Preview of the Medifocus Guidebook on: Scleroderma

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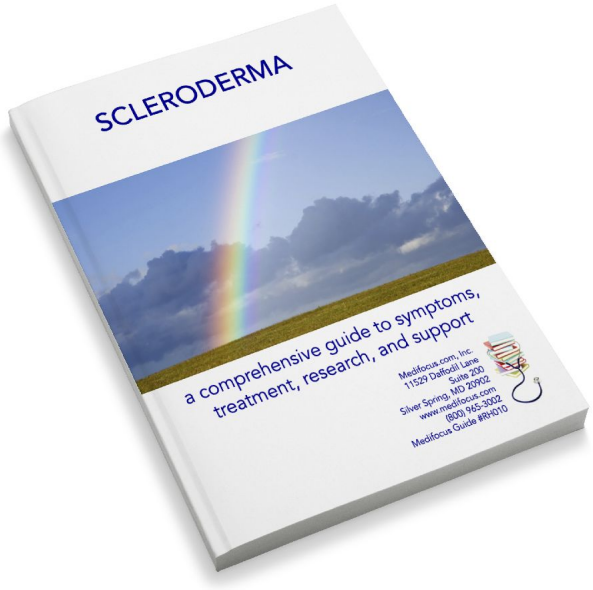

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Scleroderma**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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Table of Contents

1 - Background Information

Introduction

Chronic or life-threatening illnesses can have a devastating impact on both the patient and the family. In today's new world of medicine, many consumers have come to realize that they are the ones who are primarily responsible for their own health care as well as for the health care of their loved ones.

When facing a chronic or life-threatening illness, you need to become an educated consumer in order to make an informed health care decision. Essentially that means finding out everything about the illness - the treatment options, the doctors, and the hospitals - so that you can become an educated health care consumer and make the tough decisions. In the past, consumers would go to a library and read everything available about a particular illness or medical condition. In today's world, many turn to the Internet for their medical information needs.

The first sites visited are usually the well known health "portals" or disease organizations and support groups which contain a general overview of the condition for the layperson. That's a good start but soon all of the basic information is exhausted and the need for more advanced information still exists. What are the latest "cutting-edge" treatment options? What are the results of the most up-to-date clinical trials? Who are the most notable experts? Where are the top-ranked medical institutions and hospitals?

The best source for authoritative medical information in the United States is the National Library of Medicine's medical database called PubMed®, that indexes citations and abstracts (brief summaries) of over 7 million articles from more than 3,800 medical journals published worldwide. PubMed® was developed for medical professionals and is the primary source utilized by health care providers for keeping up with the latest advances in clinical medicine.

A typical PubMed® search for a specific disease or condition, however, usually retrieves hundreds or even thousands of "hits" of journal article citations. That's an avalanche of information that needs to be evaluated and transformed into truly useful knowledge. What are the most relevant journal articles? Which ones apply to your specific situation? Which articles are considered to be the most authoritative - the ones your physician would rely on in making clinical decisions? This is where *Medifocus.com* provides an effective solution.

Medifocus.com has developed an extensive library of *MediFocus Guidebooks* covering a wide spectrum of chronic and life threatening diseases. Each *MediFocus Guidebook* is a

high quality, up- to-date digest of "professional-level" medical information consisting of the most relevant citations and abstracts of journal articles published in authoritative, trustworthy medical journals. This information represents the latest advances known to modern medicine for the treatment and management of the condition, including published results from clinical trials. Each *Guidebook* also includes a valuable index of leading authors and medical institutions as well as a directory of disease organizations and support groups. *MediFocus Guidebooks* are reviewed, revised and updated every 4-months to ensure that you receive the latest and most up-to-date information about the specific condition.

About Your MediFocus Guidebook

Introduction

Your *MediFocus Guidebook* is a valuable resource that represents a comprehensive synthesis of the most up-to-date, advanced medical information published about the condition in well-respected, trustworthy medical journals. It is the same type of professional-level information used by physicians and other health-care professionals to keep abreast of the latest developments in biomedical research and clinical medicine. The *Guidebook* is intended for patients who have a need for more advanced, in-depth medical information than is generally available to consumers from a variety of other resources. The primary goal of a *MediFocus Guidebook* is to educate patients and their families about their treatment options so that they can make informed health-care decisions and become active participants in the medical decision making process.

The *Guidebook* production process involves a team of experienced medical research professionals with vast experience in researching the published medical literature. This team approach to the development and production of the *MediFocus Guidebooks* is designed to ensure the accuracy, completeness, and clinical relevance of the information. The *Guidebook* is intended to serve as a basis for a more meaningful discussion between patients and their health-care providers in a joint effort to seek the most appropriate course of treatment for the disease.

Guidebook Organization and Content

Section 1 - Background Information

This section provides detailed information about the organization and content of the *Guidebook* including tips and suggestions for conducting additional research about the condition.

Section 2 - The Intelligent Patient Overview

This section of your *MediFocus Guidebook* represents a detailed overview of the disease or condition specifically written from the patient's perspective. It is designed to satisfy the basic informational needs of consumers and their families who are confronted with the illness and are facing difficult choices. Important aspects which are addressed in "The Intelligent Patient" section include:

- The etiology or cause of the disease
- Signs and symptoms
- How the condition is diagnosed
- The current standard of care for the disease
- Treatment options

- New developments
- Important questions to ask your health care provider

Section 3 - Guide to the Medical Literature

This is a roadmap to important and up-to-date medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest developments and breakthroughs in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new clinical developments, and advances in research. To facilitate your review and analysis of this information, the articles are grouped by specific categories. A typical *MediFocus Guidebook* usually contains one or more of the following article groupings:

- *Review Articles:* Articles included in this category are broad in scope and are intended to provide the reader with a detailed overview of the condition including such important aspects as its cause, diagnosis, treatment, and new advances.

- *General Interest Articles:* These articles are broad in scope and contain supplementary information about the condition that may be of interest to select groups of patients.

- *Drug Therapy:* Articles that provide information about the effectiveness of specific drugs or other biological agents for the treatment of the condition.

- *Surgical Therapy:* Articles that provide information about specific surgical treatments for the condition.

- *Clinical Trials:* Articles in this category summarize studies which compare the safety and efficacy of a new, experimental treatment modality to currently available standard treatments for the condition. In many cases, clinical trials represent the latest advances in the field and may be considered as being on the "cutting edge" of medicine. Some of these experimental treatments may have already been incorporated into clinical practice.

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Article title
- Author Name(s)
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)

- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the corresponding URL address that is provided for each cited article. If you purchased a printed copy of a *MediFocus Guidebook*, you can still access the article abstracts online by entering the individual URL address for a particular article into your web browser.

Section 4 - Centers of Research

We've compiled a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of the specific medical condition. The "Centers of Research" directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of the condition.

Inclusion of the names of specific doctors, researchers, hospitals, medical centers, or research institutions in this *Guidebook* does not imply endorsement by Medifocus.com, Inc. or any of its affiliates. Consumers are encouraged to conduct additional research to identify health-care professionals, hospitals, and medical institutions with expertise in providing specific medical advice, guidance, and treatment for this condition.

Section 5 - Tips on Finding and Choosing a Doctor

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver high-level, quality medical care in accordance with curently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it. This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Section 6 - Directory of Organizations

This section of your *Guidebook* is a directory of select disease organizations and support groups that are in the business of helping patients and their families by providing access to information, resources, and services. Many of these organizations can answer your questions, enable you to network with other patients, and help you find a doctor in your geographical area who specializes in managing your condition.

2 - The Intelligent Patient Overview

SCLERODERMA

Introduction to Scleroderma

Scleroderma (Sc) describes a group of related connective tissue diseases involving skin, joints and internal organs. The term *scleroderma* literally means hardening (also called *fibrosis*) of the skin. The cause of scleroderma is unknown, but the disease process is related to a malfunction of the vascular and immune systems. Researchers believe that the immune system, which protects us against infection and cancer, becomes overactive in patients with scleroderma, resulting in the overproduction of collagen (connective tissue or "scar" tissue) in the body. The excess collagen is deposited in the skin and, in some cases, in and around the organs, and that leads to the characteristic hardening and thickening effect of the skin or of tissue surrounding joints and internal organs.

Scleroderma may be *localized*, with excess collagen building up in the skin, or it may be *systemic*, with excess collagen building up not only in the skin but in and around various organs such as the esophagus, kidneys, lungs, gastrointestinal tract, heart, and peripheral nervous system. Organ involvement leads to many accompanying complications. Almost all complications of systemic scleroderma are related to fibrotic changes in one or more organs and can occur in adults as well as children.

While localized scleroderma typically stabilizes and improves over time, systemic scleroderma is progressive, with the first two to five years following onset being a critical period due to the highest risk for rapid progression and the development of serious complications. This is often followed by a reversal and improvement of symptoms, though complications affecting organs persist. Systemic scleroderma is also referred to as "systemic sclerosis".

Most cases of scleroderma are seen initially by a dermatologist, who specializes in skin diseases. As the condition progresses, patients often are referred to the care of a rheumatologist, an internist who specializes in diseases of the autoimmune system, soft tissues, and joints. It is important for anyone diagnosed with scleroderma to be examined and followed regularly by a physician qualified to evaluate the development of scleroderma and other autoimmune conditions or complications.

Incidence of Scleroderma

Fortunately, scleroderma is relatively rare. According to an article published in 2009 in the *New England Journal of Medicine* (vol.360:pp. 1989-2003), data regarding the *prevalence* (number of cases present in the population) and *incidence* (number of people per year diagnosed) of scleroderma varies widely, but estimates are that the prevalence of scleroderma ranges from

50-300 cases per million people, and incidence ranges from 2.3 to 22.8 cases per one million people per year. This means that scleroderma is believed to affect between 40,000 and 300,000 people in the United States, and some estimates are even higher. The disorder most commonly occurs in women between the ages of 35 and 55; however, men and children can be affected as well. Women are affected approximately three to five times as frequently as men.

In the United States, there is an increased risk for developing scleroderma among African-American women when compared to non-African American women. African-American men and women are also more likely to develop severe lung complications. Native American Indians are also at a higher risk than the general population for development of scleroderma. Specifically, Choctaw Indians in Oklahoma are up to twenty times more likely to develop scleroderma than the general population.

Scleroderma is not contagious. Genetic factors are thought to be involved in scleroderma since there is a high frequency of other autoimmune disease in families of people with scleroderma. However, most people who develop scleroderma do not have relatives with scleroderma, and their children do not have a higher risk of getting the disease.

Types of Scleroderma

The two primary types of scleroderma are called *localized scleroderma* (also known as *morphea*) and *systemic scleroderma* (also known as *systemic sclerosis*).

Localized Scleroderma

Localized scleroderma, also known as *morphea*, is a rare fibrosing condition that is limited to the skin, underlying tissue and, in some cases, underlying muscle and bone. It is the result of an inflammatory response of the immune system that triggers connective tissue cells to produce too much collagen, resulting in fibrosis and hardening of the skin (*induration*). Localized scleroderma on the face and head is rare, but when present, it is indicative of underlying central nervous system involvement. Morphea is frequently accompanied by systemic symptoms such as fatigue, arthralgia (joint pain), or myalgia (muscle pain).

Localized scleroderma is increasingly considered to be a distinct and separate condition from systemic scleroderma. It is differentiated from systemic scleroderma by an absence of *sclerodactyly* (tightness of skin of fingers or toes), *Raynaud's phenomenon* (a blood vessel disorder causing discoloration of fingers and toes), *nailfold capillary changes* (changes in the capillaries of skinfolds over fingernails), and organ involvement.

The incidence of localized scleroderma is approximately 0.4 to 2.7 per 100,000 people. It occurs more commonly in Caucasians (72-80% more common) than in other races, and in females more than males (between 2.4:1 and 4.2:1). Prevalence in adults and children is equal. The average age of onset in children is below age 18 and between the ages of 20 to 50 in adults. The onset of morphea is typically gradual and the progression of the disease is slow. It is not uncommon for localized scleroderma to resolve on its own after two to five years, or to stop progressing without treatment, although the reason for its resolution is unknown.

During the initial inflammation or active stage of localized scleroderma (or morphea), the skin will develop lesions which typically present as red to dusky red patches and plaque, or raised areas of hard, reddened skin. Over time, when the active stage subsides, the patches become white, hairless, anhidrotic (dry) plaques with hyperpigmentation (dark spots). The lesions also become sclerotic (hard) due to the abundance of collagen deposits. The borders of the lesions take on a characteristic violet color.

The most common variants of localized scleroderma include:

- *Plaque morphea*, also known as *circumscribed morphea* - This is the most common type of morphea and typically consists of fewer than three discrete hardened (*indurated*) patches or plaques that appear predominantly on the trunk of the body, although they can also appear on the legs or arms. Adults who develop plaque morphea may also develop lesions on the hips, around the waist, and around the bra line. In women, breasts are commonly affected. Plaque morphea may be *superficial* and limited to the skin and *dermis* (layer of tissue underneath the skin); or *deep*, where it affects skin, subcutaneous tissue, and underlying muscle and fascia (fibrous, connective tissue around muscles).

- *Generalized morphea* - Skin patches are hard and dark and spread over larger areas of the body. Two or more body sites may be involved, but the face and hands are spared. Typically lesions are limited to the dermis. Generalized morphea is considered to be a rare variant of plaque morphea and affects 7 9% of morphea patients. Generalized morphea is often difficult to differentiate from systemic sclerosis since affected individuals often experience systemic symptoms such as fatigue, arthralgia (joint pain), and myalgia (muscle pain), and may also have elevated levels of autoantibodies (antibodies directed against oneself), especially antinuclear antibodies (ANA), which are also present in systemic sclerosis.

- *Linear morphea* - Lesions are typically lilac in color and linear (not ring-shaped), although they may also appear as bands around a limb. Linear scleroderma is typically associated with underlying tissue damage, which causes muscle atrophy, joint contractures, and limb asymmetry. It may begin on the lower limbs and spread to the upper limbs, trunk, face, and scalp. This is the most common type of morphea found in children, estimated to affect 40 60% of children with localized scleroderma. Approximately 5 25% of children with linear morphea develop bilateral involvement (on both sides of the body). Three variations of linear morphea include: *en coup de saber* (ECDS) which affects the face and scalp with a sword-shaped appearance and which is associated with minor to severe atrophy of the face, as well as underlying ocular and central nervous system involvement; *progressive hemifacial atrophy* (one side of the face) associated with atrophy of subcutaneous tissue with minimal skin changes; and *linear limb involvement*, where indurated plaques appear along the length of a limb and can result in limb asymmetry. The average age of onset of linear morphea is 13, and females are affected more than males. It typically takes nine years before a correct diagnosis of this condition is made.

- *Pansclerotic morphea* - This is the most debilitating form of morphea and is associated with considerable pathology, including muscle atrophy, joint contractures, and chronic, non-healing ulcers. Pansclerotic morphea always affects subcutaneous structures (such as fascia and muscle) all the way down to, and often including, the bone. Some individuals may

experience full-depth sclerosis in other parts of their bodies as well. It is estimated that 6.7% of individuals with pansclerotic morphea eventually develop squamous cell carcinoma (a type of skin cancer).

- *Variant morphea* - This is a combination of two or more types of morphea and occurs in up to 15% of individuals with morphea.

While localized scleroderma may cause only cosmetic changes in some individuals, others suffer from a more severe form in which skin lesions may form over much of their bodies, and thickening and scarring may spread to areas underneath the lesions, such as fat, muscle, and bone. These individuals experience a significant reduction in their quality of life and in the ability to perform activities of daily living. However, unlike systemic scleroderma, localized scleroderma, even in its severest form, does not affect internal organs. Localized scleroderma does not reduce life expectancy.

Systemic Scleroderma

Systemic scleroderma (SSc) is more extensive than localized scleroderma, affecting connective tissue, blood vessels, and major organs. Typically, the earliest changes noted in systemic scleroderma include damage to very small blood vessels, the presence of mononuclear cell infiltrates (a particular type of white blood cell), and a slowly developing fibrosis. With time, organs such as the skin (the body's largest organ), the gastrointestinal tract, muscles and joints, lungs, kidneys and heart may be affected, though the severity of organ complications varies widely.

Some cases of systemic scleroderma progress rapidly from the initial skin thickening to the point of organ involvement, while other cases are characterized by slow progressive skin involvement over decades before organ involvement develops. It is estimated that up to one-third of people with scleroderma have systemic scleroderma. Systemic scleroderma is very rare in children, who only account for 5% of all diagnosed cases.

There are two types of systemic scleroderma that can be differentiated by the extent of skin and organ involvement: *limited systemic scleroderma* and *diffuse systemic scleroderma*. *Systemic sclerosis sine scleroderma* is a subset of systemic sclerosis that is considered by some to be a third type of systemic scleroderma.

Limited Systemic Scleroderma

In *limited systemic scleroderma* (lSSc), also called *limited cutaneous scleroderma*, onset is gradual and skin involvement (fibrosis) is typically limited to the hands, arms, face, feet, and legs. It is traditionally classified by the *CREST syndrome* that represents the primary physical features associated with limited systemic scleroderma, including:

- **C**alcinosis - Deposits of calcium crystals in connective tissue under the skin and around the joints and organs. They typically form on the fingers, hands, face, trunk, and above the knees and elbows. Skin ulcers may form over these areas as the calcium crystals break down.

- **R**aynaud's phenomenon - Changes in the small arteries and capillaries that result in

constriction and a temporary disruption of circulation, usually in the extremities (fingers, toes, nose and ears), in response to exposure to cold or to anxiety. This is most commonly the first symptom of limited systemic scleroderma and may be present for several years before fibrosis evolves.

- **E**sophageal motility dysfunction - Muscles in the esophagus that are unable to contract normally due to scarring, causing heartburn, gastroesophageal reflux (GERD), or a sensation of food being stuck in the throat or chest. It is estimated that up to 90% of patients with scleroderma have esophageal involvement. Esophageal motility dysfunction can lead to difficulties in swallowing (*dysphagia*).

- **S**clerodactyly - Skin thickening and tightening of the fingers that leads to stiffness and reduced flexibility. Skin may also appear shiny and dark. Bone loss may occur in the fingers and toes.

- **T**elangiectasia - Dilation of the small vessels and capillaries near the skin surface, that causes small, flat, red marks on the palms of the hands, face and tongue.

Some clinicians are of the opinion that the CREST syndrome is no longer an effective way to classify scleroderma since it does not adequately describe the involvement of internal organs that occurs in some cases of systemic scleroderma. In addition, the CREST syndrome may be seen in more than one subgroup of patients with scleroderma. As scleroderma may also overlap with other autoimmune conditions, such as systemic lupus erythematosus or rheumatoid arthritis, it is clear that there are multiple aspects to scleroderma which are not sufficiently described by the CREST syndrome.

Gastrointestinal symptoms are common in limited systemic scleroderma and despite limited skin thickening, a subset of patients with lSSc suffers from severe lung problems.

Diffuse Systemic Scleroderma

Diffuse systemic scleroderma (dSSc) is much more severe than limited systemic scleroderma. Its onset is sudden and it is characterized by extensive skin fibrosis that usually begins with the hands and face and then extends to the upper arms and legs, chest, and abdominal area. The extent of thickening varies among individuals. Diffuse scleroderma can also cause damage to internal organs, such as the lung, intestines, heart, and kidneys. Progression of the disease is variable, but organ involvement is typically seen relatively early. Long-standing diffuse systemic scleroderma can lead to physical deformities, such as contracture of the fingers and toes, and tightening of the mouth.

Vascular changes are the earliest changes in scleroderma, particularly in the smallest blood vessels (capillaries) that service the skin and the nailfolds. In later stages of scleroderma, there is a significant reduction of blood vessels that bring blood to the capillaries (arterioles). Eventually, though, fibrosis becomes a more prominent feature than diffuse vascular changes. The deposits of collagen actually change the architecture of the tissue and blood vessels, and lead to many of the complications associated with scleroderma.

Systemic Sclerosis Sine Scleroderma

Systemic sclerosis sine scleroderma is a subtype of systemic scleroderma that affects the organs but not the skin. It is characterized by the presence of Raynaud's phenomenon, sclerodactyly, and complications related to internal organ involvement. Systemic sclerosis sine scleroderma represents only about 10% of cases of diffuse systemic scleroderma.

Complications of Systemic Scleroderma

There are many complications related to systemic scleroderma (SSc) and all are related to fibrotic and vascular changes that take place throughout the body.

Raynaud's Phenomenon

One of the first symptoms of systemic scleroderma (SSc) is Raynaud's phenomenon (RP), which was first documented by Maurice Raynaud in 1862. He described symptoms of patients developing specific symptoms of cold hands and feet when exposed to cold temperatures or to emotional stress. Raynaud's phenomenon is characterized initially by a paleness or whitening of the extremities (fingers or toes), then cyanosis (skin turns blue), and finally, erythema (reddening) of the skin accompanied by tingling of the fingers as the blood flow returns. Raynaud's phenomenon can be highly variable among people, lasting from minutes to hours and ranging from being painless to uncomfortable sensations of tingling, numbness, and throbbing. This reaction is caused by changes in the small arteries and capillaries of the hands and feet. Skin sores, called *digital ulcers* most commonly occur on fingers, toes, and joint surfaces, such as the elbow. They are painful, difficult to heal, and cause a major impact on quality of life. The reduced blood flow also affects any cuts or abrasions to the skin that cannot heal properly due to lack of adequate circulation.

Raynaud's phenomenon is a nearly universal finding in people who are diagnosed with systemic scleroderma and is known as "secondary RP". It is rarely seen in localized scleroderma. Individuals with limited systemic scleroderma may suffer from RP for several years before other symptoms appear, whereas in individuals with diffuse systemic scleroderma, the interval is much shorter (weeks or months) between the appearance of RP and progressive, rapid skin changes. The pattern of onset and presence of RP are considered major factors in the diagnosis of limited or diffuse scleroderma in both children and adults.

While 85-95% of patients with diagnosed scleroderma experience RP, it appears in approximately 3-10% of the general population. When RP is unrelated to any other medical condition, it is known as "primary RP". There are also "Raynaud's-like" symptoms which may appear with conditions such as fibromyalgia or other conditions that affect the circulatory system. It is important to distinguish between RP and other similar syndromes. One of the most reliable distinguishing factors of primary RP and scleroderma-related RP is the presence of antinuclear antibodies (ANA) in patients with clinically diagnosed scleroderma.

Skin Complications

The buildup of collagen causes stiffness, thickening, and hardening of the skin. The excess collagen also crowds out sweat and oil glands, leading to varying degrees of dry skin. Skin complications also include some of the CREST symptoms such as calcinosis, sclerodactyly, and

telangiectasia.

Gastrointestinal Complications

Scleroderma can affect any part of the digestive system, including the esophagus. Gastrointestinal (GI) symptoms are often one of the earliest symptoms experienced by individuals with systemic scleroderma. Approximately 90% of individuals with systemic scleroderma experience some gastrointestinal difficulty. These include:

- Heartburn
- Coughing due to esophageal dysfunction
- Abdominal distention from excessive gas
- Diarrhea or constipation
- Nausea
- Early satiety when eating (feeling full after eating a few bites)
- Difficulty swallowing (*dysphagia*)
- Bowel perforation

Esophageal motility dysfunction is the most common organ complication and is the cause of heartburn and other GI symptoms. If left untreated, severe and chronic heartburn can lead to Barrett's esophagus, a precancerous condition.

Vascular Complications

Vascular complications associated with systemic scleroderma affect medium and small blood vessels. There is evidence that just as there are repeated episodes of RP in the skin, there are also repeated episodes of ischemia (reduced oxygen) to organs due to vascular damage. Low blood flow to organs leads to multiple problems including:

- Poor oxygenation of organs
- Poor delivery of nutrients to organs
- Development of fibrosis due to the activation of fibroblasts (a type of cell associated with the formation of collagen)

There are three types of changes that may affect the blood vessels in scleroderma:

- Vasospasm (spasm of the blood vessels)
- Thickening of the walls of the blood vessels
- Clots that block the lumen (opening) of the blood vessels

Pulmonary (Lung) Complications

There is almost always a reduction in pulmonary function in both limited and diffuse systemic scleroderma. The two types of pulmonary complications associated with systemic scleroderma include:

- Interstitial lung disease - This involves injury to lung tissue around the air sacs of the lungs (interstitial), such as *pulmonary fibrosis* (scarring) and *inflammation*, both of which are more common in diffuse than in limited SSc. Pulmonary fibrosis causes reduced lung function as

well as a reduction in lung vital capacity (the maximum amount of air a person can expel after taking a deep breath). The most common symptom is shortness of breath after exertion, and a non-productive cough may also develop. There is rarely chest pain.

- Pulmonary Arterial Hypertension (PAH) - This involves increased pressure in the pulmonary artery carrying blood from the heart to the lungs and is more common in limited scleroderma than diffuse scleroderma. Mean pulmonary arterial pressure (PAP) is elevated during exercise (>30mmHg) and at rest (>25mmHg). The increase in PAP results in elevated pulmonary vascular resistance and lower blood flow, which ultimately leads to right ventricular (heart) failure. Early symptoms of pulmonary hypertension include fatigue, chest pain, shortness of breath, near fainting, palpitations, and leg swelling. Pulmonary arterial hypertension is classified according to the stages of the New York Heart Association Functional Class scale (NYHA-FC) where Class I represents slight impairment and Class IV represents the inability to perform physical activity at rest.

The National Conference on Scleroderma reported that the likelihood of developing severe Pulmonary Arterial Hypertension (PAH) is 13% after 3.2 years of follow-up from the time of diagnosis. Overall, the prevalence of PAH is thought to be up to 30% of scleroderma patients. Scleroderma-related PAH is thought to be the cause of death in up to 50% of patients with limited SSc who die of scleroderma-related complications.

PAH is a very serious complication of scleroderma and has a significant impact on prognosis for recovery and survival rates. In 2004, The American College of Chest Physicians (ACCP) published guidelines on screening, early detection, and diagnosis of pulmonary arterial hypertension in which it recommended that patients with scleroderma be screened on a regular basis for signs of PAH. To read the Guidelines of the ACCP, please click on the following link: http://www.ncbi.nlm.nih.gov/pubmed/15249493

Other lung conditions that may develop with scleroderma include:

- Pleuritis - inflammation of the membranes surrounding the lungs
- Pleural effusion - increased fluid in the pleural (lung) cavity due to inflammation

Patients with systemic scleroderma may experience some improvement after the initial decline of lung function, but they must be monitored on a regular basis to ensure early detection of the presence of lung disease, or for signs of progression of lung disease.

Renal Complications

Renal (kidney) complications occur in approximately 10% of patients with scleroderma and they occur relatively early in the course of diffuse scleroderma. Often, the earliest symptom may be a change in blood pressure. Other symptoms may include:

- Hyperreninemia - elevation of renin (kidney enzyme) levels in the blood
- Uremia - toxic levels of urea in the blood, usually excreted by the kidneys
- Microangiopathic hemolytic anemia - loss of red blood cells by destruction

A subset of patients with systemic scleroderma develops a condition called *scleroderma renal crisis*, usually within four years of the onset of the disease. Scleroderma renal crisis is a serious condition that leads to uncontrolled hypertension (high blood pressure) and can quickly result in kidney failure. All patients with renal complications should be monitored regularly for any progression of disease and should report any changes of their health status (e.g., the onset of headaches or abdominal pain) to their health care providers immediately.

Oral, Dental, and Facial Complications

Problems with oral health and dental hygiene are common in patients with systemic scleroderma. Some of the complications they may experience include:

- Excessive dryness of the mouth due to salivary gland damage or the presence of *Sjogren's syndrome*. Sjogren's syndrome is an autoimmune condition characterized by dry eye and dry mouth and is thought to occur in up to 20% of people with systemic scleroderma. Oral dryness leads to increased dental caries (cavities), difficulty eating, and difficulties speaking.
- Gradual reduction of the size of the mouth opening due to the increasing tightening and thickening of the facial skin, making effective dental care difficult.
- Damage to connective tissue in the mouth that can lead to loose teeth.
- Reduced capacity to display facial expressions as the facial skin tightens.
- Reduction in tear production (in the presence of Sjogren's syndrome) that can create significant dry eye discomfort.

Cardiac Complications

Cardiac complications of systemic scleroderma are not common but, if they occur, they are usually a late complication. Early cardiac involvement carries a poor prognosis for the outcome of systemic scleroderma. Cardiac complications may include:

- Fibrosis of the heart muscles
- Congestive heart failure
- Arrhythmia (heart rhythm disturbances)
- Hypotension (low blood pressure)

Other Complications

Other possible complications of systemic scleroderma include:

- Risk of premature birth or low birth weight babies
- Osteoporosis (degenerative bone disease)
- Biliary (liver) cirrhosis (degenerative liver disease)
- Neuropathy (nerve disease that may result if fibrosis impinges on a nerve)
- Trigeminal neuralgia, when there is facial nerve involvement
- Hypothyroidism (if there is fibrosis around the thyroid gland)
- Impotence
- Stomach cancer
- Lung cancer

Etiology of Scleroderma

The underlying cause of scleroderma is unknown but it is thought to be a combination of genetic predisposition and environmental factors that trigger the development of the condition. While both localized and systemic scleroderma are characterized by an autoimmune response that causes increased production of collagen and extracellular matrix deposits (protein fibers that surround connective tissue), the initiating trigger for these changes is unknown. The most current theory is that vascular injury, due to infection, environmental exposure, or the presence of certain antibodies, is responsible. It is thought that the vascular injury increases the production of *adhesion molecules* that then attract inflammatory cells to the site. Through a series of steps, the balance of the production and destruction of collagen is disrupted and an overabundance of collagen develops. In addition, there is also evidence that insulin-like growth factor (IGF) may be involved, which also enhances collagen production.

Another factor that appears to be related to the development of scleroderma is *microchimerism*. Chimeric cells are cells that are transferred from a fetus to the mother during pregnancy. This transfer of fetal cells is known as *fetomaternal microchimerism*. Recent studies have demonstrated an increased number of microchimeric cells in the blood and tissue of patients with scleroderma. Because the incidence of scleroderma is higher following a woman's child-bearing years, one theory that has been proposed suggests that circulating left-over fetal cells from pregnancy may trigger an autoimmune response leading to scleroderma. Ongoing investigation continues to focus on understanding this relationship between microchimerism and the scleroderma.

Risk Factors for Scleroderma

Although the exact cause of scleroderma remains unclear, there are certain conditions that appear to be "risk factors", meaning that they increase the likelihood of developing a disease or condition.

Risk factors for *localized* scleroderma include:

- Age - Linear morphea is most commonly seen in children and adolescents, while plaque morphea is more common in adults.
- Gender - Morphea is two to three times more common in females than in males.
- Ethnicity - Localized scleroderma is more common in people of European than African-American descent.
- Medications - Individual cases of morphea have been association with several medications including bleomycin, bisoprolol (Zebeta™), and bromocriptine (Parlodel™). Lesions may develop one to thirty months after starting a medication.
- Infection - Morphea has been associated with *Borrelia burgdorferi* (the agent for Lyme disease, a bacterial infection) in several studies. Approximately 50% of patients with morphea test positive for Borrelia burgdorferi antibodies. The nature of this relationship is not clearly understood.
- Autoimmune conditions - Coexisting autoimmune conditions, such as psoriasis, vitiligo (white patches of skin), Graves' disease, and type 1 diabetes mellitus occur in 2 5% of children and in 30% of adults. In addition, 20-80% of morphea patients test positive for the presence of ANA (antinuclear antibody), an autoimmune-related antibody.

- Trauma - One study identified preceding trauma in 13% of children with morphea.
- Radiation therapy - Morphea occurs in approximately one in 500 people undergoing radiation therapy. Women receiving radiation therapy for breast cancer are at the highest risk for developing morphea.

Risk factors for *systemic* scleroderma (SSc) include:

- Gender - Systemic scleroderma occurs approximately three to four times more frequently in women than in men. Between the ages of 30-55, women develop scleroderma at a rate seven to twelve times that of men. While the hormonal connection seems obvious, it is not currently understood.
- Age - Average age of onset is 30-55 years old.
- Infections - Some researchers suspect that infections may "trigger" the process leading to the development of scleroderma. Studies are ongoing to learn more about the potential role of persistent viral and bacterial infections as a possible cause of SSc.
- Genetic predisposition - Genetic factors appear to play a role in scleroderma. Many patients with scleroderma have family members with other autoimmune diseases, known as *familial clustering*, which indicates an underlying genetic mechanism.
- Ethnicity - The incidence of SSc is highest among the Choctaw Native Americans and lowest among Japanese-Americans. African-Americans are affected by systemic scleroderma and lung involvement at a higher rate than Caucasians and have a worse prognosis for the course of the disease.
- Chemical exposure - Environmental or occupational exposure to certain toxic chemicals such as epoxy resins, benzene, vinyl chloride, and silica dust is associated with the development of SSc.
- BCG and Tetanus Vaccination - Morphea-like lesions have been reported to occur in rare cases after Bacillus Calmette-Guerin (BCG) and tetanus vaccinations.
- Vitamin K injections - In rare cases, injection of Vitamin K has been associated with the development of scleroderma.

Cancer and Scleroderma

For reasons that are not clear, patients with systemic scleroderma are at an elevated risk for developing certain types of cancer. It is estimated that between 3-10% of patients with SSc may develop a malignancy. The most common cancers associated with SSc are lung cancer, breast cancer, and hematological (blood) cancers. Risk according to gender is unclear, as one study identified women as being at higher risk, while a second study identified men as being at higher risk. Diffuse SSc at an increased age also appears to elevate the risk of cancer. Ongoing monitoring and preventive measures are recommended for patients with SSc.

To read more about two studies published on cancer and scleroderma, please click on the following links: http://www.ncbi.nlm.nih.gov/pubmed/20854403 and http://www.ncbi.nlm.nih.gov/pubmed/18176294

The **Intelligent Patient Overview** in the complete **Medifocus Guidebook on Scleroderma** also includes the following additional sections:

- **Diagnosis of Scleroderma**
- **Treatment Options for Scleroderma**
- **Lifestyle Modifications and Quality of Life in Scleroderma**
- **New Developments in Systemic Sclerosis**
- **Questions to Ask Your Health Care Provider about Scleroderma**

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Or Call 800-965-3002 (USA) or 301-649-9300 (Outside USA)

3 - Guide to the Medical Literature

Introduction

This section of your *MediFocus Guidebook* is a comprehensive bibliography of important recent medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest advances in clinical medicine and biomedical research. A broad spectrum of articles is included in each *MediFocus Guidebook* to provide information about standard treatments, treatment options, new developments, and advances in research.

To facilitate your review and analysis of this information, the articles in this *MediFocus Guidebook* are grouped in the following categories:

- Review Articles - 66 Articles
- General Interest Articles - 60 Articles
- Clinical Trials Articles - 27 Articles

The following information is provided for each of the articles referenced in this section of your *MediFocus Guidebook:*

- Title of the article
- Name of the authors
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)
- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your *MediFocus Guidebook* include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your *MediFocus Guidebook* by clicking on the URI that is provided for each cited article. If you purchased a printed copy of the *MediFocus Guidebook*, you can still access the abstracts online by entering the individual URI for a particular abstract into your computer's web browser.

Recent Literature: What Your Doctor Reads

Database: PubMed <January 2014 to July 2018>

Review Articles

1.

Scleroderma skin ulcers definition, classification and treatment strategies our experience and review of the literature.

Authors: Giuggioli D; Manfredi A; Lumetti F; Colaci M; Ferri C
Institution: Chair and Rheumatology Unit, University of Modena and Reggio Emilia, Medical School, Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy. Electronic address: clferri@unimore.it.
Journal: Autoimmun Rev. 2018 Feb;17(2):155-164. doi: 10.1016/j.autrev.2017.11.020. Epub 2017 Dec 2.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=RH010&ID=29196241

2.

Intestinal Involvement in Systemic Sclerosis: A Clinical Review.

Authors: Sakkas LI; Simopoulou T; Daoussis D; Liossis SN; Potamianos S
Institution: Department of Rheumatology and Clinical Immunology, Faculty of Medicine, School of Health Sciences, University of Thessaly, 41110, Larissa, Greece. lsakkas@med.uth.gr. of Health Sciences, University of Thessaly, 41110, Larissa, Greece. Health Sciences, University of Patras, Patras, Greece. Health Sciences, University of Patras, Patras, Greece. University of Thessaly, Larissa, Greece.
Journal: Dig Dis Sci. 2018 Apr;63(4):834-844. doi: 10.1007/s10620-018-4977-8. Epub 2018 Feb 21.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=RH010&ID=29464583

The **Guide to the Medical Literature** in the complete **Medifocus Guidebook on Scleroderma** includes the following sections:

- Review Articles - 66 Articles
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4 - Centers of Research

This section of your *MediFocus Guidebook* is a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition. The *Centers of Research* directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of this disorder.

Use the *Centers of Research* directory to contact, consult, or network with leading experts in the field and to locate a hospital or medical center that can help you.

The following information is provided in the *Centers of Research* directory:

- **Geographic Location**
    - United States: the information is divided by individual states listed in alphabetical order. Not all states may be included.
    - Other Countries: information is presented for select countries worldwide listed in alphabetical order. Not all countries may be included.
- **Names of Authors**
    - Select names of individual authors (doctors, researchers, or other health-care professionals) with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition, who have recently published articles in leading medical journals about the condition.
    - E-mail addresses for individual authors, if listed on their specific publications, is also provided.
- **Institutional Affiliations**
    - Next to each individual author's name is their **institutional affiliation** (hospital, medical center, or research institution) where the study was conducted as listed in their publication(s).
    - In many cases, information about the specific **department** within the medical institution where the individual author was located at the time the study was conducted is also provided.

Centers of Research

United States

CA - California

Name of Author	Institutional Affiliation
Chung L	Division of Rheumatology and Immunology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA. Pavilion C, Suite 242, Redwood City, CA 94063, USA. 300 Pasteur Drive, Stanford, CA 94305, USA; Division of Rheumatology, VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA. Electronic address: Shauwei@stanford.edu.
Czirjak L	Department of Rheumatology and Immunology, Medical School, University of Pecs, Pecs. Hungary. CA, USA. Pharmacy, Bucharest, Romania. Michigan, Ann Arbor, MI, USA. CA, USA. Pecs.
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Jackson CT	Dermatology Department, University of California Medical Center , San Francisco, California , USA.
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Maibach HI	Dermatology Department, University of California Medical Center , San Francisco, California , USA.
Postolova A	Division of Rheumatology and Immunology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305, USA. Pavilion C, Suite 242, Redwood City, CA 94063, USA. 300 Pasteur Drive, Stanford, CA 94305, USA; Division of Rheumatology, VA Palo Alto Health Care System, 3801 Miranda Avenue, Palo Alto, CA 94304, USA. Electronic address: Shauwei@stanford.edu.
Tashkin DP	Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA. Electronic address: dtashkin@mednet.ucla.edu. Angeles, CA. Angeles, CA. Los Angeles, CA. Angeles, CA.
Volkmann ER	University of California, Los Angeles.

The **Centers of Research** in the complete **Medifocus Guidebook on Scleroderma** includes the following sections:

- Centers of Research for relevant states in the United States
- Centers of Research listed for relevant countries outside the United States

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5 - Tips on Finding and Choosing a Doctor

Introduction

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver a high level and quality of medical care in accordance with currently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it.

The process of finding and choosing a physician to manage your specific illness or condition is, in some respects, analogous to the process of making a decision about whether or not to invest in a particular stock or mutual fund. After all, you wouldn't invest your hard eared money in a stock or mutual fund without first doing exhaustive research about the stock or fund's past performance, current financial status, and projected future earnings. More than likely you would spend a considerable amount of time and energy doing your own research and consulting with your stock broker before making an informed decision about investing. The same general principle applies to the process of finding and choosing a physician. Although the process requires a considerable investment in terms of both time and energy, the potential payoff can be well worth it--after all, what can be more important than your health and well-being?

This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Tips for Finding Physicians

Finding a highly qualified, competent, and compassionate physician to manage your specific illness or condition takes a lot of hard work and energy but is an investment that is well-worth the effort. It is important to keep in mind that you are not looking for just any general physician but rather for a physician who has expertise in the treatment and management of your specific illness or condition. Here are some suggestions for where you can turn to identify and locate physicians who specialize in managing your disorder:

- **Your Doctor** - Your family physician (family medicine or internal medicine specialist) is a good starting point for finding a physician who specializes in your illness. Chances are that your doctor already knows several specialists in your geographic area who specialize in your illness and can recommend several names to you. Your doctor can also provide you with information about their qualifications, training, and hospital affiliations.

The **Tips on Finding and Choosing a Doctor** in the complete **Medifocus Guidebook on Scleroderma** includes additional information that will assist you in locating a highly qualified and competent physician to manage your specific illness.

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6 - Directory of Organizations

American Autoimmune Related Disease Association (AARDA)
22100 Gratiot Avenue; East Detroit, MI 48021-2227
586.776.3900
www.aarda.org

American College of Rheumatology
1800 Century Place Suite 250; Atlanta, GA 30345
404.633.3777
acr@rheumatology.org
www.rheumatology.org

Arthritis Foundation; American Juvenile Arthritis Organization
POB 7669; Atlanta, GA 30309
800.283.7800
arthritisfoundation@arthritis.org
www.arthritis.org

Bay Area Scleroderma Support Group
www.bayareasclero.org

International Scleroderma Network
7455 France Avenue South; #266; Edina, MN 55435
800.564.7099; 952.831.3091
site-inquiries@sclero.org
www.sclero.org

Juvenile Scleroderma Network, Inc.
1204 W. 13th Street; San Pedro, CA 90731
310.519.9511; 866.338.5892
jsdinfo@jsdn.org
www.jsdn.org

The **Directory of Organizations** in the complete **Medifocus Guidebook on Scleroderma** includes a list of selected disease organizations and support groups that are helping people diagnosed with Scleroderma.

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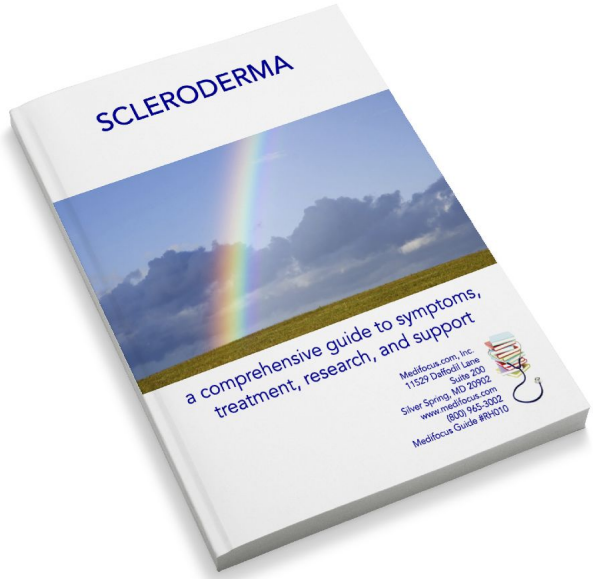

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Scleroderma**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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