INTRODUCTION

Scleroderma is a systemic autoimmune disease of unknown aetiology whose hallmark features include endothelial cell dysfunction, fibroblast proliferation and immune dysregulation. Although virtually any organ can be pathologically involved in scleroderma, lung complications including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading cause of death in patients with this condition. Currently, the molecular mechanisms leading to development of scleroderma-related lung disease are poorly understood. However, the systemic nature of this condition has led to implicate circulating factors in the pathogenesis of some of its organ impairment ***(Avouac et al., 2016).***

ILD is a non-specific term that refers to any chronic inflammatory disease of the lung interstitium. However, in patients with scleroderma, the term ILD often means a more serious condition that is associated with progressive scarring of the lung and carries a poor prognosis. The precise incidence of ILD in patients with scleroderma varies depending on how it is defined, more sensitive measurements such as high resolution CT scanning of the lung suggest that interstitial lung abnormalities are present in most patients with this disease. Fortunately, life-threatening ILD occurs in only one-fifth of individuals with scleroderma. Although immunosuppressive agents have been shown to slow the progression of ILD in some

patients with scleroderma, the overall efficacy of these treatments is quite limited ***(Launay et al., 2011).***

Interstitial lung disease (ILD) is a major cause of morbidity and mortality in patients with systemic sclerosis (SSc). Although a large proportion of systemic sclerosis patients have only limited interstitial involvement with an indolent course, in a significant minority ILD is progressive, requiring prompt treatment and careful monitoring. One of the main challenges for the clinician treating this highly variable disease is the early identification of patients at risk of progressive ILD, while avoiding potentially toxic treatments in those whose disease is inherently stable. Easily available and repeatable biomarkers that allow estimation of the risk of ILD progression and early response to treatment are highly desirable. Peripheral blood biomarkers offer the advantages of being readily obtained, non-invasive and serially monitored ***(Cappelli et al., 2013).***

Remodelling of the extracellular matrix and maintenance of basement membrane integrity involve a balance between the matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs). MMP-7 (matrilysin), a metalloproteinase which targets a broad range of extracellular matrix proteins, was originally found to be highly overexpressed in IPF lungs and subsequently in other interstitial lung diseases ***(Dancer et al., 2011)***.

Among systemic sclerosis patients, higher levels of serum MMP-7 were seen in patients with lung fibrosis compared to those without lung fibrosis, although the association of MMP-7 levels with ILD progression was not evaluated. Notably, patients with lung fibrosis and concomitant pulmonary hypertension had higher mean MMP-7 serum levels compared to those with lung fibrosis alone ***(Moinzadeh et al., 2011).***

AIM OF THE STUDY

The aim of this study is to evaluate the relation between serum level of matrix metalloproteinase -7 (MMP-7) and interstitial lung disease in patients with systemic sclerosis.

Chapter 1

SYSTEMIC SCLEROSIS

Scleroderma or Systemic Sclerosis (SSc), is a chronic multisystem autoimmune disease characterized by vasculopathy, diffuse fibrosis of skin and various internal organs and immune abnormalities. The name scleroderma is derived from the Greek for 'hard skin' and emphasises the dermatological component of the disease. It was described by Hippocrates. There is a localised form of scleroderma, also known as morphoea. The clinical manifestations of this disease are extremely heterogeneous and depend on the presence and degree of various internal organ involvement ***(Goundry et al., 2012).***

Classification:

There are two major forms of scleroderma, localized scleroderma and systemic scleroderma (sclerosis). Diffuse (dcSSc) and limited (lcSSc) scleroderma are the two main types of systemic sclerosis.

A- Localized Scleroderma:

The more common form of the disease, localized scleroderma, only affects the skin without any internal organ involvement. It often appears in the form of waxy patches (morphea) or streaks on the skin (linear scleroderma). It is not uncommon for this less-severe form of scleroderma to regress

or stop progressing without treatment. Localized scleroderma can be disfiguring and sometimes requires systemic therapy to control disease activity ***(Avouac et al., 2011).***

B- Systemic Scleroderma:

Systemic scleroderma always leads to some internal organ involvement. It is further divided into two subsets of disease, limited or diffuse. According to LeRoy and colleagues, limited or diffuse disease is based on the extent of skin tightening. In limited disease (formerly called CREST [*c*alcinosis, *R*aynaud's phenomenon, *e*sophageal dysmotility, *s*clerodactyly, and *t*elangiectasias] syndrome), skin tightening is confined to the fingers, hands and forearms distal to the elbows with or without tightening of skin of the feet and of the legs distal to the knees. Proximal extremities and the trunk are not involved ***(LeRoy et al., 1988)***.

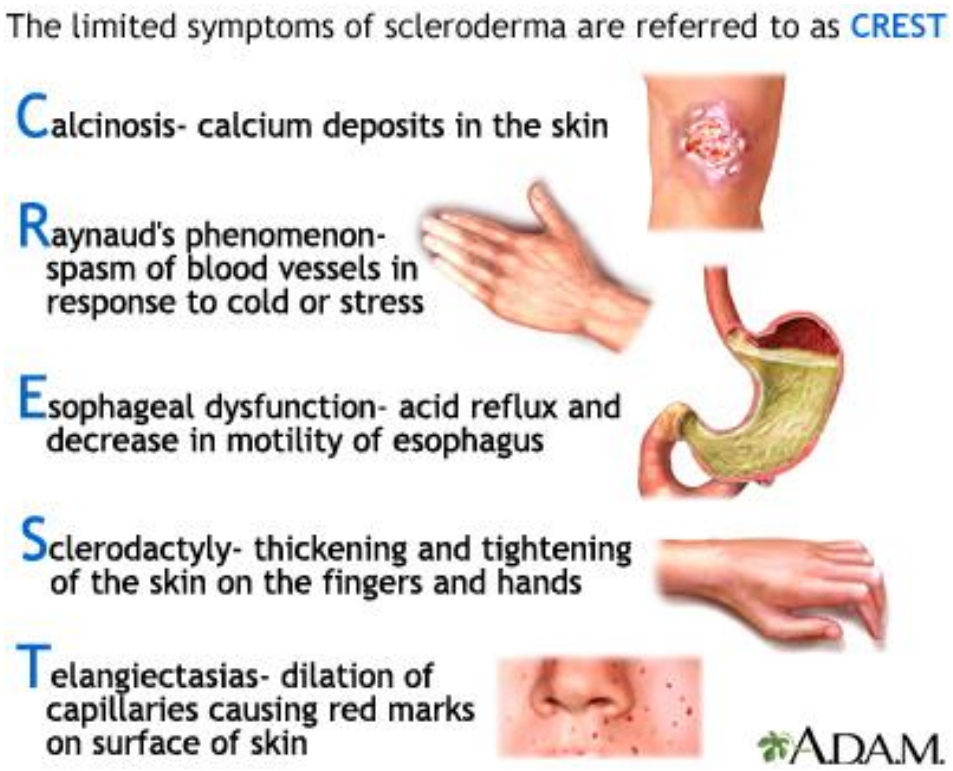

Figure (1): Showing symptoms of limited scleroderma ***(Fransen et al., 2012)***.

In diffuse disease or diffuse cutaneous systemic sclerosis (dcSSc), the skin of the proximal extremities and trunk is also involved. Both dcSSc and lcSSc are associated with internal organ involvement.However, patients with dcSSc are at greater risk for clinically significant major organ dysfunction ***(Fransen et al., 2012)***.

Systemic sclerosis sine scleroderma (ssSSc) is a rare disorder in which patients develop vascular and fibrotic damage to internal organs (phenotypically similar to that in limited scleroderma), in the absence of cutaneous sclerosis **(*Johnson et al., 2012).***

Table (1): Classification of Scleroderma ***(Johnson et al., 2012).***

Localized Scleroderma (Localized cutaneous fibrosis)
▪ Limited or generalized morphea: Circumscribed patches of sclerosis ▪ Linear scleroderma: Linear lesions seen in childhood ▪ En coup de sabre: Linear lesions of the scalp or face
Systemic Scleroderma (Cutaneous and noncutaneous involvement)
▪ Limited cutaneous systemic sclerosis (lcSSc), formerly called CREST syndrome (calcinosis of the digits, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasias) ▪ Diffuse cutaneous systemic sclerosis (dcSSc): Sclerosis of proximal extremities, trunk, and face ▪ Systemic sclerosis sine scleroderma (ssSSc): Organ fibrosis only; no skin thickening

Table (2): Subsets of systemic sclerosis ***(Johnson et al., 2012).***

Diffuse cutaneous systemic sclerosis (dcSSc)
▪ Onset of Raynaud's within 1 year of onset of skin changes (puffy skin) ▪ Truncal and acral skin involvement ▪ Presence of tendon friction rubs ▪ Early and significant incidence of interstitial lung disease, oliguric renal failure, diffuse gastrointestinal disease and myocardial involvement ▪ Absence of anticentromere antibodies ▪ Nail fold capillary dilation and capillary destruction ▪ Anti topoisomerase antibodies (30% of patients)
Limited Cutaneous Systemic Sclerosis (LcSSc)
▪ Raynaud's phenomenon for years (occasionally decades) ▪ Skin involvement limited to hands, face, feet and forearms (acral) ▪ A significant late incidence of pulmonary hypertension, with or without interstitial lung disease, trigeminal neuralgia, skin calcifications and telangiectasia ▪ A high incidence of anticentromere antibodies (70%-80%) ▪ Dilated nailfold capillary loops, usually without capillary dropout

Epidemiology:

Systemic Scleroderma is a rare disorder.Women are roughly four times more likely than men to develop systemic scleroderma. Most patients with systemic scleroderma present in the third or fourth decade of life. Age and gender adjusted mortality rates for patients with dcSSc are approximately five to eight times greater than those of the general population. Survival, which is strongly dependent on the degree of internal organ involvement, has improved over the past few decades due to the advent of newer classes of drugs ***(Steen et al., 2012).***

Pathophysiology and Pathogenesis:

Scleroderma is characterized by immune system activation, endothelial dysfunction and enhanced fibroblast activity. The earliest stage in the development of the scleroderma lesion is endothelial cell activation and vascular damage and the precise inciting events of which are unknown. This is followed by the extravasation of inflammatory cells, which initially are of the monocytic lineage. Later, there is a lymphocyte-predominant infiltrate. Eventually, a population of fibroblasts is activated. The autonomous activated fibroblasts continue to produce the excessive extracellular matrix that underlies the ultimate fibrotic pathology of scleroderma. Within the advanced lesional skin, there is very little visible evidence

of ongoing inflammation suggesting that this is a self-perpetuating fibrotic process ***(Jimenez, 2013).***

The endothelium contributes to the regulation of the contraction and relaxation of vascular smooth muscle cells through the production and release of endothelium-derived vasoactive substances including prostacyclin (prostaglandin I_2), endothelium-derived relaxing factor (EDRF or nitric oxide) and endothelin. The impairment of endothelium-dependent vascular smooth muscle relaxation has been confirmed by the evidence of reduced serum levels of nitric oxide and prostacyclin in scleroderma. This state is probably worsened by increased endothelin levels that contribute to vasospasm and smooth muscle hypertrophy ***(Pattanaik et al., 2011).***

Vascular injury occurs before clinically evident fibrosis. There is an altered functional state of the endothelium characterized by increased permeability, enhanced vasoreactivity, enhanced expression of adhesion molecules, altered balance between hemostatic and fibrinolytic factors, platelet activation and altered vascular wall growth. Most damage occurs at the level of the cutaneous circulation and in the microvasculature of various internal organs. Small arteries and capillaries constrict. Fibroproliferative changes in the vasculature ensue later, eventually leading to obliteration of the vascular lumen resulting in ischemia ***(Luo et al., 2013).***

Endothelin-1 plays an important role in the pathogenesis of scleroderma. Elevated plasma endothelin is seen in scleroderma-associated pulmonary hypertension. During an episode of Raynaud's phenomenon, endothelin release is augmented. Increased endothelin-1 is also found in the bronchoalveolar lavage fluid from scleroderma patients and in prescleroderma skin and early diffuse skin lesions. Scleroderma lung fibroblasts shows elevated endothelin-1 expression and increases in endothelin-1 binding sites ***(Luo et al., 2013).***

There are many other potent mediators of tissue fibrosis that are believed to play an important role in the pathogenesis of scleroderma. One of the key factors that has received the most attention as a very potent profibrotic factor, indirectly implicated very strongly in the pathogenesis of systemic sclerosis, is transforming growth factor (TGF)-β1. A number of studies have shown that TGF-β1 is a potent profibrotic factor in vitro and that TGF-β1 ligand expression is upregulated in the skin and the lungs of scleroderma patients ***(Pattanaik et al., 2011).***

Other key growth factors that have also been implicated in the pathogenesis are connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), the beta chemokines monocyte chemoattractant protein (MCP)-1 and MCP-3. There may be a sequential interplay between these growth factors as the disease develops ***(Mayes et al., 2014).***

Chemokine expression is an early feature of skin sclerosis and fibroblasts are producers of these chemokines. Data suggest that PDGF receptor and ligand expression and tumor necrosis factor (TNF)-α expression also occur. All of these factors are considered to be important early in the pathogenesis of scleroderma. Connective tissue growth factor was originally speculated to be an important downstream mediator of TGF-β1, but now it seems more likely to be a cofactor in TGF-β1–mediated activation of fibroblasts ***(Mayes et al., 2014).***

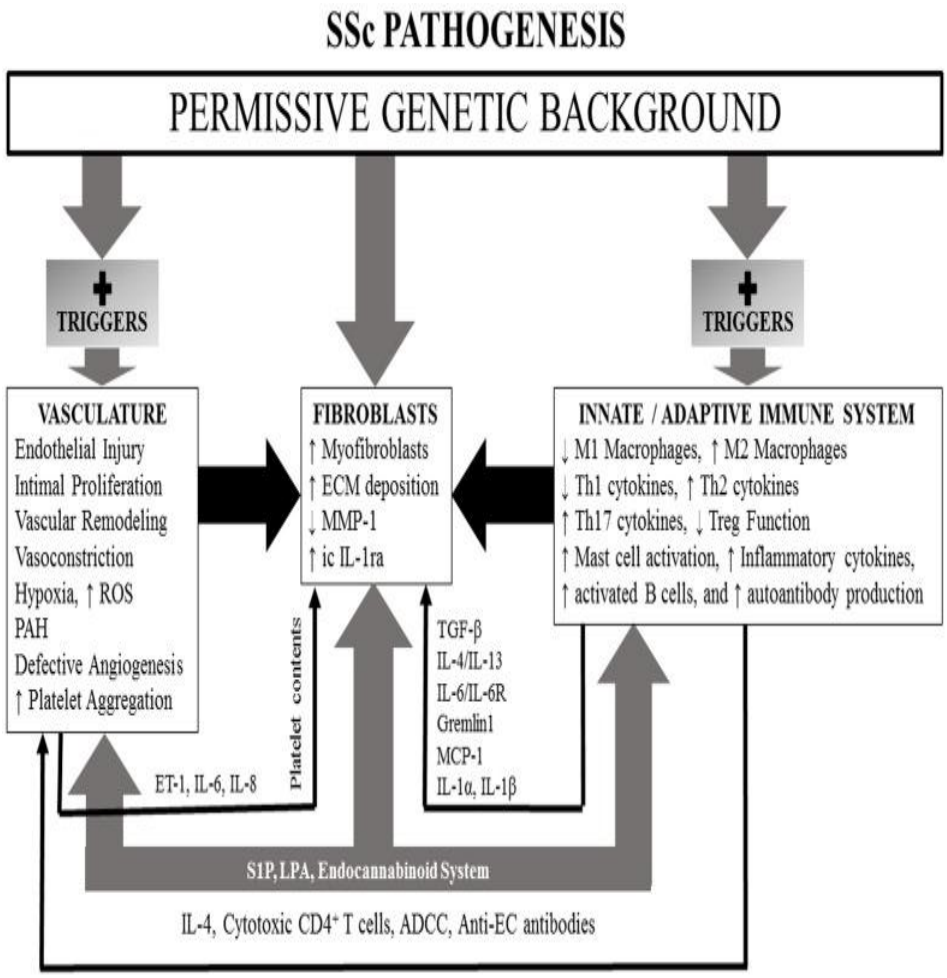

Figure (2): Showing pathogenesis and fibrotic process in systemic sclerosis ***(Jimenez, 2013).***

Clinical manifestations:

Clinical manifestations of systemic sclerosis are heterogeneous and vary as a result of type of disease (limited or diffuse) and organ involvement. Patients with diffuse disease (dcSSc) are at risk of developing rapidly progressive skin fibrosis and widespread severe internal organ involvement. Patients with lcSSc have a disease course characterized by

slowly progressive skin changes not extending beyond the elbows and knees into the proximal extremities or trunk along with varying degrees of internal organ involvement ***(Johnson et al., 2012).***

Table (3): Clinical manifestations of systemic sclerosis ***(Johnson et al., 2012).***

Cutaneous
▪ Diffuse edema of hands and feet (early stages) ▪ Progressive skin tightening ▪ Sclerodactyly ▪ Calcinosis ▪ Telangiectasias ▪ Digital ulcers and pits ▪ Contractures ▪ Hyperpigmentation, hypopigmentation, salt and pepper skin ▪ Characteristic facies
Vascular
▪ Raynaud's phenomenon ▪ Nail fold capillary changes ▪ Digital ischemia and ulcers ▪ Vasculitic leg ulcers (rare)
Pulmonary
▪ Interstitial lung disease, including alveolitis and interstitial fibrosis ▪ Pulmonary hypertension ▪ Recurrent aspiration pneumonitis caused by esophageal reflux and dysmotility ▪ Chest wall restriction (decreased thoracic compliance) ▪ Respiratory muscle weakness
Cardiac
▪ Cardiomyopathy (systolic and diastolic dysfunction): Congestive heart failure ▪ Conduction defects

○ Septal infarction pattern ○ Ventricular conduction abnormalities ○ Arrhythmias ○ Heart blocks ▪ Pericarditis or pericardial effusion (impending renal crisis)
Renal
▪ Scleroderma renal crisis (hypertension, renal failure and microangiopathic hemolytic anemia)
Musculoskeletal
▪ Arthralgia ▪ Tendon friction rubs (relatively specific for diffuse scleroderma) ▪ Inflammatory arthritis, erosive arthropathy (rare) ▪ Myopathy, myositis
Gastrointestinal
▪ Gastroesophageal reflux ▪ Esophageal dysmotility, aperistaltic esophagus ▪ Adenocarcinoma arising in Barrett's esophagus (occasionally) ▪ Watermelon stomach (gastric antral vascular ectasias (GAVE)) ▪ Decreased peristalsis throughout the GI tract leading to bloating, early satiety, stasis and pseudo-obstruction ▪ Bacterial overgrowth and malabsorptive diarrhea, alternating diarrhea and constipation ▪ Megacolon (rare)
Endocrine
▪ Hypothyroidism
Neurologic
▪ Carpal tunnel syndrome ▪ Trigeminal neuralgia