Project on

A review on Diagnosis and Treatment of Scleroderma

[In the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy]

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The Department of Pharmacy,

Faculty of Allied Health Sciences,

Daffodil International University

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APPROVAL

This project paper, **"A review on Diagnosis and Treatment of Scleroderma",** submitted to the Department of Pharmacy, Faculty of Allied Health Sciences, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to its style and contents.

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DECLARATION

I hereby declare that this project report, **"A review on Diagnosis and Treatment of Scleroderma",** is done by me under the supervision Most. Sumaiya Khatun Khli Lecturer, I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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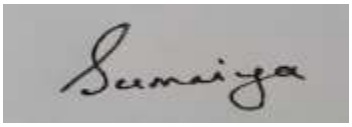

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My Parents

The persons who always encourage me in every sphere of my life

Abstract

Clinical signs of scleroderma, also known as progressive systemic sclerosis, include skin thickening, Raynaud's phenomenon, and visceral organ participation. Serological tests reveal different autoantibody subclasses. These separate the illness into "limited" and "diffuse" types. Additionally, 'regionalized' scleroderma, a unique type of scleroderma, is distinguished by skin thickening without visceral implication. The purpose of this review to learn about Scleroderma treatment & diagnosis methods that have been approved. Methods for assembling and evaluating data were gathered from a variety of linked reviews published between 1995 and 2022 utilizing search engines like PubMed, Research Gate, Google Scholar, and Medline, among others. Scleroderma was formerly mostly treated symptomatically and with immunosuppression medications that targeted the offending organ system and the aberrant immune system. Drug therapeutics that target the pathogenetic pathways of fibrosis, vasculopathy, and autoimmunity are now being developed as a result of improved discoveries into the pathogenesis of disease. Endothelin receptor blockers, phosphodiesterase inhibitors, Endothelin-1 receptor antagonist, Prostanoids, Angiotensin converting enzyme inhibitors, Riociguat, Cyclophosphamide, Fluoxetine, Prostacyclin analogues, Methotrexate and autologous stem cell transplant are a few of the more recent treatments, while others are currently in development. They might be the key to improving this disease's prognosis in the future, which was long believed to be completely incurable.

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Chapter 1
Introduction

1.1 Introduction

The main characteristic of the collagen material condition scleroderma is the thickness and hardness of the skin. Greek word "dermis" signifies skin, while the combined form "sclero" means "hard." Scleroderma comes in two main varieties: regional and widespread (also called systemic sclerosis). Scleroderma that is localized primarily impacts the skin, though it can also have an effect on the muscles and bones. Internal organs, including the gastrointestinal tract, heart, lungs, and kidneys, among many others, are affected by systemic scleroderma. Scleroderma can differ in severity and prognosis. [1] [2]

1.2 Etiology

Scleroderma's origins are not entirely understood. There is some proof that the development of scleroderma is influenced by both genetic and environmental factors. Systematic scleroderma is known to include risk factors, including silica and several organic solvents. The end effect is immune system stimulation, which damages blood vessels and tissues, leading scar tissue to develop and an overabundance of collagen to accumulate. There is at least some genetic influence. Three US cohorts found that first-degree relations of scleroderma victims had a disease prevalence that was 13 times greater than the general public. Systemic scleroderma is associated with OX40L gene polymorphism. The IRF5 gene was discovered to be associated with both the development of interstitial lung disease throughout scleroderma and systemic scleroderma. [3][4][5][6] Scleroderma's precise origin is not known. Scleroderma or conditions that resemble it may be caused by a variety of environmental causes, such as absorption to silica dust, vinyl chloride, epoxy resins, and other organic solvents. Geographic clusters has been observed in a few studies, which is also associated with potential environmental risk factors. [7] The easiest way to think of scleroderma is as an illness with two elements: a genetic predisposition and a trigger incident, such exposure to silica dust. Several academics have looked into the potential connection among silicone breast implants and scleroderma. All of these research has not yet demonstrated a causal connection. The prevalence of auto-immune abnormalities between these women is consistent with the expected prevalence in this midlife female population, despite the fact that there are undoubtedly many reported instances of scleroderma and other auto-immune illnesses between many women who have had breast implants. [8] This is the same workforce demographic that are the majority likely

to experience auto-immune illnesses example scleroderma in any case. According to some study, a small percentage of people with scleroderma may have mycoplasma or bacterial infections as a possible cause of their condition. Additionally, it seems that a sizable portion of those with Lyme sickness possibly will also have mycoplasma or other co-infections. [9]

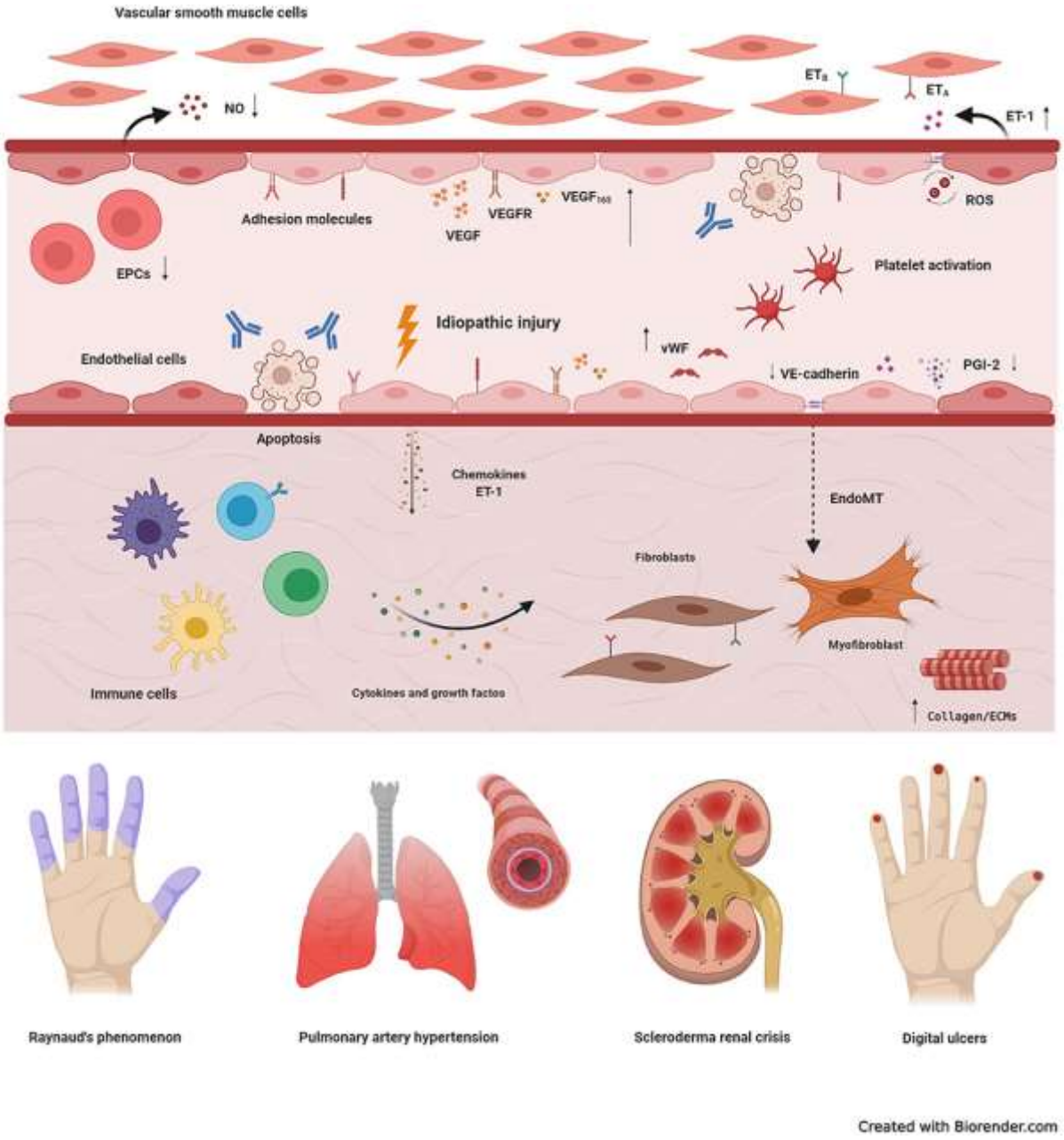

Figure 1: Basic mechanisms of systemic sclerosis-related vasculopathy. [10]

1.3 Epidemiology and Genetic Susceptibility

As a result of methodological different variants in case accurate estimation and geographic differences in these measurement techniques, the results of research on the prevalence and incidence of scleroderma are contradictory. According to the information that is currently available, there are between 50 and 300 cases per million people and between 2.3 and 22.8 cases per million people annually. Between 3:1 to 14:1, women are much more likely than men to get scleroderma. [11] Black people have a marginally higher risk of developing scleroderma, according to reports. Families with scleroderma patients frequently have other autoimmune diseases, and there are variations in phenotypes according to race and ethnicity. All imply that scleroderma may be caused by hereditary reasons. There have been reports of cytokine, cytokine receptor, chemokine, and extracellular protein gene polymorphisms related with scleroderma. Although several of these variations have been connected to patient cohorts, only a small number have been independently verified. Contrarily, there is compelling evidence connecting specific HLA class II molecules with specific clinical symptoms and autoantibodies. [12] The information supports the idea that scleroderma is a syndrome spanning numerous phenotypes rather than a single, clearly characterized illness. Viruses, medications, vinyl chloride, and silica are a few examples of environmental factors that can cause clinical phenotypes that are like to or identical to scleroderma. Furthermore, according to a number of accounts, fetal or maternal lymphocytes can traverse the placenta throughout pregnancy and start a graft-versus-host reaction that results in scleroderma. [13] Scleroderma and chronic graft-versus-host disease (GVHD) share clinically, serologic, and histological characteristics, and allogeneic cells have been found in peripheral blood and skin biopsy samples taken from scleroderma patients. Furthermore, there is insufficient solid proof that these cells contribute to the pathophysiology of scleroderma. [14]

1.4 Pathophysiological Mechanisms scleroderma

Systemic sclerosis (SSc; scleroderma) has a complicated and poorly understood pathophysiology. The advancement of this disease is known to be influenced by immune activation, vascular damage, extreme extracellular matrix synthesis, and enhanced written statement of structurally normal collagen [15]. Cell-cell, cell-cytokine, and cell-matrix conversations lead to the development of these processes. The variety of contributions

made by each of these pathogenic factors can most likely be seen in the heterogeneity of the clinical characteristics of SSc patients. The majority of pathogenesis theories for SSc center on how early immunological occurrences interact with vascular changes to produce an inhabitants of stimulated fibrotic fibroblasts, which are generally thought to be the disease's effector cells. [16] Though it is uncertain what the formation of groups are and how various processes including both trigger, amplify, and promote the onset of the skin- and organ-based fibrosis with vasculopathy that is the hallmark of the illness, there is no denying that vascular and immunologic processes are central to the pathogenesis of scleroderma. Given the diagnostic distinctions among scleroderma and other autoimmune rheumatic diseases and the moderate consequences of immunosuppressive medications (such as cyclophosphamide) in clinical trials, it may come as a surprise that genetic and serologic approaches to comprehending the pathogenesis of scleroderma have emphasized the significance of cellular and humoral immunity. [17] Numerous genetic loci linked to systemic lupus and other autoimmune diseases are also linked to scleroderma sensitivity in large-scale genetic analysis [18]. Furthermore, hallmark scleroderma autoantibodies frequently establish relationships between non-immune genes in sub phenotype investigations of genetic loci [19], further demonstrating the critical role of the immune system in the emergence and clinical manifestations of the illness. Here is a discussion of the several elements thought to play a role in the pathogenesis of SSc. Separate discussions are made of the SSc's potential etiology, clinical symptoms, diagnosis, and therapy options.

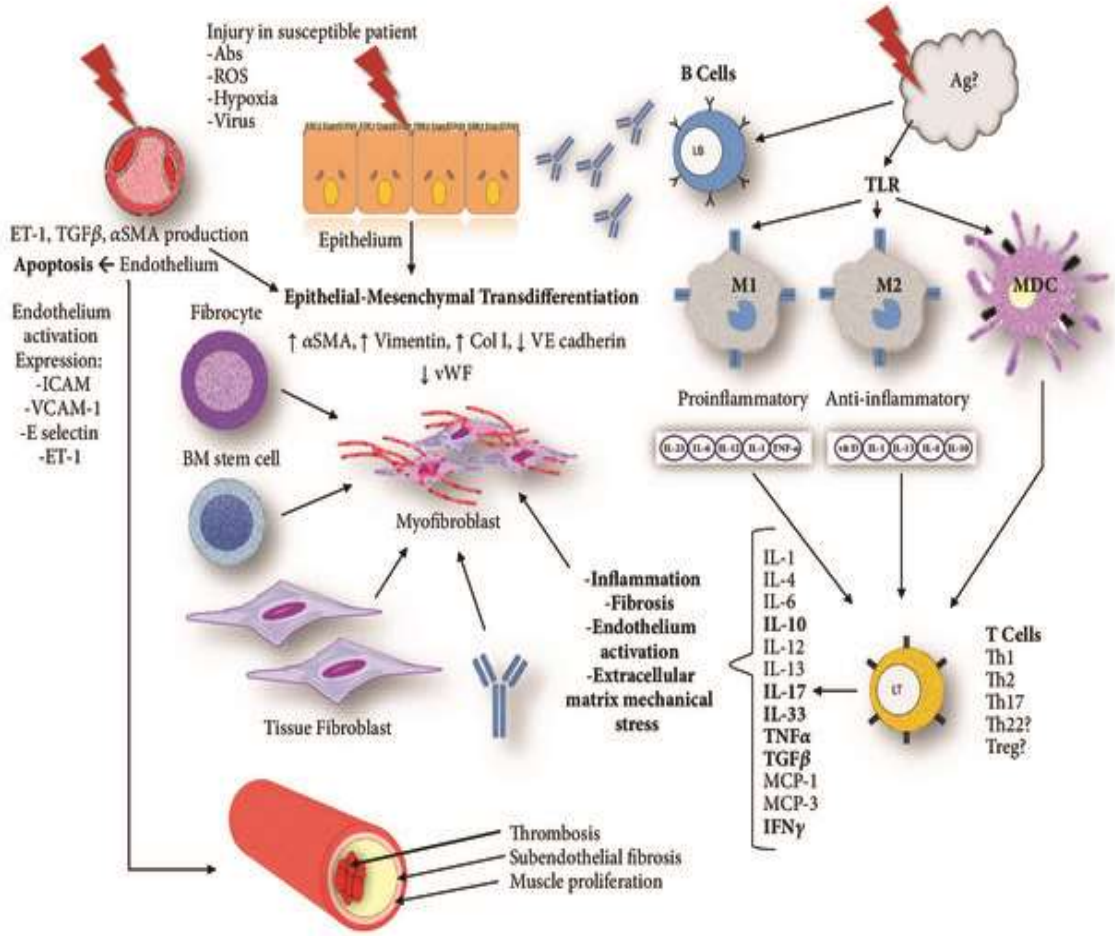

Figure 2: Systemic Sclerosis Pathogenesis and Emerging Therapies [20]

Peripheral sclerosis pathogenesis diagram. participation of fibroblasts, endothelium, epithelium, and immune system. Basically, a self or foreign antigen (Ag) causes endothelium and/or epithelial cell injury by inducing an autoimmune response in a susceptible individual. Autoantibodies and proinflammatory and profibrotic cytokines are produced as a result of abnormally activated innate and adaptive immune systems. [21]

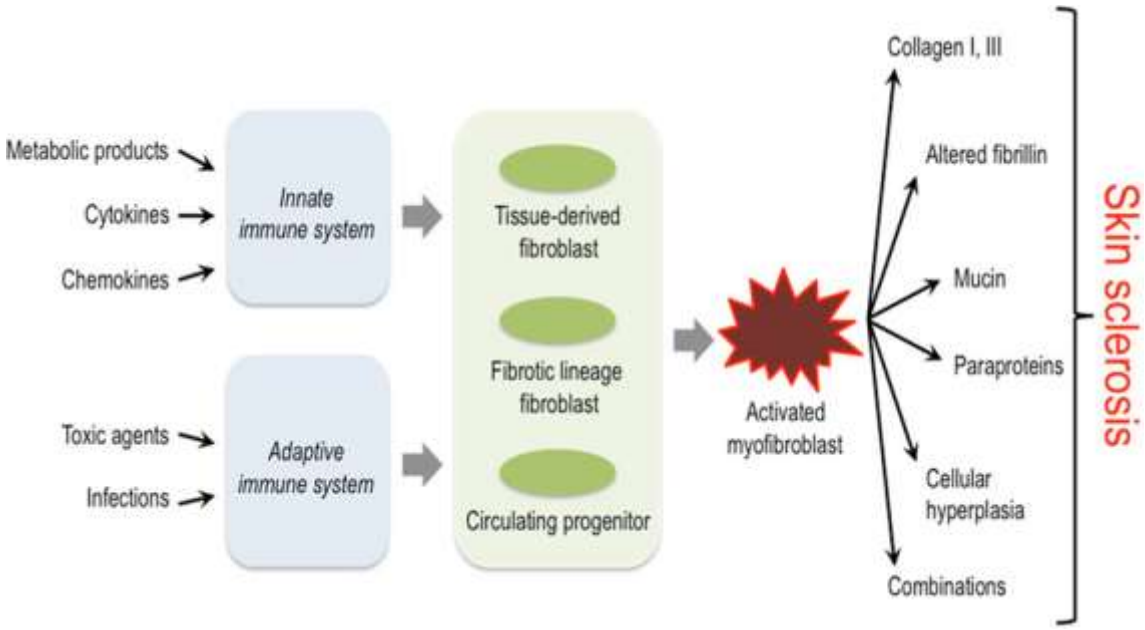

Figure 3: Pathophysiological Mechanisms in Sclerosing Skin Diseases [22]

1.5 Risk factors of Scleroderma

Scleroderma can affect everyone, but women are far more likely to develop it than men are. Scleroderma susceptibility appears to be influenced by a number of interrelated variables, including: [23]

Genetics: It appears that people with specific gene variants are more likely to get scleroderma. This may aid in understanding why some instances of scleroderma seem to run in families and why some ethnic groups are more likely to develop specific kinds of the disease. [24]

Immune system difficulties: It is thought that scleroderma is an autoimmune condition. It follows that it happens in part as a result of the body's immune system attacking the connective tissues. Scleroderma patients may also exhibit signs of other autoimmune diseases, including such lupus, rheumatoid arthritis, or Sjogren's syndrome. [26]

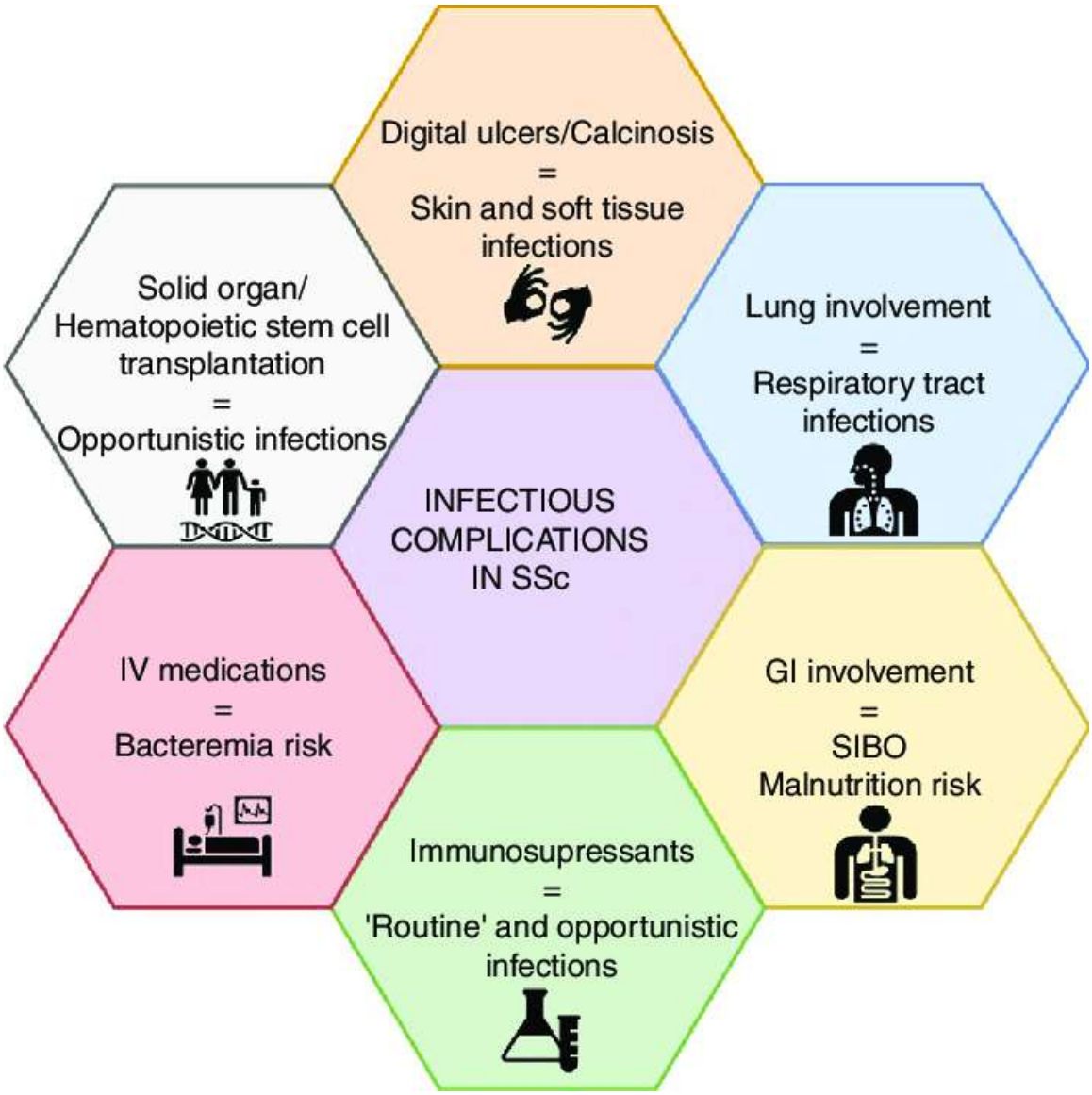

Figure 4: Infectious complications and risk factors in systemic sclerosis. [27]

Chapter 2

Purpose of the study

2.1 Purpose of the study

The skin is the predominant organ system affected in isolated scleroderma; muscles and bones may or may not also be affected. Internal organs like the gastrointestinal system, heart, lungs, and kidneys may be impacted by systemic scleroderma. This disorder can range in severity. Purpose of this review to know the following points.

- To achievement a systematic understanding of the disease, including its cause, signs and symptoms, consequences
- The purpose of this research was to understand more about Scleroderma in Bangladesh
- To know the transmission process of Scleroderma
- To learn about Scleroderma treatment methods that have been approved
- The goal of this inquiry was to learn more about Bangladesh Scleroderma status
- To gain a better accepting of the many diagnostic procedures used to identify this sickness

Chapter 3
Materials and methodology

3.1 Data collection procedure

Methods for assembling and evaluating data were gathered from a variety of linked reviews published between 1995 and 2022 utilizing search engines like PubMed, Research Gate, Google Scholar, and Medline, among others. The procedures employed in the investigation are covered in this chapter. Some basic terms, such as "Scleroderma pathogenesis," "Scleroderma treatment," "Scleroderma diagnostic technique," and "Scleroderma preventive measures," were used to search for me. I learned more by reading every collected review paper. The information acquired has been finally summarized.

3.2 Data analysis strategy

Data assembly, cleansing, and organization are mutual actions encompassed in data analysis techniques. The data must go through these events, which typically involve using data investigation software, in order to be prepared for business use. Data analytics, another name for data analysis, is well-defined as the science of inspecting raw data in order to make defensible extrapolations about the data.

Chapter 4

Literature review

4.1 Scleroderma: from pathophysiology to novel therapeutic approaches

Systemic scleroderma might serve as a template for orphan illnesses, where the rarity, distinct subgroups, and varying disease activity pose significant barriers to understanding their causes and developing effective treatments. Significant progress has recently been made in our comprehension of the physiology of connective tissue, growth factor activity, and their receptors. A better understanding of the pathophysiology of scleroderma was obtained in particularly, emphasizing the importance of hypoxia, cellular stress, and a confluence of conflicting cytokines. Numerous cytokines and growth factors, such as transforming growth factor-b and platelet-derived growth factor, which are crucial in the pathophysiology of SSc, have been demonstrated to be controlled by tyrosine kinases. For the therapy of this fatal condition, researchers are actively looking at new pharmaceutical substances that engage with signaling cascades brought on by hypoxia and intracellular signal transduction pathways of mesenchymal cells, such as tyrosine kinase inhibitors. [28]

4.2 Diagnosis and treatment of systemic and localized scleroderma

Clinical signs of skin thickening, Raynaud's occurrence, and abdominal organ participation, as well as certain autoantibody subsets, help to diagnosis scleroderma or progressive systemic sclerosis. These distinguish between the "limited" and "diffuse" forms of the disease. Additionally, a unique type of scleroderma known as "contained" scleroderma is distinguished by skin thickening without visceral activation. Scleroderma was formerly mostly treated symptomatically with immunosuppressant’s that targeted the affected organ system and the abnormal immune system. Drug therapeutics that address the pathogenetic pathways of fibrosis, vasculopathy, and autoimmunity are now being developed as a result of newer discoveries into the pathogenesis of disease. Endothelin receptor blockers, phosphodiesterase antagonists, tyrosine kinase inhibitors, and autologous stem cell transplant are a few of the more recent treatments, while others are currently in development. They might be the key to improving this disease's prognosis in the future, which was long believed to be absolutely incurable. [29]

4.3 Management of Endothelial Dysfunction in Systemic Sclerosis: Current and Developing Strategies

Systemic sclerosis (SSc) is an autoimmune condition characterized by immune system dysregulation, tissue fibrosis, and vascular dysfunction. The illness is characterized by vascular remodeling, endothelial injury, and insufficient endothelial repair. Endothelial cell (EC) degradation and death have been linked to periventricular inflammation, oxidative stress, and tissue hypoxia from the early stages of SSc, which can develop in a variety of clinical symptoms. Quality of life and longevity are significantly impacted by Raynaud's paradox, edematous puffy hands, digital ulcers, pulmonary artery pressure, erectile dysfunction, scleroderma renal crisis, and heart participation. In order to direct treatment measures, it is crucial to comprehend the pathogenic features and biomarkers that represent endothelium degradation in SSc. Pharmacological methods to increase blood flow and tissue perfusion and, more subsequently, biological treatments to accelerate endothelium repair, induce angiogenesis, and heal wounds are some of the treatment modalities documented for SSc-associated vasculopathy. In this brief review, known and emerging therapeutic strategies for enhancing the vascular segment are discussed together with current understanding of cellular and molecular components of SSc vasculopathy. [30]

Chapter 5

Results & discussion

5.1 Diagnosis of scleroderma

Scleroderma is typically diagnosed clinically based on the presence of Raynaud's syndrome, common skin thickening, and visceral participation. The results of laboratory studies are encouraging. Serology for autoantibody profiles aids in defining the disease's subtype and ruling out other illnesses that resemble scleroderma. To assess the degree and degree of visceral engagement brought on by the illness processes, organ-specific examinations are helpful. [31] The American College of Rheumatology (ACR) has created initial categorization criteria to ensure consistency in clinical research [32]. The development of sclerodermatous skin alterations close to the metacarpophalangeal joint is the main requirement. Sclerodactyly, digital pitted scarring, tissue loss in the volar cushions of the finger tips, and bibasilar pulmonary fibrosis are considered minor requirements. Scleroderma is diagnosed when two or even more subsidiary requirements, in addition to the major criteria, are present. [33] Nevertheless, not all individuals may meet these requirements, and they may not be applicable in practical reality. Recently, it has been proposed that anticentromere antibodies (ACA) and nailfold capillary microscopy abnormalities should be incorporated into the secondary requirements to more effectively integrate individuals with the specific subset of the condition [34]. Contrary to recognized illness, early disease diagnostics may be challenging. These patients may initially solely exhibit Raynaud's phenomenon and not exhibit any additional clinical symptoms. When this occurs, autoantibody testing and nailfold capillaroscopy alterations (capillary loss and dilatation) may be helpful examinations for predicting the progression of the condition to a more severe disease [35]. The early identification of scleroderma is thought to be aided by a series of criteria that have subsequently been found. by the scleroderma trials and research teams of the European League against Rheumatism (LAR). Each of the three domains—skin (puffy fingers/puffy swelling digits becoming sclerodactly); vascular (Raynaud's phenomenon; aberrant capillaroscopy with scleroderma pattern); and laboratory—contains seven elements. In a prospective observational cohort, these measures are subsequently being validated to develop diagnostic criteria [36]. Based on the degree of skin thickness, two different subsets of scleroderma have been discovered. The distal extremity (distal to elbows and knees) and face of the limited variety have symmetrically thicker skin. The skin on the face, trunk, and proximal and distal extremities

thickens in the widespread type. The key distinctions among these two categories, albeit there is some overlap. Either of these variants may coexist with overlapping diseases, including polymyositis and systematic lupus erythematosus (SLE), in which scleroderma-like characteristics are also apparent (PM). [37] Scleroderma mimics are a group of illnesses that have characteristics with scleroderma. These must be disregarded because the therapy and results may vary. Scleredema adultorum of Buschke manifests as an abscess of the face, trunk, and proximate appendages that is painless and edematous [38], and it is occasionally linked to diabetes mellitus. Typically, it self-limits. The lack of Raynaud's and distal development, as well as the histological deposit of mucopolysaccharide material in the dermis, set it apart from scleroderma. A rare condition known as scleromyxedema (papularmucinosis) is characterised by papular skin lesions linked to sclerosis and monoclonal gammopathy. [39]

5.2 Treatment of scleroderma

5.2.1 Calcium channel blocker

Calcium channel blockers lower intracellular calcium levels, which causes smooth muscle relaxation and vasodilation. Dihydropyridines are generally advised. to lessen the severity and occurrence of simple RP in scleroderma. Both short-term and long-term usage of calcium channel blockers reduced the levels of oxidative stress markers in the blood, and in vitro, nicardipine shielded ECs from oxidative damage. [40] In patients with scleroderma-associated PAH, calcium channel blockers also reduced blood levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), suggesting a potential antispasmodic and vasodilatory impact on the pulmonary circulation, though not supported by hemodynamic changes. Nifedipine and nicardipine enhanced myocardial permeability and left ventricle function in patients with scleroderma for less than five years, corroborating the theory that scleroderma causes a myocardial Raynaud's condition. [41]

5.2.2 Endothelin-1 receptor antagonist

Endothelin-1 antagonists focus on ET-1, a significant scleroderma vasculopathy trigger. Bosentan and Macitentan are dual inhibitors that engage either type A and type B receptors, whereas Ambrisentan is a selective type A endothelin blocker. Bosentan did not treat current DU in randomized controlled clinical tests, although it did obstruct the emergence

of new DU. [42] Ambrisentan decreased pain and impairment while also reducing the number of active and new DU in scleroderma patients. In individuals with systemic scleroderma-PAH, bosentan and ambrisentan enhanced hemodynamic measures. Additionally, endothelial activating markers ICAM-1, VCAM-1, P-selectin, and PECAM-1 serum levels were reduced by the drug. [43]

5.2.3 Phosphodiesterase-5A inhibitor

Cyclic guanosine-5-monophosphate (cGMP), connected to the nitric oxide (NO) vasodilator route, is hydrolyzed by phosphodiesterase-5A (PDE-5A). PDE-5A inhibitors increase the vasodilatory properties of NO by reducing the metabolism of cGMP (102). PDE-5A drugs enhanced DU healing, lowered impairment and suffering brought on by RP, and lowered the incidence and length of RP bouts in scleroderma patients. [44] Sildenafil decreased pulmonary artery pressure in scleroderma-PAH patients, improving cardiopulmonary condition. Improved outcomes for scleroderma-PAH were seen with combined therapy using tadalafil and ambrisentan than with either drug used alone. However, in scleroderma patients with vasculopathy, sildenafil had no impact on the quantity of circulating EPCs or the quantities of VEGF in the serum. PDE-5 antagonists have also been researched as a potential treatment for erectile dysfunction, albeit on-demand delivery does not work well for scleroderma patients. [45]

5.2.4 Prostanoids

Vascular ECs produce prostacyclin, also referred as prostaglandin I-2 (PGI-2), which promotes vasodilation while reducing platelet aggregation, inflammation, and the development of vascular smooth muscle. Pharmacological drugs that boost the prostacyclin route and hence encourage vasodilation include the prostacyclin receptors stimulant (selexipag) and prostacyclin analogs (iloprost, beraprost, treprostinil, and epoprostenol). [46] In addition to lowering blood levels of ICAM-1, VCAM-1, and E-selectin, which indicates lessened EC activation, iloprost was helpful for treating RP, DU, and PAH in scleroderma patients. Combination therapy using iloprost and bosentan enhanced the quantity of capillaries in the nailfold. Beraprost had no impact on the hemodynamic parameters in scleroderma-PAH and failed to prevent the development of DU. Epoprostenol, on the other hand, enhanced clinical condition and hemodynamic

Prostacyclin agonists have numerous adverse effects, a short half-life, and a high rate of administration. [47] Therefore, medications with more practical posologies have been researched. Selexipag, an oral specific prostacyclin receptor agonist, has been proven to be helpful for PAH by promoting vasculature by raising cyclic adenosine monophosphate concentrations. Although, the effectiveness of this medication for vasculature is still up for discussion. While selexipag did not lower the incidence of RP incidents in a randomized, placebo-controlled research, an open followup investigation revealed significant reduction in RP, indicating that selexipag may be helpful for DU repair and relief of DU-related pain. [48]

5.2.5 Angiotensin converting enzyme inhibitors

Blood pressure is quickly controlled by angiotensin-converting enzyme (ACE) antagonists because they prevent angiotensin I from becoming the vasoconstrictor agent angiotensin II. ACE medications significantly improved the prospects of scleroderma patients with scleroderma renal crises (SRC) over the past few decades by reducing the requirement for dialysis and raising survival rates. Furthermore, preventative use did not lower the frequency and was linked to a poor prognosis and a higher death risk following the beginning of SRC. [49]

5.2.6 Riociguat

Riociguat is a soluble guanylate cyclase (sGC) stimulant that has potent pulmonary artery vasodilator effects (138–144). Advancements in pulmonary vascular resistance were seen in clinical studies involving PAH patients, including SSc (145). Initial research did not find any substantial improvements in the plasma levels of VEGF, Eselectin, VCAM-1, or ICAM-1, nor did it show any substantial reduction of productive or painful DU; however, long-term observations revealed comprehensive recovery of the DU (146), as well as decrease in pain and disability related to RP (147). Greater research is needed to ascertain how riociguat affects the peripheral vascular. [50]

5.2.7 Cyclophosphamide

In both experimental and clinical settings, the immunosuppressive medication cyclophosphamide (CYC), which is primarily prescribed for interstitial pulmonary disease associated with scleroderma, also has an impact on the vascular compartment.

Cyclophosphamide enhanced the capillaroscopic patterns of the nailfolds, raised the number of EPCs in circulation, and decreased serum levels of VEGF, Eselectin, and thrombomodulin, markers of endothelial injury and activation. [51] These findings suggest that CYC may have an impact on the pathogenic processes that cause to lung damage and fibrosis, such as re-endothelialization and re-epit. In comparison to dermal MVECs subjected to serum from uncontrolled scleroderma patients, those subjected to the serum of CYC-treated scleroderma patients exhibited superior multiplication and less apoptosis. [52]

5.2.8 Fluoxetine

A selective serotonin reuptake inhibitor called fluoxetine has been suggested as a therapy for scleroderma RP attacks. Serotonin plays a role in the pathophysiology of the Raynaud's concept. Fluoxetine functions as a stimulant, but it also has paradoxical vasodilation properties that alter the NO and calcium cascades and are regulated by 5HT7 and 5HT2B receptors. Fluoxetine, however, had no effect on soluble P-selectin or wWF levels, only on the intensity of RP assaults in scleroderma patients. [3]

5.2.9 Prostacyclin analogues

In patients with systemic sclerosis, an imbalance between prostacyclin (PGI2) and thromboxane A2 has been seen. PGI2 prevents platelet aggregation and leukocyte proliferation in addition to decreasing operational vasospasm. As a result, the vascular action lasts longer. PAH and Raynaud's phenomenon are both commonly treated with PGI2 and its analogs. Iloprost, a stable counterpart of prostacyclin, is administered intermittently intravenously (IV) to patients with systemic sclerosis to relieve Raynaud's phenomenon and lessen the intensity and frequency of the attacks. [55] Digital ulcers can benefit from it as well. Kidney vasospasm is alleviated with intravenous iloprost. It might also stop PAH from growing in the first place. It has not been demonstrated that the oral route is as efficient as the IV approach. Epoprostenol PGI2 is effective. Patients with PAH related to scleroderma respond with epoprostenol continual IV infusion, which improves cardiopulmonary hemodynamics and exercise capacity and increases longevity. Today, it is regarded as a first-line therapy for patients with advanced PAH. Additionally, improvements have been noted in digital ulcers and the Raynaud's phenomenon. It has been

demonstrated that the prostacyclin analogue treprostinil, which is suited for continuous subcutaneous administration, has very mild effects on hemodynamics and discomfort in PAH. [56] The US FDA has given the drugs epoprostenol and treprostinil the go-ahead to treat PAH. Moreover, they need ongoing parenteral therapy and are linked to a number of negative side effects. The necessity of administering iloprost via inhalation on a regular basis limits its usefulness. [57]

5.3 Methotrexate

Numerous randomized controlled studies have shown methotrexate to be beneficial in terms of skin thickening, either in terms of trending or actual significance. It is suggested by EULAR/EULAR Scleroderma Trial and Research Group as a therapy for early diffuse scleroderma because the majority of patients handle it well. [58]

5.4 Hematopoietic stem cell transplantation

In comparison to traditional therapy, autologous stem cell transplantation (AHSCT) has improved survival, illness management, and life satisfaction for hundreds of patients with severe and progressing Scleroderma during the past 25 years. The primary fibrosis-related symptoms of Scleroderma, such as skin thickening and interstitial lung disease, are considerations for AHSCT. [59] Thorough cardiac screening is advised to prevent the admission of patients with asymptomatic cardiac involvement and individuals with significant vascular symptoms, particularly those with pulmonary hypertension or scleroderma renal crises, are typically excluded. The method resets the immune system and encourages improved regulation of the fibrosis, inflammation, and auto reactivity pathways. Little is understood about how AHSCT affects Scleroderma-associated vasculopathy as of yet. [60] Dermal artery density as measured by immunostaining for endothelial indicators CD31, VE-cadherin, and vWF was unaffected by stem cell transplantation. AHSCT, in contrast hand, raised capillary counts, corrected epidermal levels of VE-cadherin, and lowered the development of Interferon mRNA in the skin, which is recognized as a selective inhibitor of angiogenesis. Nailfold video capillaroscopy was used to analyze the microvascular morphology. After AHSCT, serum VEGF levels dropped, which is a positive development as disturbed VEGF overexpression is linked to aberrant vessel shape in Scleroderma. [61]

Chapter 6
Conclusion

6.1 Conclusion

Scleroderma is a complex illness with a variable autoantibody composition and uncertain disease progression. Although the majority of the time the diagnosis has been made, it is important to focus on early illness identification and therapeutic action to avoid the potentially irreversible fibrotic phase of the disease. Despite the numerous current therapeutic approaches and targeted paths, treating Scleroderma-related vasculopathy remains challenging. Patients appear to have significant vascular participation thus far, with artery rupture and ischemic lesions, from early disease stages. The diverse pathophysiological manifestations and potential treatment window make it difficult to create novel approaches. Since there are no good indicators for vascular severity or extension, it is frequently too late to identify patients who have life-threatening or debilitating vascular participation. The important treatment results also include enhancement of blood flow in the pulmonary, renal, and peripheral vascular beds as well as the repair of ulcers.

Chapter 7
Reference

Reference

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