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Overview of Scleroderma (Systemic Sclerosis), Pathogenesis, and Treatment

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Abstract: **Systemic sclerosis (SSc), also known as scleroderma, is an unusual connective tissue disease that SSc preferentially affects mostly women, but still can affects males too, and generally begins in between 45 and 65 years. This review will focus on the Pathogenesis of SSc, also intended to discuss the treatment approaches of this dermatological disease, in addition aiming to emphasize the potential role of the genetics, epithelium, fibroblasts and immune system in the pathogenesis of SSc. A comprehensive search was performed to identify studies published in PubMed and the Cochrane database up to December 2016, in English language and involving human subject only and recently published abstracts were also reviewed our search was for detection of studies that discussing the pathogenesis and treatment of SSc. The pathogenesis of SSc is intricate and appears to include endothelium, epithelium, fibroblasts and immunological mediators, leading to dysregulated vascular renovation and, eventually, vasculopathy. Endothelial cell injury is an early and probably starting event, however the exact aetiology stays uncertain. Although the pathogenesis of SSc stays evasive, we are learning more about the disease systems, which will assist detectives in developing more targeted therapies for this devastating disease. A coherent unifying hypothesis to discuss the varied symptoms of SSc, including its vascular, immune, and fibrotic aspects, extremely comprehensive and could discuss the pathogenesis behind the SSc.**

Keywords: **Systemic sclerosis (SSc), Pathogenesis, and Treatment.**

1. INTRODUCTION

Systemic sclerosis (SSc), also known as scleroderma, is an unusual connective tissue disease that SSc preferentially affects women (female-to-male ratio around 8:2) and generally begins in between 45 and 65 years. This connective tissue disease has an around the world circulation, the precise prevalence stays uncertain with a considerable disparity between countries and locations: reports vary from 30.8 to 286 cases per million [(1,2)]. Typically, it affects middle-aged women, in whom the average age of start is 45 years; however, it can likewise affect males, children, and the elderly. Its pathogenesis includes abnormalities of the immune and vascular systems, which ultimately lead to pathologic fibrosis of end organs (**Figure 1**) [(3)]. Vasculopathy includes fibrointimal proliferation of small vessels and vasospastic episodes triggered by cold or stress; this condition, scientifically described as Raynaud's phenomenon, causes tissue ischemia. Vasculopathy in the larger vessels can manifest as lung arterial hypertension (PAH) or scleroderma renal crisis (SRC). Autoimmune dysregulation includes lymphocyte activation that causes autoantibody production, aberrant cytokine and chemokine release, and dysregulation of the innate body immune system. Fibrosis can lead to internal organ dysfunction, which may manifest as lung fibrosis, intestinal dysmotility and malabsorption, or impaired cardiac function. Lung participation in SSc is the most common cause of death in these patients [(2)]. Although less common than other rheumatic diseases, it has one of the highest mortality rates [(1,2,3)]. There are minimal therapeutic choices, so advances in medical understanding for the advancement of unique treatments are important. SSc presents with heterogeneous medical manifestations that make early, accurate medical diagnosis challenging. Microarray research studies have revealed more subsets of SSc than were formerly appreciated, 2 well-recognized clinical subsets are conventionally utilized to describe patients on the basis of the extent of skin participation: the restricted cutaneous subset (lcSSc) and the scattered cutaneous subset (dcSSc) [(3,4,5)]. The latter generally begins with symmetric finger and hand swelling that generalizes to include the lower arms, arms, face, trunk, and lower extremities. Gradually, the edema evolves into firm bound-down induration and

fibrosis that eventually trigger defects of the digits, which usually reveal fixed-flexion contractures of the proximal interphalangeal joints (**Figure 2**) [3]. The etiology of SSc is currently an expanding location of research study, since the specific nature of the events underlying this disease stays uncertain [6]. SSc might be started in the vasculature, with evidence recommending that some morphological changes may appear prior to disease start [6]. The pathological occasions in SSc might consist of impaired interaction between endothelial cells, epithelial cells and fibroblasts; lymphocyte activation; autoantibody production; inflammation; and connective tissue fibrosis [6]. These events lead to an accumulation of constituents of the extracellular matrix (ECM) (**Figure1**), which changes the regular tissue architecture, which in turn can culminate in organ failure [3,6].

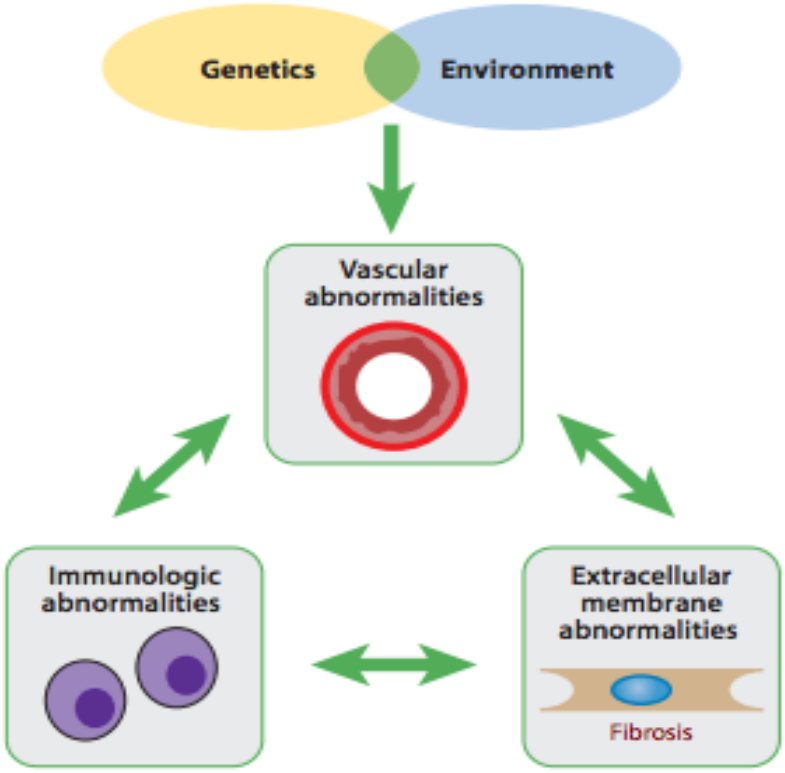

Figure 1: Schematic overview of systemic sclerosis (SSc) pathogenesis. [3]

This review will focus on the Pathogenesis of SSc, also intended to discuss the treatment approaches of this dermatological disease, in addition aiming to emphasize the potential role of the genetics, epithelium, fibroblasts and immune system in the pathogenesis of SSc.

2. METHODOLOGY

A comprehensive search was performed to identify studies published in PubMed and the Cochrane database up to December 2016, in English language and involving human subject only and recently published abstracts were also reviewed our search was for detection of studies that discussing the pathogenesis and treatment of SSc. We used following Mesh terms in searching relevant articles; “systemic sclerosis”, and “scleroderma”, “pathogenesis”, And “treatment”.

3. RESULTS

The pathologic skin modifications observed in SSc patients depend in part on whether the lesions are early or late, the SSc subset of the patient, and the place of the biopsy specimen [7,8]. In early sores, there is edema of the papillary and reticular dermis. The 3 main problems are increased collagen, irregular blood vessels, and an inflammatory infiltrate. Collagen in the dermis and subcutis is compressed with a homogeneous, hyalinized pattern that extends from the papillary dermis to the subcutis, changing subcutaneous fat and surrounding atrophic gland [7,8].

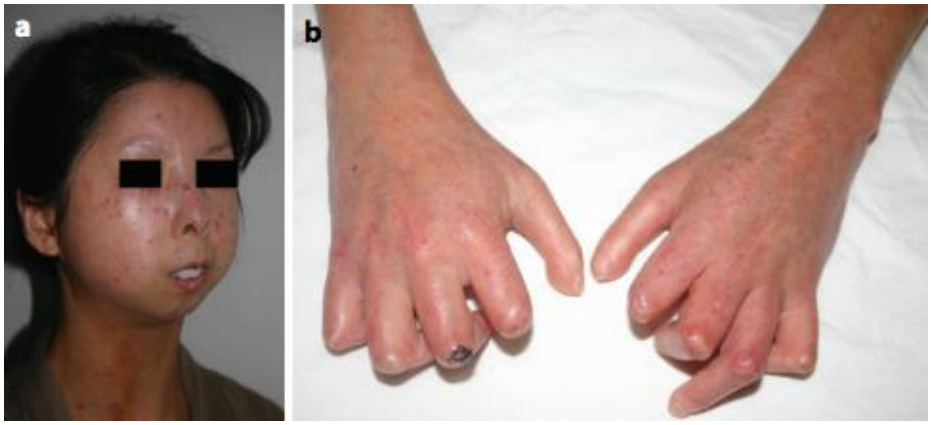

Figure 2: Clinical features of systemic sclerosis. (a) Facial features of a young woman with diffuse cutaneous systemic sclerosis (dcSSc). Note the pulled, shiny skin with micrognathia, thin lips, and pinched nose. Multiple squared-off telangiectasias are evident over her face and neck. (b) Hands of the same patient with dcSSc [3]

- ***Pathogenesis of Scleroderma:***

A. The potential role of the epithelium in pathogenesis of SSc:

The epithelium can be discovered widespread throughout the body, as the outer covering of the skin, and internal both lining organs and body cavities (e.g. mucous membranes, gut and lungs). It has an extensive variety of functions that consist of secretion, absorption, protection, transcellular transportation, feeling detection and selective permeability. Following tissue injury, the epithelium plays a crucial function in repairing injuries and re-surfacing tissue. In patients with SSc, nevertheless, there is proof that this regrowth might be dysregulated. Numerous epithelial-derived factors affect the behaviour of fibroblasts, with some soluble arbitrators understood to display profibrotic activities, including transforming growth factor-β (TGF-β) and ET-1 (**Figure 3**) [9]. There is also proof that epithelial-to-mesenchymal transdifferentiation (EMT) happens in lung fibrosis [10,11], and this process is known to be affected or moderated by TGF-beta, and potentially ET-1 [11,12].

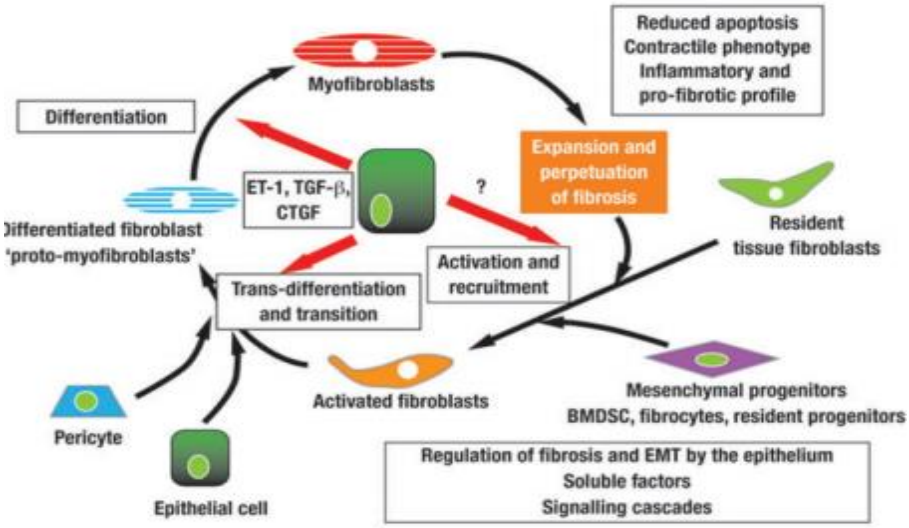

Figure 3: The role of the epithelium in the pathogenesis of SSc.

B. Vascular roles in SSc pathogenesis:

Small blood vessels' involvement contributes substantially to SSc morbidity and death. Dysfunction of peripheral microvasculature is shown in RP attacks. Intermittent vasoconstriction will advance to blood vessels narrowing, obliteration and insufficient blood supply. Ischaemia and reperfusion attenuate oxidative stress with excessive production of reactive oxygen species that even more worsen endothelial cells damage. Activated endothelial cells secrete vasoactive conciliators such as nitric oxide, prostacyclin, endothelin-1 (ET-1), platelet-activating factor and soluble adhesive particles (vascular cellular adhesive molecules (sVCAM-1) and sE-selectin). Interaction between endothelial cells and T

lymphocytes is achieved via lymphocyte function-associated antigen-1, really late antigen-4 and L-selectin revealed on lymphocytes, while their counter-receptors, intercellular adhesive molecule (ICAM-1), VCAM-1 and CD34/endoglycan, are expressed on endothelial cells. Endothelial cells induce regional inflammatory cell activation with TNF-a, transforming growth factor-β (TGF-β), IL-1a, interferon-g (IFN-g) and chemokines release [13]. The production of antibodies to endothelial cells has been reported in SSc, and greater levels of anti-endothelial cells antibodies associated with parameters showing microangiopathy: carbon monoxide diffusing capability (DLCO), lung arterial high blood pressure (PAH), digital ulcers and capillaroscopic problems [14]. Anti-endothelial cell antibodies from SSc patients might cause endothelial cells apoptosis. High titers of anti-endothelial cell antibodies correlated with apoptotic endothelial progenitor cells in bone marrow [15]. A range of changes was demonstrated on nail-fold capillaroscopy in SSc: sac-like, huge and bushy blood vessels, microhaemorrhages and capillary loss [16]. Decreased capillary density was shown in SSc patients, most prominent in patients with SSc-related PAH [17]. Irregularities in skin, renal and lung microvasculature in patients with digital ulcers, PAH and scleroderma kidney crisis are similar and show malfunctioning angiogenesis in SSc. Concentric intimal proliferation and luminal obstruction in small- and medium-sized lung vessels and myocardial tissue were shown on autopsy of a SSc patient who passed away from PAH [18]. Microangiopathy in SSc is a spread phenomenon and presumed to be responsible for dangerous organ participation, such as PAH, scleroderma kidney crisis, cardiomyopathy, vascular ectasia and atrophy in the gastro-intestinal tract. Neo-vascularisation is a complicated procedure that requires both mobilisation of endothelial progenitor cells from bone marrow and proliferation and distinction of resident cells (endothelial cells and pericytes). In typical circumstances, tissue hypoxia is followed by the expression of vascular endothelial growth factor (VEGF), platelet-derived development factor (PDGF), TGF-β, et-1 and mcp-1, which then set off the migration of endothelial cells from pre-existing vessels, endothelial cells proliferation and new vessels formation. In SSc patients, neo-angiogenesis is impaired despite elevated levels of VEGF and its receptors. Upregulation of VEGF is believed to be accountable for the look of huge blood vessels telangiectasias [19]. Vasculogenesis describes the development of brand-new vessels by flowing endothelial progenitor cells, which need to refill harmed capillary. In SSc, the numbers and function of bone marrow-derived CD34þ/ endothelial progenitor cells are depleted [20]. Ischaemia stimulates production of TGF-β and CTGF followed by fibroblast activation and extreme extracellular matrix production. Microvascular pericytes contribute to neo-vascularisation. Pericytes might become triggered and transform to collagen-producing myofibroblasts [21], ET-1 caused endothelial cells expansion, smooth muscle hypertrophy and permanent vascular obliteration. Elevated levels of ET- 1 associated with severity of RP, digital ulcers, PAH and kidney failure in SSc patients [22] ET-1 participates in the fibrotic cascade by stimulation of fibroblast collagen production and inhibition of matrix metalloproteinase-1 activity. There are 2 types of receptors to ET-1: ET-A and ET-B. ET-A receptors are revealed by vascular smooth muscle cells and moderate vasoconstriction, smooth muscle cell proliferation and fibrosis. ET-B receptors are mainly revealed on endothelial cells and mediate vasodilation with release of nitric oxide. In SSc patients, ET-B receptors are down- managed, which might displace the balance towards vasoconstriction and fibrosis [22]. Prostacyclin is the primary arachidonic acid metabolite of endothelial cells and vascular smooth muscle cells that reveal vasodilator homes and prevent platelet adhesion. The ability of endothelial cells to launch and synthesise prostacyclin is reduced in patients with RP and SSc. Production of thromboxan A2 prospective vasoconstrictor and platelets activator is boosted in SSc patients. Irregular balance between prostanoids on behalf of thromboxan A2 may contribute to vasoconstriction in SSc, vessels obliteration and in situ thrombosis [23]. The role of nitric oxide in SSc is complex: scleroderma endothelial cells reveal minimized endothelial nitric oxide synthase and increase inducible nitric oxide synthase activity, leading to a tissue, inflammation and vasoconstriction damage. Just recently, the progressive disappearance of lymphatic vessels has actually been reported in scleroderma [24].

C. The role of fibroblasts and the immune system in pathogenesis of SSc:

The role of fibroblasts Fibroblasts maintain the structural stability of connective tissue, secreting fibrillar procollagens, fibronectin and managing the turnover and structure of the ECM by means of extremely specific proteases such as collagenase. Various subtypes of fibroblasts exist and can perform a range of functions in various locations (e.g. papillary fibroblasts, dermal papilla fibroblasts, myofibroblasts). Although morphologically similar, these various fibroblast subpopulations are appreciable by their gene expression profiles and practical activities [25,26]. For instance, whilst papillary fibroblasts produce thin collagen bundles and have a high rate of proliferation, reticular fibroblasts produce thick collagen bundles and abundant versican, and promote rapid lattice contraction [27]. Following tissue injury, quiescent fibroblasts are triggered throughout the wound healing and inflammation phase, producing granulation tissue and a provisionary matrix, a process that is consequently reversed to redesign the scar. In human disease, such as hypertrophic keloid scarring or SSc, this scar tissue is not properly terminated or remodelled resulting in extreme scar formation. Fibroblasts can be classified according to various stages of distinction [28], along with their levels of collagen production [29]. In SSc patients, triggered fibroblasts are accountable for the development of fibrosis and build-up of ECM molecules.

These fibroblasts are characterized by an overproduction of collagen and the induction of collagen-modifying enzymes. The gene expression profile of fibroblasts is affected by their environment [30]. Quiescent fibroblasts reveal ET-1 and intercellular adhesion molecule-1, whereas the fibroblasts subject to mechanical tension may reveal -TGF-β, ecm and sma genes. The phenotype of SSc fibroblasts is equivalent with that of fibroblasts that have actually been exposed to excessive signaling by TGF-β which recommends a potential underlying system [31,32].

D. Contribution of Genetic factors in pathogenesis of SSc:

SSc happens more commonly in families with SSc (1.6%) than in the basic population. Though favorable family history represents the strongest factor identified, indicating an essential role for genetics, the probability of establishing disease is < 1% among offsprings of patients [33]. The presence of SSc in a first-degree relative gives a substantially increased risk of SSc, Raynaud's phenomenon (RP), interstitial lung disease, and other autoimmune diseases [34]. Vasculopathy is the most important heritable component and fibrosis is less polygenic.

Molecular subsets in the gene expression signature of scleroderma skin have been recognized using genome-wide expression profiling. The dcSSc subset has actually been identified with the fibro-proliferative gene expression, whereas lcSSc and few cases of diffuse type possess the inflammatory gene expression signature [35]. Particular alleles in the genes for changing growth factor-β (TGF-β), monocyte chemoattractant protein-1 (MCP-1), interleukin 1-a (IL-1a), tumor necrosis factor-α (TNF-α), connective tissue growth factor (CTGF), fibrillin-1, interferon regulatory factor-5 (IRF-5), signal transducer and activator-4 have been related to disease susceptibility and scientific features [36].

The principle of shared genetic risk factors for the development of autoimmune diseases is seen in SSc [37]. Just recently several genes involved in immune guideline consisting of BANK1, C8 or f13-BLK, IL-23R, IRF5, STAT4, TBX21, and TNFSF4 have actually been determined as susceptibility genes for SSc advancement [37]. PTPN22 has actually been related to SSc and also with the advancement of type I diabetes mellitus, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). STAT4 and IRF5 are associated with SSc susceptibility and have actually been identified as vulnerability genes for the advancement of SLE and RA. TNFSF4, BANK1, and C8orf13-BLK have actually signed up with the list of shared autoimmune genes with risk association with SSc and SLE. BANK1, IRF5, and STAT4 risk alleles displayed a 1.43-fold increased risk of dcSSc [33]. A strong and reproducible association of the STAT4 gene is seen with lcSSc, suggesting that this gene seems to be one of the genetic markers influencing SSc phenotype [38]. The conclusive involvement of CTGF variants in the hereditary background stays to be developed [33]. Various genetic, contagious, and environmental factors have actually been linked; vascular injury, fibrosis, and immune activation form the essential parts in pathogenesis as shown in (**Figure 4**) [33].

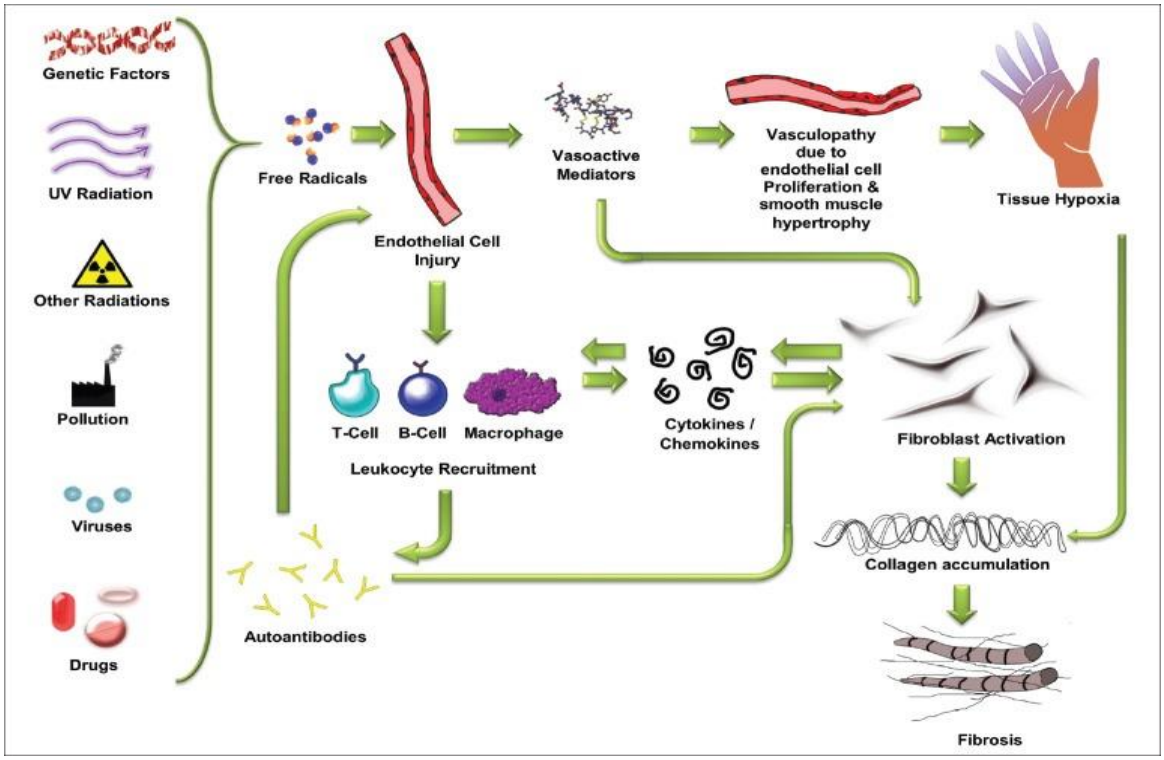

Figure 4: summary of etiological factors and pathogenesis of systemic sclerosis [33]

- ***Treatment approaches of SSc:***

Treatment of SSc generally concentrate on the dealing with the techniques of dermatological symptoms, the cutaneous symptoms depend on stage/subset of the disease. Skin sclerosis is a primary symptom [40,41]. RP is the 2nd most common finding seen in more than 95% of patients [41]. Ischemic digital ulcers, a devastating manifestation, is prevalent in roughly 50% of patients [41,42]. Coloring is more typical in Hispanics and African Americans than in Caucasians [43]. The authors have found this to be a providing function in numerous patients of SSc in the Indian subcontinent. Calcinosis cutis, leg ulcers, telangiectasia, and sexual dysfunction are the other concerns postured to the skin specialist. The clinical manifestations have a profound impact on the patient's quality of life [44].

The therapy of cutaneous manifestations depends on the stage/subset of the disease. SSc has been divided into an inflammatory and fibroproliferative group based upon genome-wide molecular profiling [45]. Future idea of dealing with SSc may progress into a customized technique based on gene expression signature. Vascular and inflammatory damage precedes fibrotic component; this is important because treatment that does not target inflammatory component may not be able to target all the symptoms. The prominent cutaneous symptoms and treatment techniques have actually been summed up in (**Table 1**) [44].

Table 1: Salient dermatological manifestations and their treatment modalities [44]

Dermatological manifestations	Treatment modalities
Skin sclerosis	Immunosuppressives, biologicals, tyrosine kinase inhibitors, hematopoietic stem cell transplantation
Raynaud's phenomenon and digital vasculopathies	Calcium-channel blockers/alpha blockers Angiotensin receptor inhibitors, prostacyclin analogs, PDE-5 inhibitors, EtA receptor antagonists
Pigmentation	Role of EtA receptor antagonists, vitamin D analogs
Calcinosis	Diltiazem, minocycline, bisphosphonates, probenecid, low-dose warfarin, surgical excision, CO2 laser
Leg ulcers	Bosentan, erythropoeitin, platelet gel, becaplermin, G-CSF, hydrocolloid dressings, low-molecular-weight heparin, pentoxyfylline, revascularization surgeries
Telangiectasia	Flash lamp pumped pulsed dye laser, Intense Pulse Light
Sexual dysfunction	PDE-5 inhibitors

PDE-5: Phosphodiesterase type 5, G-CSF: Granulocyte colony-stimulating factor

4. CONCLUSION

The pathogenesis of SSc is intricate and appears to include endothelium, epithelium, fibroblasts and immunological mediators, leading to dysregulated vascular renovation and, eventually, vasculopathy. Endothelial cell injury is an early and probably starting event, however the exact etiology stays uncertain. Although the pathogenesis of SSc stays evasive, we are learning more about the disease systems, which will assist detectives in developing more targeted therapies for this devastating disease. A coherent unifying hypothesis to discuss the varied symptoms of SSc, including its vascular, immune, and fibrotic aspects, extremely comprehensive and could discuss the pathogenesis behind the SSc.

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