following Raynaud's phenomenon
- Early appearance of visceral involvement
- Poor prognosis

Limited cutaneous systemic sclerosis

1) symmetric restricted fibrosis

- affecting the distal extremities and face/neck

2) prolonged delay in appearance of distinctive internal manifestation

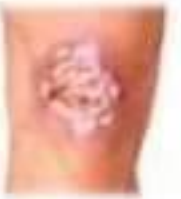
3) prominence of calcinosis and telangiectasia

4) good prognosis

* CREST syndrome

CREST syndrome

Calcinosis- calcium deposits in the skin

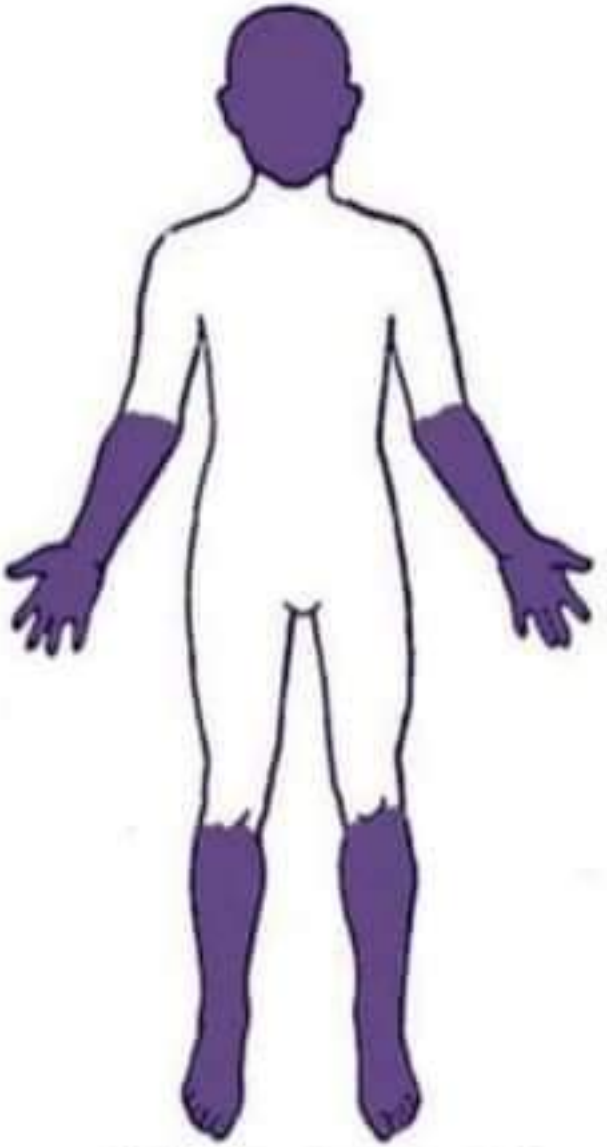


Raynaud's phenomenon- spasm of blood vessels in response to cold or stress

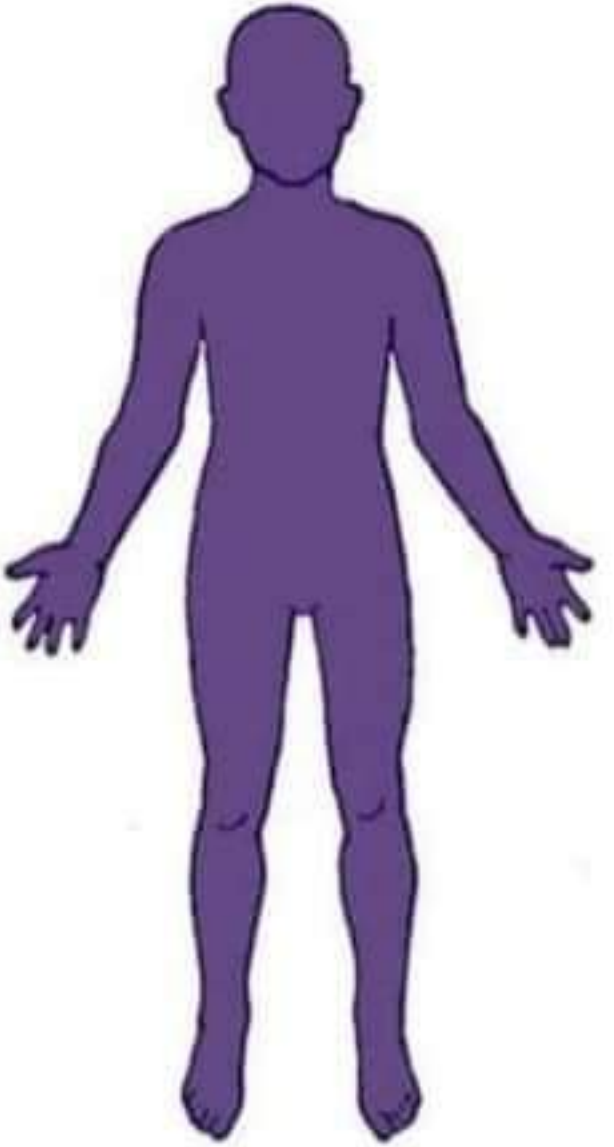
Esophageal dysfunction- acid reflux and decrease in motility of esophagus

Sclerodactyly- thickening and tightening of the skin on the fingers and hands

Telangiectasias- dilation of capillaries causing red marks on surface of skin



Limited cutaneous SSc

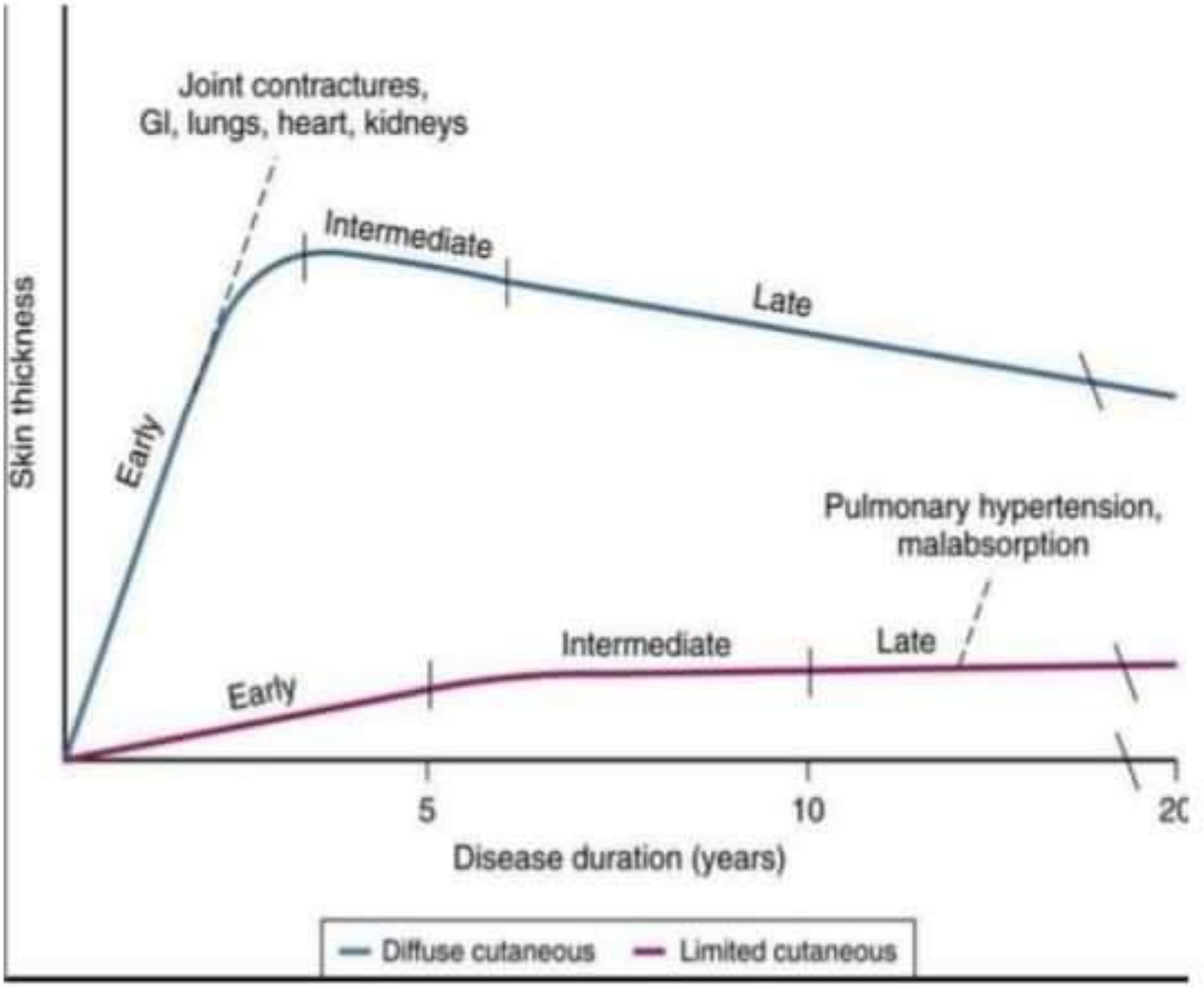


Diffuse cutaneous SSc

CLASSIFICATION

	PRE-SCLERODERMA	SCLERODERMA SINE SCLERODERMA	LIMITED SCLERODERMA	DIFFUSE SCLERODERMA
RAYNAUD	YES	POSSIBLE	YES	YES
SKIN INVOLVMENT	NO	NO	YES (focal)	YES (diffuse)
MUSCULO-SKELETAL	NO	NO	YES	YES
GASTRO-INTESTINAL	NO	YES	YES	YES
CARDIO-PULMONARY	NO	YES	YES	YES
RENAL	NO	YES	RARE	YES

Limited vs. Diffuse Scleroderma	
Limited	**Diffuse**
Distal skin involvement (distal to the elbows and knees, no truncal involvement), but may involve the face and neck	Proximal to the elbows and/or knees, or truncal involvement and also distal skin involvement, may involve the face and neck
Often Raynaud's phenomenon occurs years prior	Raynaud's phenomenon may onset around the same time that the skin changes start
Usually there are no tendon friction rubs	Tendon friction rubs may be present
Most positive ANA	Most are ANA positive
Many have positive anti-centromere	Often nucleolar or speckled patterns
Rare renal, heart	Scl 70 (anti-topoisomerase I) in 30%, correlates with pulmonary fibrosis
Lung involvement is less common and more mild usually	Renal crisis with RNA polymerase
May develop PAH in older age at onset and long-standing diseases	May develop PAH at any stage
	Higher mortality


Joint contractures,
GI, lungs, heart, kidneys
Intermediate
Late
Skin thickness
Early
Pulmonary hypertension,
malabsorption
Intermediate
Late
Early
5
10
20
Disease duration (years)
Diffuse cutaneous
Limited cutaneous

Localized scleroderma

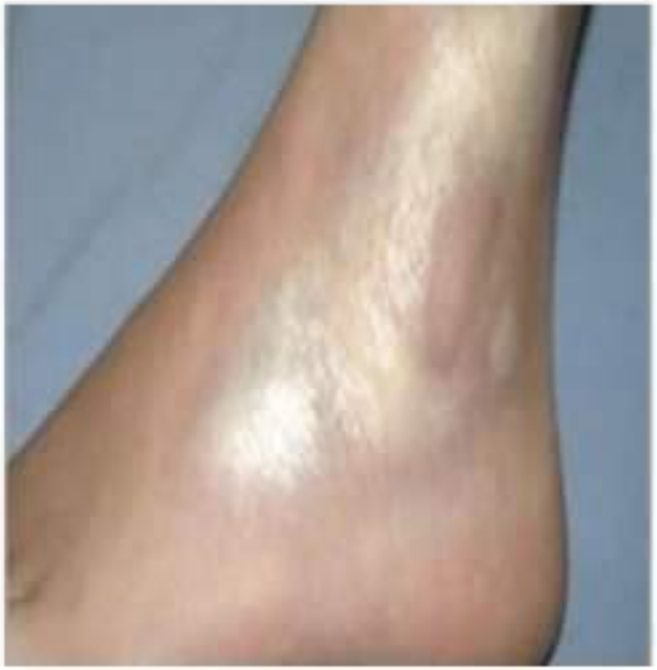
MORPHEA

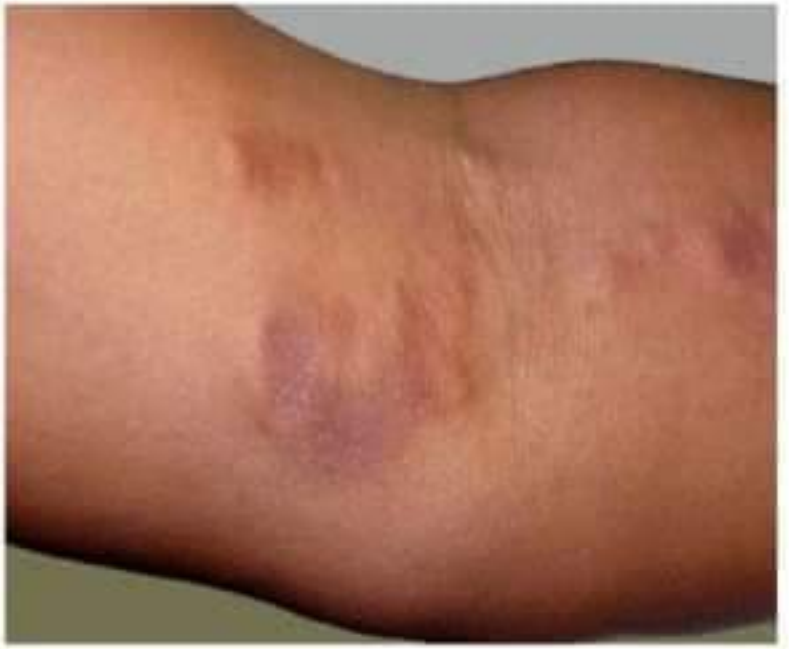
- A rare skin condition that causes reddish or purplish patches on your skin.
- Tends to affect only the outermost layers of your skin-the dermis and the fatty tissue just beneath the dermis.
- Location – Abdomen, chest and back

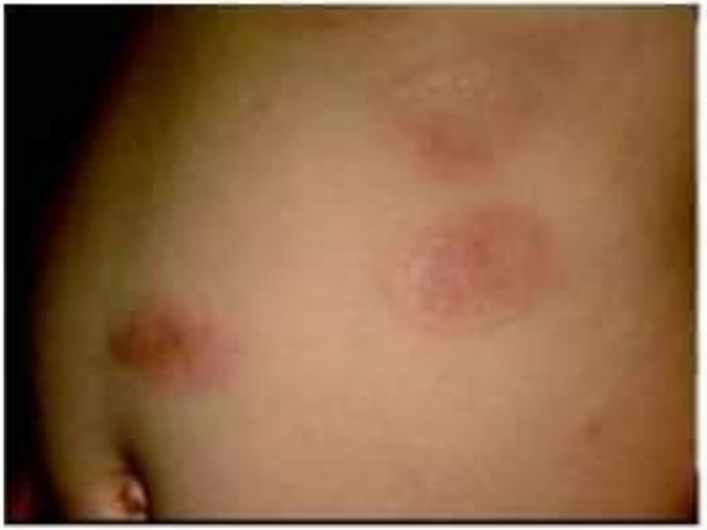
  Face, Arms and legs

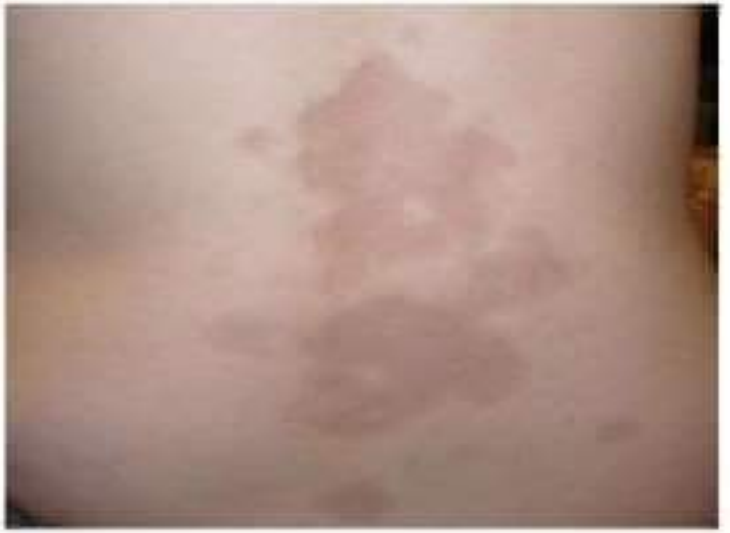
Signs of morphea

- **Hardening and thickening of the skin.**
- **Discoloration of the affected skin to look** lighter or darker than the surrounding area.
- **Oval-shaped patches that may change** colors and gradually develop a whitish center.
- **Linear patches, especially when on arms** and legs
- **Loss of hair and sweat glands in the** affected area over time.

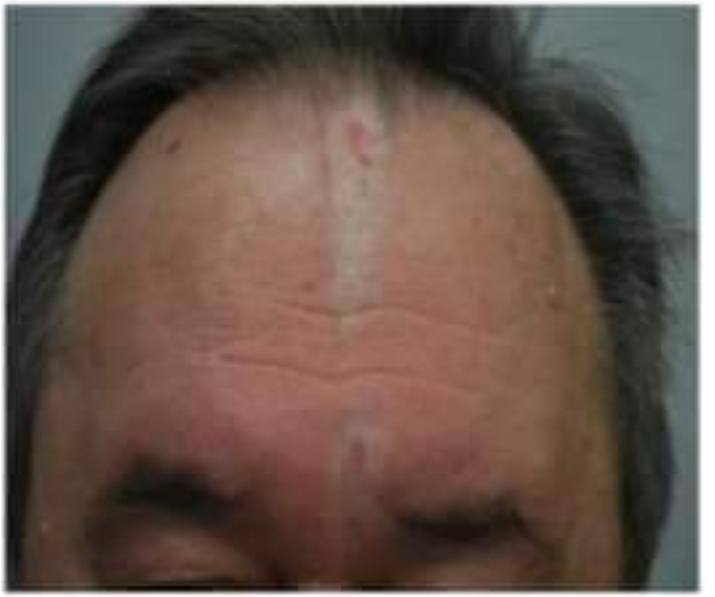


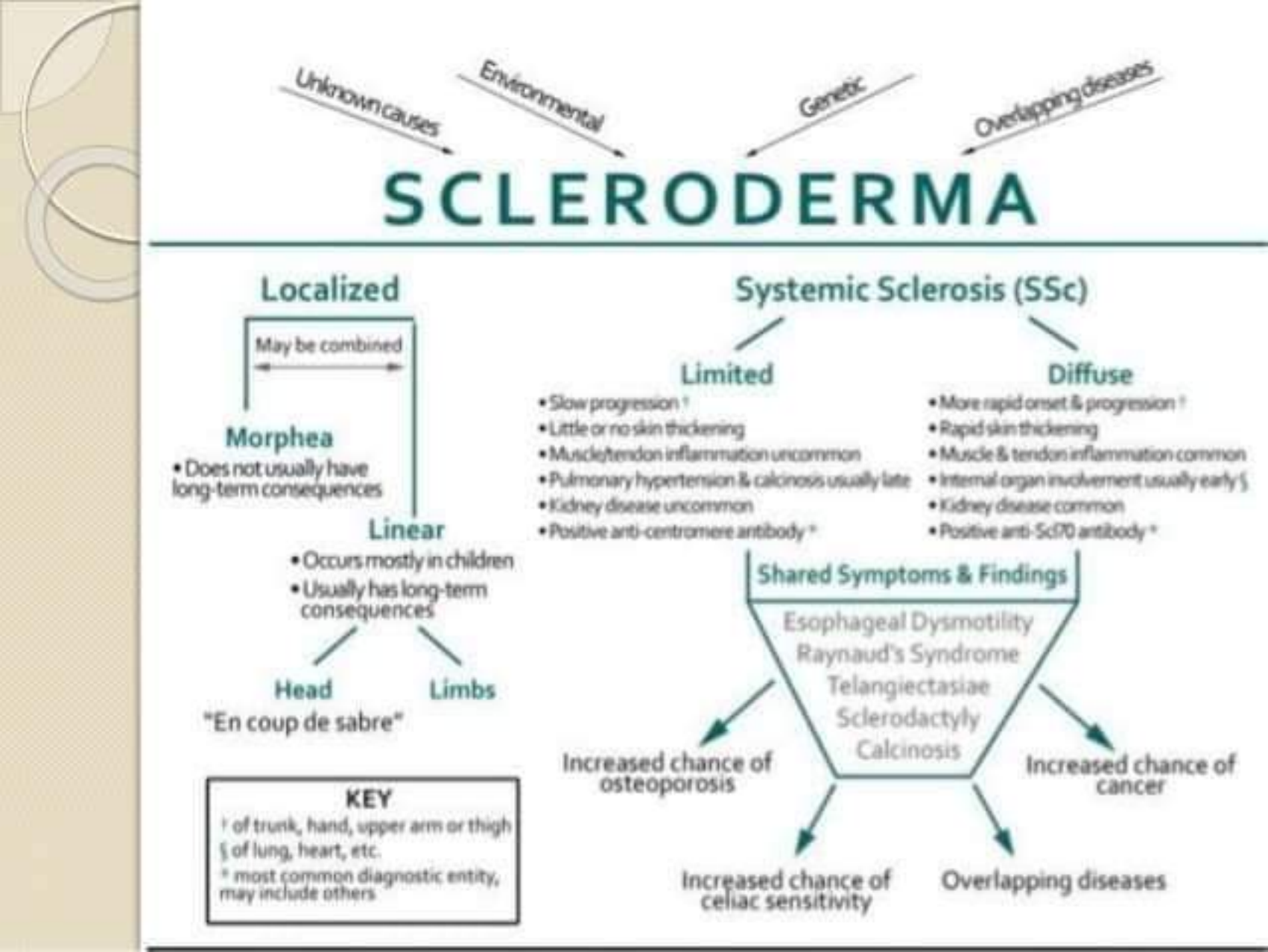






Linear scleroderma




Unknown causes
Environmental
Genetic
Overlapping diseases
SCLERODERMA
Localized
May be combined
Morphea
• Does not usually have long-term consequences
Linear
• Occurs mostly in children
• Usually has long-term consequences
Head
Limbs
"En coup de sabre"
KEY
† of trunk, hand, upper arm or thigh
§ of lung, heart, etc.
* most common diagnostic entity, may include others
Systemic Sclerosis (SSc)
Limited
• Slow progression †
• Little or no skin thickening
• Muscle/tendon inflammation uncommon
• Pulmonary hypertension & calcinosis usually late
• Kidney disease uncommon
• Positive anti-centromere antibody *
Diffuse
• More rapid onset & progression †
• Rapid skin thickening
• Muscle & tendon inflammation common
• Internal organ involvement usually early §
• Kidney disease common
• Positive anti-Scl70 antibody *
Shared Symptoms & Findings
Esophageal Dysmotility
Raynaud's Syndrome
Telangiectasiae
Sclerodactyly
Calcinosis
Increased chance of osteoporosis
Increased chance of cancer
Increased chance of celiac sensitivity
Overlapping diseases

Demographics

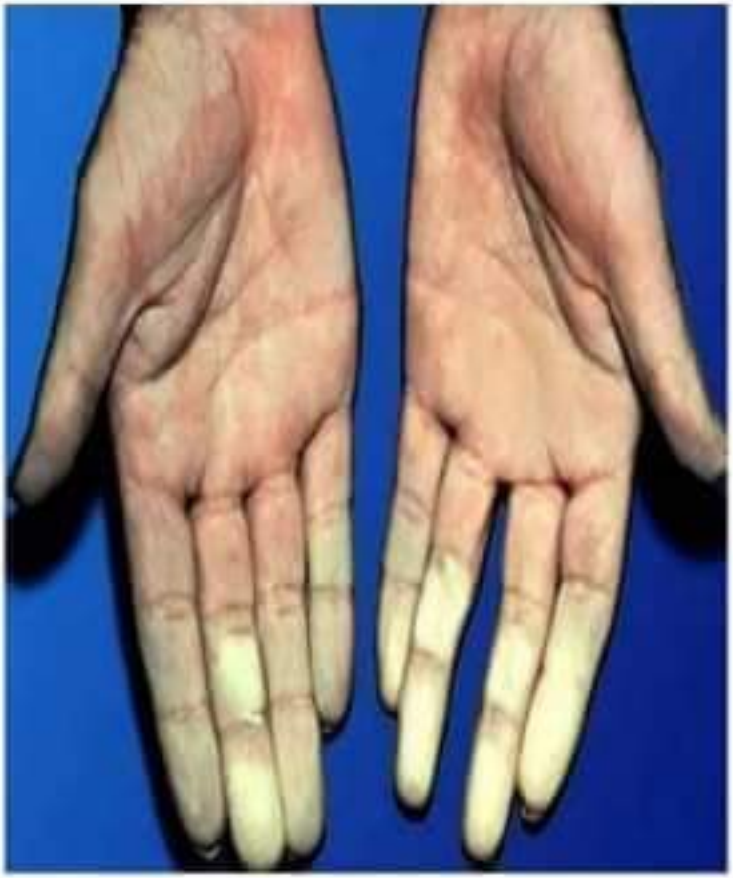
- Incidence : 9-19 cases/million/year
- Age: middle age (30-50)
- Sex: F>M (3:1)

Clinical features

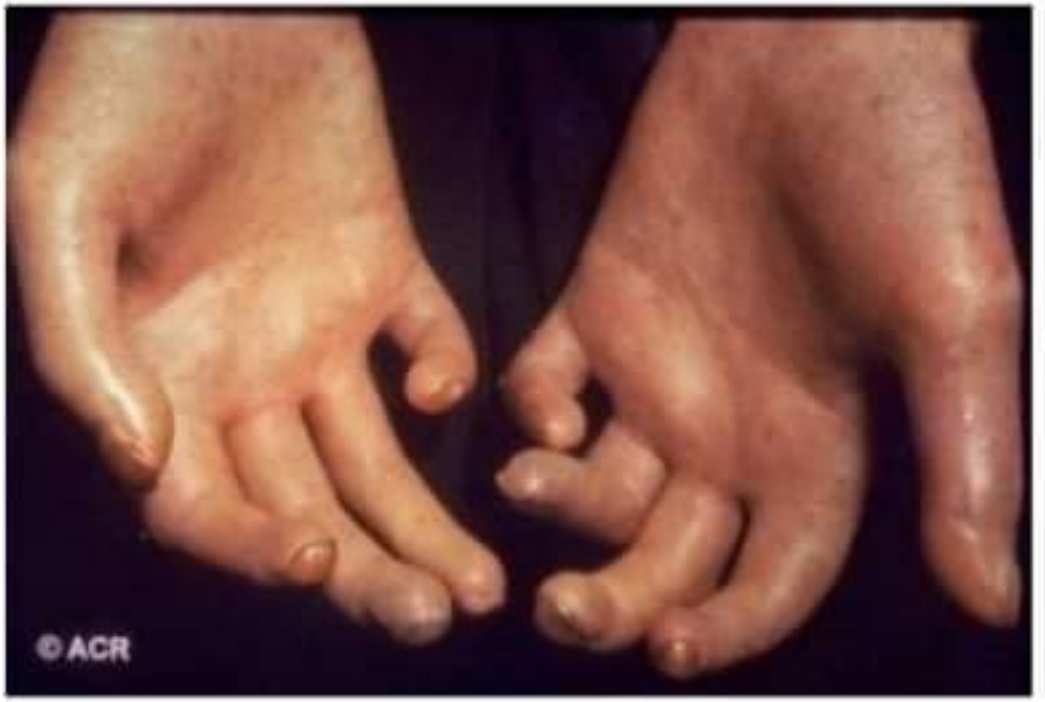
Vascular abnormalities

- **Raynaud's phenomenon**
  - Cold hands and feet with reversible skin colour change (white to blue to red)
  - Induced by cold temperature or emotional stress
  - Initial complaint in 3/4 of patients
  - 90% in patients with skin change (prevalence in the general population: 4-15%)
- **Digital ischemic injury**

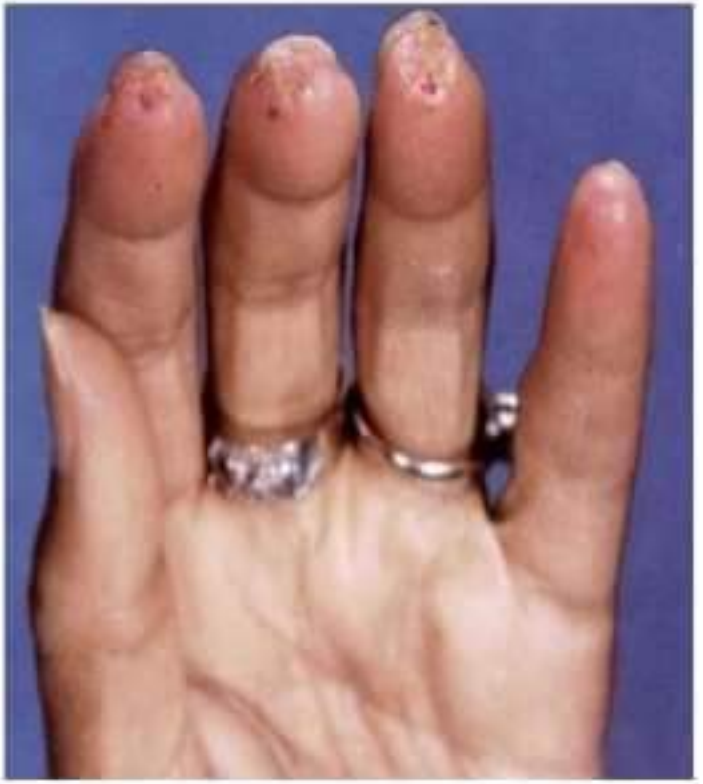
Raynaud's phenomenon



Terminal digital resorption



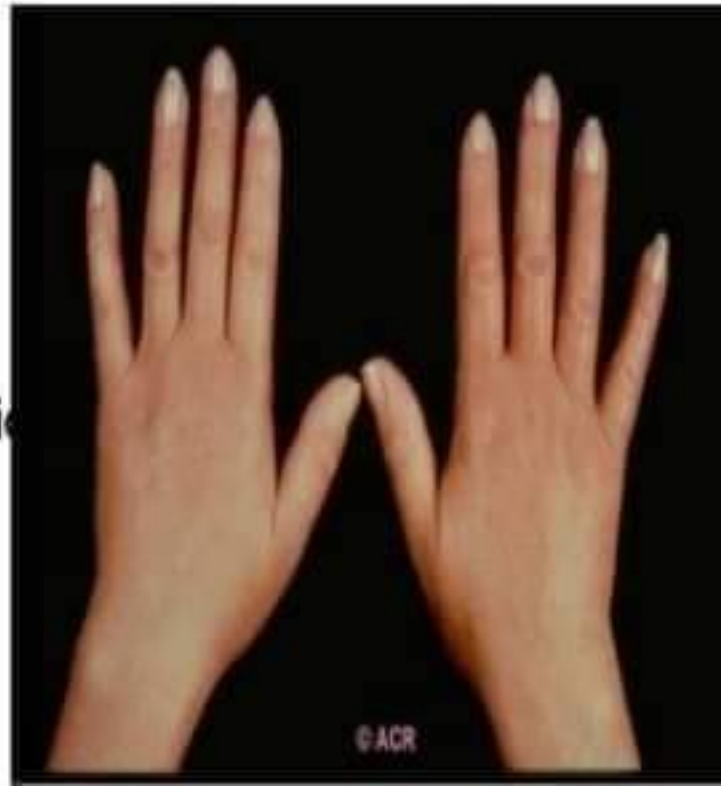
Digital ulcers



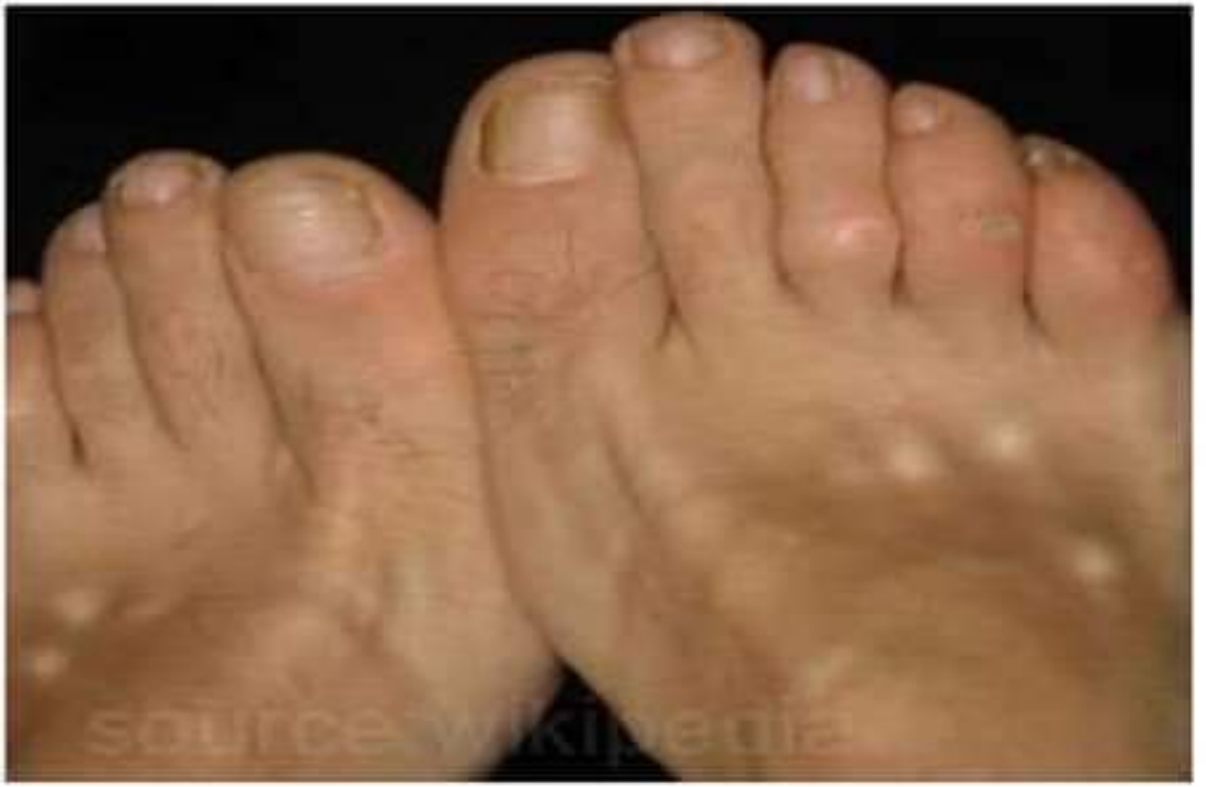
Skin thickening

- Basically this is water in the tissues = edema
- Binding of water to increased extracellular
- connective tissue matrix
- Inflammation
- Poor lymphatic return
- Microvascular injury with flui

extravasation

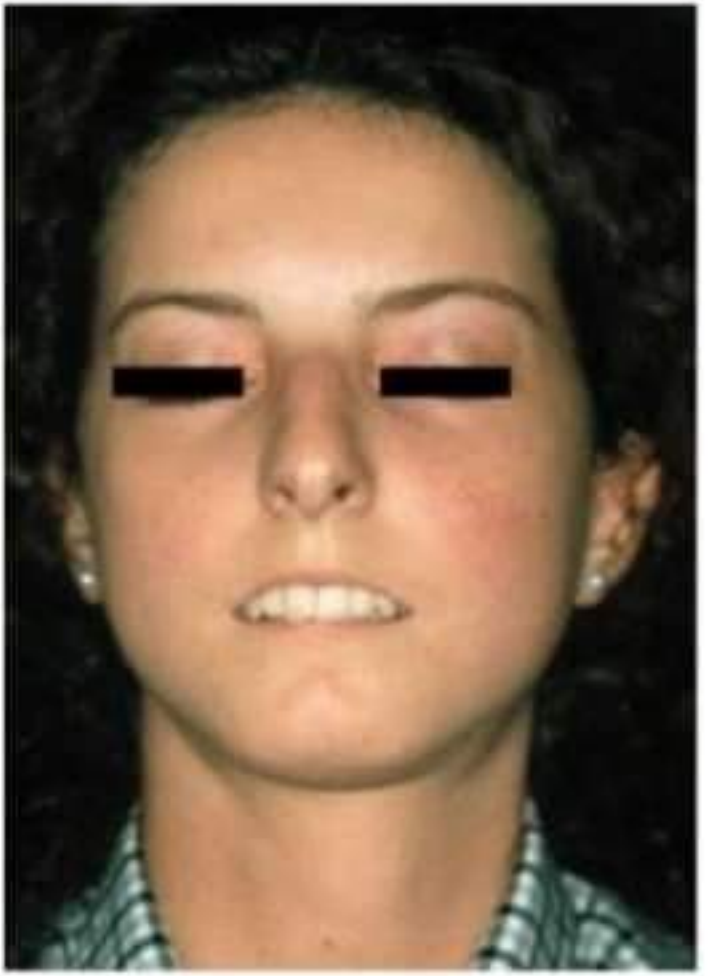


Calcinosis



Facial changes

- Pinched nose (mauskopf)
- Pursed lips
- Cannot evert eyelids
- Lip thinning and
- retraction
- Immobile facies



Intestinal involvement

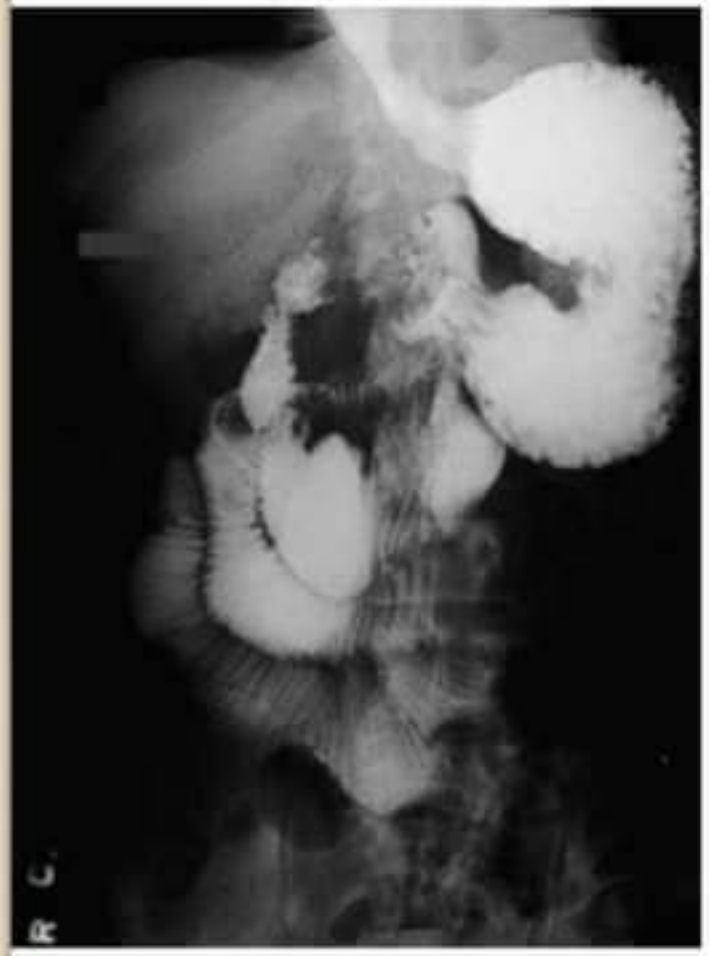
1. **Esophagus:** hypomotility and retrosternal pain, reflux esophagitis, stricture
2. **Stomach:** delayed emptying
3. **Small intestine:** pseudo-obstruction, paralytic ileus, malabsorption
4. **Large intestine:** chronic constipation and fecal impaction diverticula

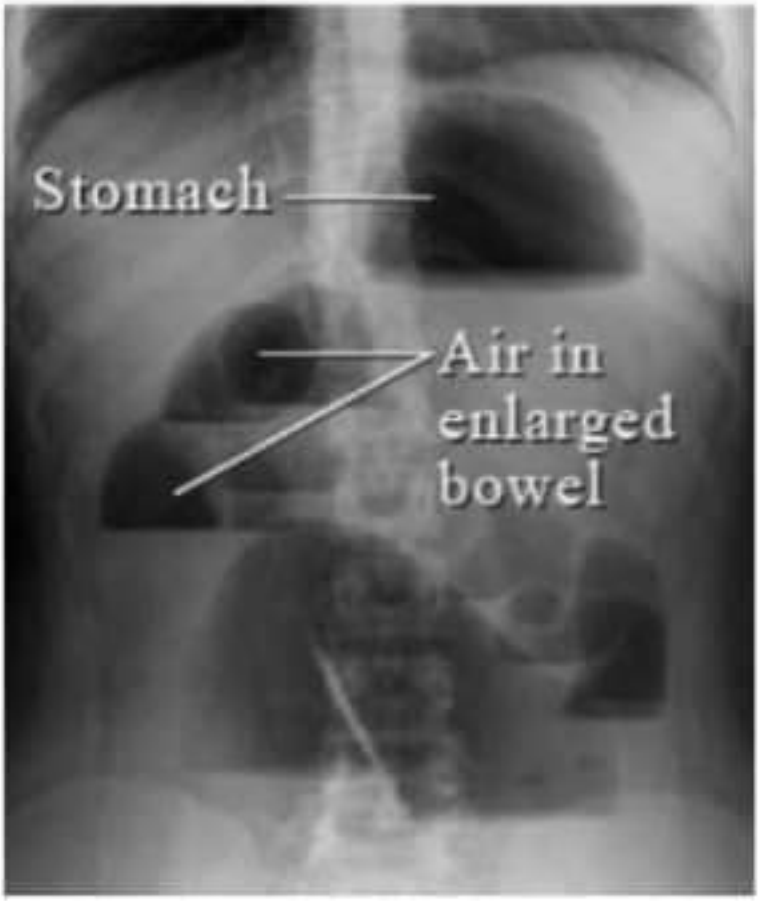
Gastrointestinal

- Disordered peristalsis of the lower two thirds of the esophagus presents as **dysphagia**
- Impaired function of the lower esophageal sphincter
- Chronic esophageal reflux include **erosive esophagitis with bleeding, Barrett's esophagus, and lower esophageal stricture**
- Involvement of the stomach occurs in systemic sclerosis and presents clinically as ease of satiety and on occasion as either **functional gastric outlet obstruction or acute gastric dilatation**.

Small bowel involvement

- Intermittent bloating with abdominal cramps, intermittent or chronic diarrhea, and presentations suggestive of intestinal obstruction.
- Malabsorption occurs
- Bacterial overgrowth in areas of intestinal stasis occurs frequently



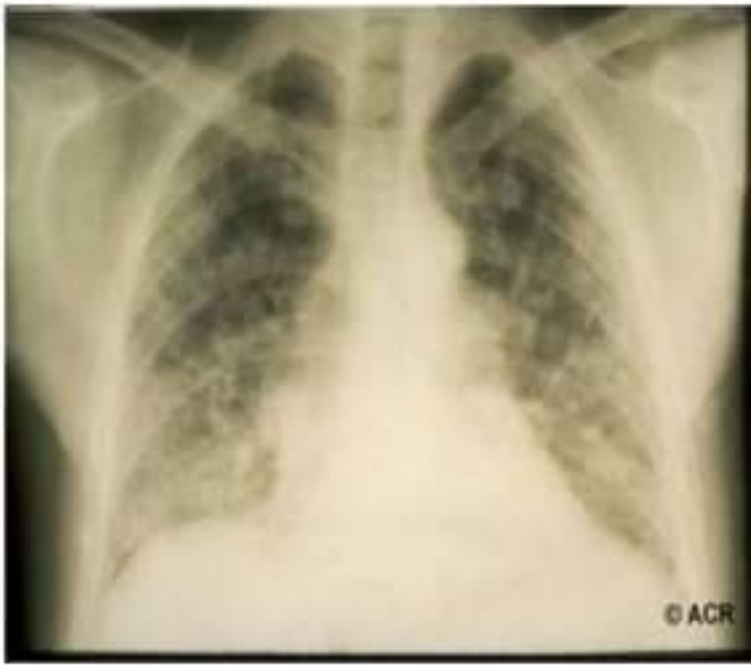

Stomach
Air in
enlarged
bowel

Colonic involvement

- Is present in the majority of patients with systemic sclerosis
- Is infrequently a prominent cause of clinical symptoms
- Constipation, obstipation, and Pseudo-obstruction may occur and are related to abnormal colonic motility

Lung involvement

2/3rd of patients affected- leading cause of mortality and morbidity in later stage of systemic sclerosis



Pathology

Interstitial fibrosis

Intimal thickening of pulmonary arterioles (**pulmonary hypertension)**

Heart involvement (10%)

1. Pericarditis
2. Heart failure
3. Arrhythmia
4. Myocardial fibrosis

Kidney involvement

1. Diffuse scleroderma in association with rapid progression of skin involvement

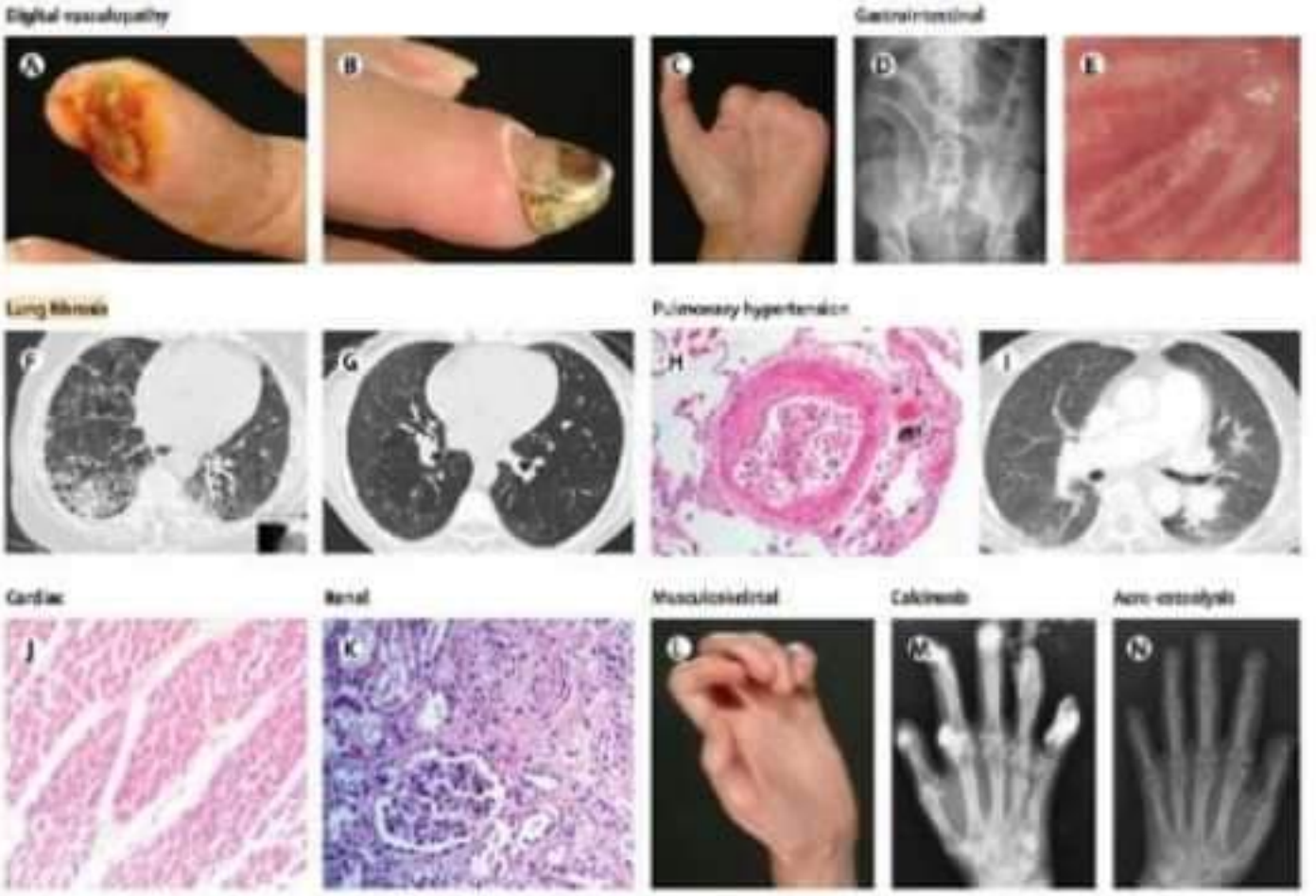
2. Pathology

- - intimal hyperplasia of the interlobular artery
- - fibrinoid necrosis of afferent arterioles
- - glomerulosclerosis

3. Proteinuria, abnormal sediment, azotemia,

4. Microangiopathic hemolytic anemia (scleroderma renal crisis), renal failure

Summary of major complication



Box 1 - American college of rheumatology diagnostic criteria for systemic sclerosis.[9]

Major criterion

- Proximal sclerodermatous skin changes (proximal to the metacarpophalangeal joints)

Minor criteria

- Sclerodactyly
- Digital pitting scars of fingertips or loss of substance of the distal finger pads
- Bibasilar pulmonary fibrosis

* The patient should fulfill the major criterion or two of the three minor criteria.

Deficiency in ACR criteria

- Fails to include some patients with limited scleroderma or CREST Syndrome.
- Does not include subtle features of the disease.
- Does not include serological markers.

2013 ACR / EULAR Criteria For The Classification Of Systemic Sclerosis (Scleroderma)*

Item	Sub-items(s)	Weight/score †
Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints *(sufficient criterion)*	-	9
Skin thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
Fingertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease *(maximum score is 2)*	Pulmonary arterial hypertension	2
	Interstitial lung disease	2
Raynaud's phenomenon	-	3
SSc-related autoantibodies (anticentromere, anti–topoisomerase I [anti–Scl-70], anti–RNA polymerase III) *(maximum score is 3)*	Anticentromere 3 Anti–topoisomerase I Anti–RNA polymerase III	3

* The criteria are not applicable to patients with skin thickening sparing the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, generalized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host disease, diabetic cheiroarthropathy).

† The total score is determined by adding the maximum weight (score) in each category.
Patients with a total score of ≥ 9 are classified as having definite scleroderma.

Sensitivity 91% Specificity 92%

Van den Hoogen et al. 2013 Classification Criteria for Systemic Sclerosis. Arthritis and Rheumatism. Vol. 65, No. 11, November 2013, pp 2737–2747

Diagnosis

1. ANA, RF
2. Anti-Scl-70 (DNA topoisomerase I) antibody
   1) 20-40% in diffuse scleroderma
   2) 10-15% in limited scleroderma
3. Anticentromere antibody
   1) 50-90% in limited scleroderma
   2) 5% in diffuse scleroderma

Antibodies	Prevalence (%)	Clinical association
Anticentromere	20–30	Limited scleroderma, Crest syndrome, pulmonary hypertension
Antitopoisomerase (anti-Scl-70)	15–20	Diffuse scleroderma, interstitial lung disease
Anti-PM-Scl	2–3	Polymyositis/scleroderma overlap
Anti-To/Th	2–5	Limited scleroderma
Anti-RNA polymerase	20	Diffuse scleroderma
Antifibrillarin	4	Diffuse scleroderma, myositis, pulmonary hypertension, renal disease
Anti-Ku, anti-Sm, anti-U1RNP	Rare	Overlap syndromes with features of scleroderma
Anticardiolipin antibodies	20–25	Limited/diffuse subsets, features of secondary antiphospholipid antibody syndrome rare

Medscape

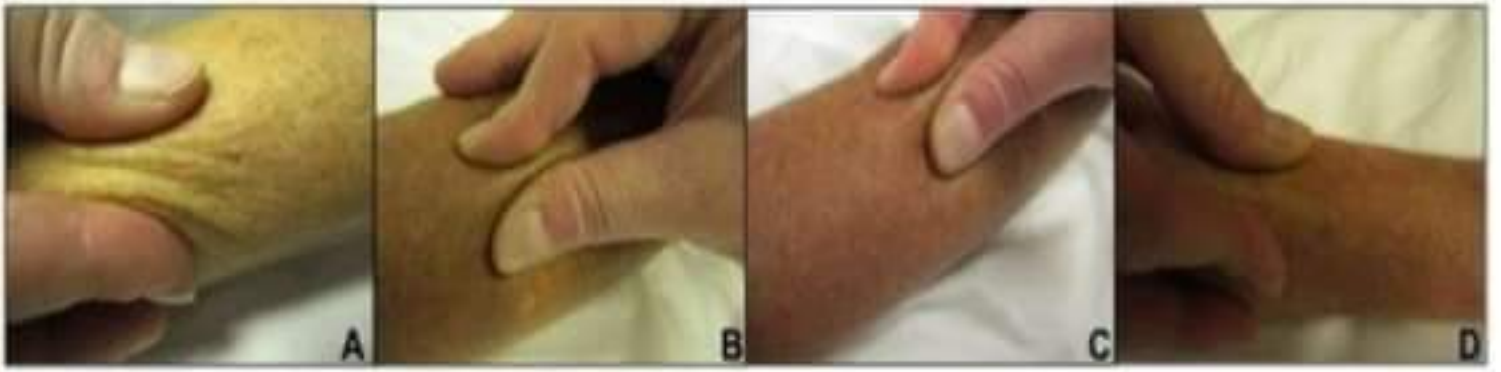
Monitoring disease activity

Skin thickness scores:

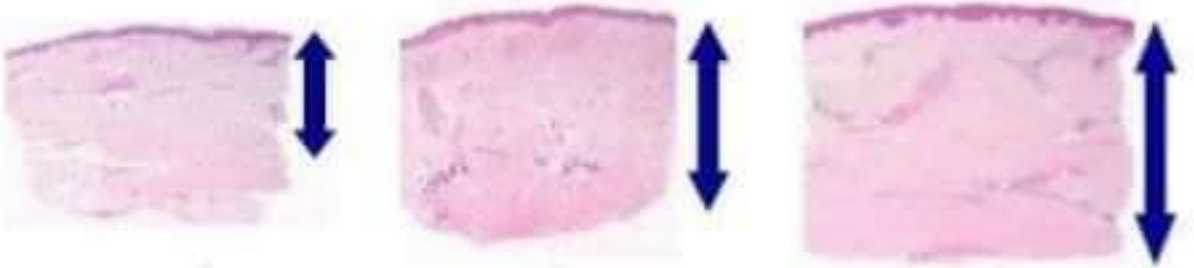
- The most widely accepted method for monitoring skin changes in systemic sclerosis is by simple clinical palpation.
- The modified Rodnan skin score employs a qualitative rating scale (**0, normal skin; 1, mild; 2, moderate; 3, severe thickening)** of the findings on clinical palpation of 17 body areas
- Is a semi-quantitative tool for clinical research as well as a measure of clinical progress in the individual

The Modified Rodnan Skin Score

- **17 different body areas**
  (fingers, hands, forearms, upper arms, chest, abdomen, thighs, lower legs, feet)
- **The maximum score is 51**



0=normal 1=mild 2=moderate 3=severe



1 2 3

Histological correlation of skin score

Monitoring disease activity

- **Health assessment questionnaire (HAQ)–Disability**

  Index (DI) has been shown to be the most accurate predictor of survival.

- It outperformed a variety of clinical and laboratory features.

- DI score correlates well with total skin thickness score, reduced fist closure, and proximal muscle weakness IJDVL March-April 2004 Vol 70 Issue 2

Prognosis

- Quite variable and difficult to predict
- Cumulative survival

	Diffuse	limited
5 yr	70%	90%
10 yr	50%	70%

- Major cause of death

1) Renal involvement

2) Cardiac involvement

3) Pulmonary involvement

Mortality in scleroderma

- Result of internal organ involvement
  - pulmonary fibrosis
  - pulmonary arterial hypertension (PAH)
  - gastrointestinal dysfunction
  - various cancers
  - scleroderma renal crisis (SRC)

10 th edition Brenner and Rector's The Kidney

Goal of the treatment

1. Prevent internal organ damage.
2. Arrest or slow the deterioration of function in previously involved organs.
3. Improve the function of previously involved organs, including the skin.

IJDVL March-April 2004 Vol 70 Issue 2