INTRODUCTION

Systemic sclerosis (SSC) is a rare multisystemic connective tissue disease characterised by microvascular damage, fibrosis of the skin and internal organs and specific immunologic abnormalities. The clinical recognisable disease is classified on the basis of extent of skin involvement into subsets with diffuse cutaneous involvement (DCSSC) and limited cutaneous involvement (LCSSC) ***(Smith et al., 2012).***

Systemic sclerosis (scleroderma, SSC) is an autoimmune disease in which fibrosis of the skin and internal organs occurs in association with small vessel vasculopathy and autoantibody production. Organ-specific and non-organ specific impairments lead to a spectrum of mild to severe limitations in physical, work and social activities, ultimately influencing health-related quality of life ***(Assassi et al., 2011).***

The extent of skin involvement is the major criterion in currently existing classification systems and subset classification for SSC. Skin thickening is a universal feature of SSc. At least in the DCSSC subset, more extensive skin involvement coincides with more severe internal organ manifestation(s), poor prognosis and increased disability. Skin thickness is caused by increased collagen, intercellular matrix formation in the dermis and by oedema probably caused by both microvascular injury and perhaps inflammation. Because of the accumulation of collagen and fluid, the skin becomes

thickened, making it impossible to pinch it into a normal skin fold ***(Czirja'k et al., 2008)***.

Over the past years, there have been several studies regarding the incidence and prevalence of SSC. The reported studies continue to show variation by geographic region. Incidence rates and prevalence estimates are fairly similar for Europe, the United States, Australia, and Argentina suggesting a prevalence of 150-300 cases per million with a lower prevalence noted in Scandinavia, Japan, the UK, Taiwan and India ***(Barnes and Mayes, 2012).***

As with many other autoimmune disorders, scleroderma is approximately 4–5 times more common in women than men. The average age at the time of diagnosis is approximately 50 years ***(Hummers and Wigley, 2013).***

AIM OF THE WORK

The aim of this study was to estimate the frequency of epidemiological, clinical and laboratory characteristics of progressive systemic sclerosis (PSS) in a cohort of patients from Egypt to elicit any difference from that of other ethnic group.

REVIEW OF LITERATURE

Systemic sclerosis

Introduction:

Systemic sclerosis is an autoimmune disease that is characterized by the distinctive pathogenetic triad of microvascular damage, dysregulation of innate and adaptive immunity, and generalized fibrosis in multiple organs. Although skin fibrosis is the distinguishing hallmark, the pathological changes in the lungs, gastro-intestinal tract, kidneys and heart determine the clinical outcome. In general, the extent of skin involvement and its rate of progression reflect the severity of visceral organ complications ***(Nihtyanova et al., 2014 and Domsic et al., 2011).***

A striking feature of systemic sclerosis is its patient-to-patient variability, and heterogeneity has been observed in clinical manifestations, autoantibody profiles, tempo of disease progression, response to treatment and survival. On the basis of the extent of their skin involvement, patients are grouped into limited cutaneous systemic sclerosis (LCSSC) and diffuse cutaneous systemic sclerosis (DCSSC) subsets ***(Allanore et al., 2015)***.

In LCSSC, skin fibrosis is restricted to the fingers (sclerodactly), distal extremities and face, whereas in DCSSC, the trunk and proximal extremities are also affected. In patients

with LCSSC, Raynaud phenomenon typically precedes skin involvement and other disease manifestations by months to years, whereas patients with DCSSC have rapid disease progression with extensive skin changes and early development of visceral organ complications ***(LeRoy et al., 1988).***

Autoantibodies are particularly helpful in systemic sclerosis for both diagnosis and classification. LCSSC is commonly associated with centromere-specific antibodies, whereas DCSSC is more often associated with topoisomerase I- or RNA polymerase III-specific antibodies ***(Steen, 2005).***

However, not all patients with systemic sclerosis fall clearly into one of these two disease subsets, and some can change their subset assignment over time. Furthermore, some individuals present with hallmark clinical and serological features of systemic sclerosis in the absence of detectable skin involvement (systemic sclerosis sine scleroderma); others manifest features of another connective tissue disease, such as rheumatoid arthritis or polymyositis, in overlap with systemic sclerosis (overlap syndrome) ***(Allanore et al., 2015)***.

Epidemiology and pathogenesis:

Epidemiology:

The extent of systemic sclerosis around the world varies substantially. Lower estimates of prevalence (<150 per million) and incidence (<10 per million per year) have been observed in

northern Europe and Japan, whereas higher estimates of prevalence (276–443 per million) and incidence (14–21 per million per year) have been reported in southern Europe, North America and Australia ***(Barnes and Mayes, 2012).***

Age at onset of the disease varied according to gender and ethnic background. SSC (systemic sclerosis) is rare in childhood and increases in incidence to reach a peak in the fifth decade. Most studies indicated that SSC occurs more frequently in women than in men (as for most autoimmune rheumatic diseases) with an earlier age at onset for women ***(Chifflot et al., 2008)***.

The 2013 ACR–EULAR classification criteria are more sensitive than the criteria published in the 1980s because they include patients who are positive for centromere-specific antibodies and who have limited cutaneous involvement. As a consequence, the estimated prevalence of systemic sclerosis based on the ACR–EULAR classification criteria (for example, 88 per million in men, 514 per million in women and overall 305 per million in Sweden) was much higher than previously published estimates ***(Andréasson et al., 2014).***

The development of systemic sclerosis is sex dependent and, as is true for all connective tissue diseases, is much more common in women (Fig. 1). However, the EULAR Scleroderma Trials and Research (EUSTAR) cohort has revealed some unusual features in men. In a cross-sectional

study of 9,182 patients with systemic sclerosis, including 1,321 men, male sex was independently associated with a higher risk of DCSSC (odds ratio (OR) 1.68; 95% CI 1.45–1.94; P < 0.001), a higher frequency of digital ulcers (OR 1.28; 95% CI 1.11–1.47; P < 0.001) and pulmonary arterial hypertension (PAH; OR 3.01; 95% CI 1.47–6.20; P < 0.003). In a longitudinal study (mean follow-up 4.9 ± 2.7 years), male sex was predictive of new onset of PAH (hazard ratio (HR) 2.70; 95% CI 1.38–5.29; P = 0.004), heart failure (HR 2.15; 95% CI 1.03–4.48; P = 0.04) and all-cause mortality (HR 1.48; 95% CI 1.19–1.84; P < 0.001). Male sex has been consistently shown to be a poor prognostic factor in systemic sclerosis ***(Elhai et al., 2014).***

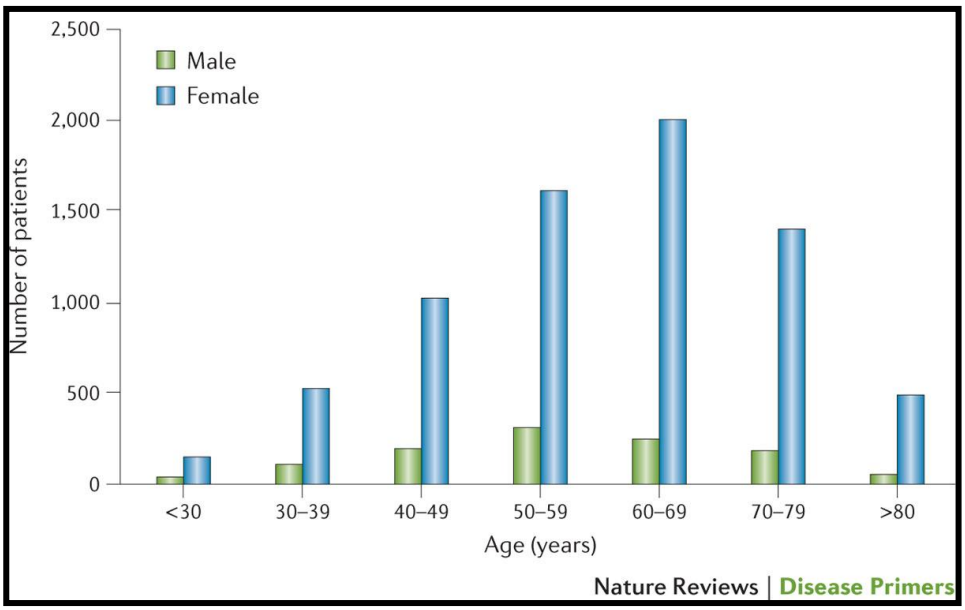

Figure (1): Characteristics of the EUSTAR cohort.

As in other connective tissue disorders such as systemic lupus erythematosus, ethnicity has a role in systemic sclerosis. A large US study showed that African American patients presented at a younger mean age than white patients (47 years versus 53 years; P <0.001). Furthermore, two-thirds of white patients exhibited LCSSC, whereas the majority of black patients had DCSSC (P < 0.001). The race differential was mirrored by the finding that African Americans with systemic sclerosis were more likely to have antibodies against topoisomerase I and less likely to be positive for centromere-specific anti-bodies. In addition, African American patients experienced an increase in risk of mortality (relative risk (RR) 1.8; 95% CI 1.4–2.2) after adjustment for age at disease onset and disease duration. Thus, race is related to a distinct phenotypic profile, and there is a trend towards less favorable outcomes in African American patients ***(Gelber et al., 2013).***

The overlap between systemic sclerosis and other connective tissue disorders has been recognized for some time. The links between connective tissue diseases are further supported by the results from genome-wide association studies (GWASs) that highlight the critical role of shared autoimmunity. The co-occurrence of another autoimmune disease with systemic sclerosis was investigated in a meta-analysis of 6,102 patients with systemic sclerosis obtained from 10 studies. Of these patients, 1,432 had one or more additional auto-immune disease corresponding to a weighted prevalence

of poly-autoimmunity of 26% (20–32%). Thus, these results confirm that poly-autoimmunity is frequent in systemic sclerosis. It remains to be determined how this finding might affect the outcomes and how it could be used to guide the choice of treatments and also the positioning of potential biologic agents ***(Elhai et al., 2013).***

Cigarette smoking is well known to contribute to cardiovascular disease in the general population. In addition, it has also been associated with lower esophageal sphincter dysfunction and gastro-esophageal reflux disease, as well as chronic obstructive lung disease ***(Nilsson et al., 2004).***

Festi and colleagues reviewed the evidence concerning the association between smoking and gastroesophageal reflux disease (GERD). They found numerous studies and compelling evidence that smoking significantly increased the risk of GERD in the general population ***(Festi et al., 2009).***

There is an evidence that smoking has a deleterious effect on SSC, and that these effects can be long-lasting (e.g., respiratory outcomes), but also that smoking cessation could be beneficial with respect to several other outcomes (e.g., reduced severity of Raynaud's phenomenon) ***(Hudson et al., 2011).***

Cigarette smoking was not found to increase the risk of developing SSC but appears to contribute to disease severity. It is likely that there is an increased risk of cancer among SSC

patients, but reports vary about the magnitude of this risk and the type of malignancy. Exposure to silica dust appears to be an environmental trigger, but this only accounts for a small proportion of male cases ***(Barnes and Mayes, 2012).***

Mechanisms/pathophysiology:

Systemic sclerosis is thought to be caused by environmental events in a genetically susceptible individual that trigger a chronic and self-amplifying multifocal process characterized by vascular alterations, inflammation and autoimmunity, and fibrosis ***(Katsumoto et al., 2011)*** (Fig. 2).

Cell types prominently implicated in the disease process include endothelial cells, platelets, structural cells (pericytes, vascular smooth muscle cells, fibroblasts and myofibroblasts) and immune cells (T cells, B cells, monocytes, macrophages and dendritic cells). Prominent mediators of cell activation include transforming growth factor-β (TGFβ), platelet-derived growth factor (PDGF), IL-6 and IL-13, endothelin 1, angiotensin II, lipid mediators and autoantibodies, along with reactive oxygen species (ROS) and numerous other biologically active substances ***(Bhattacharyya et al., 2012)***.

Still poorly understood is the pathogenetic basis for female predominance, the disease heterogeneity and variable outcomes, the nature of environmental triggers and their interplay with the genetic background, and the precise

contribution of these interactions to disease susceptibility and phenotype ***(Allanore et al., 2015)***.

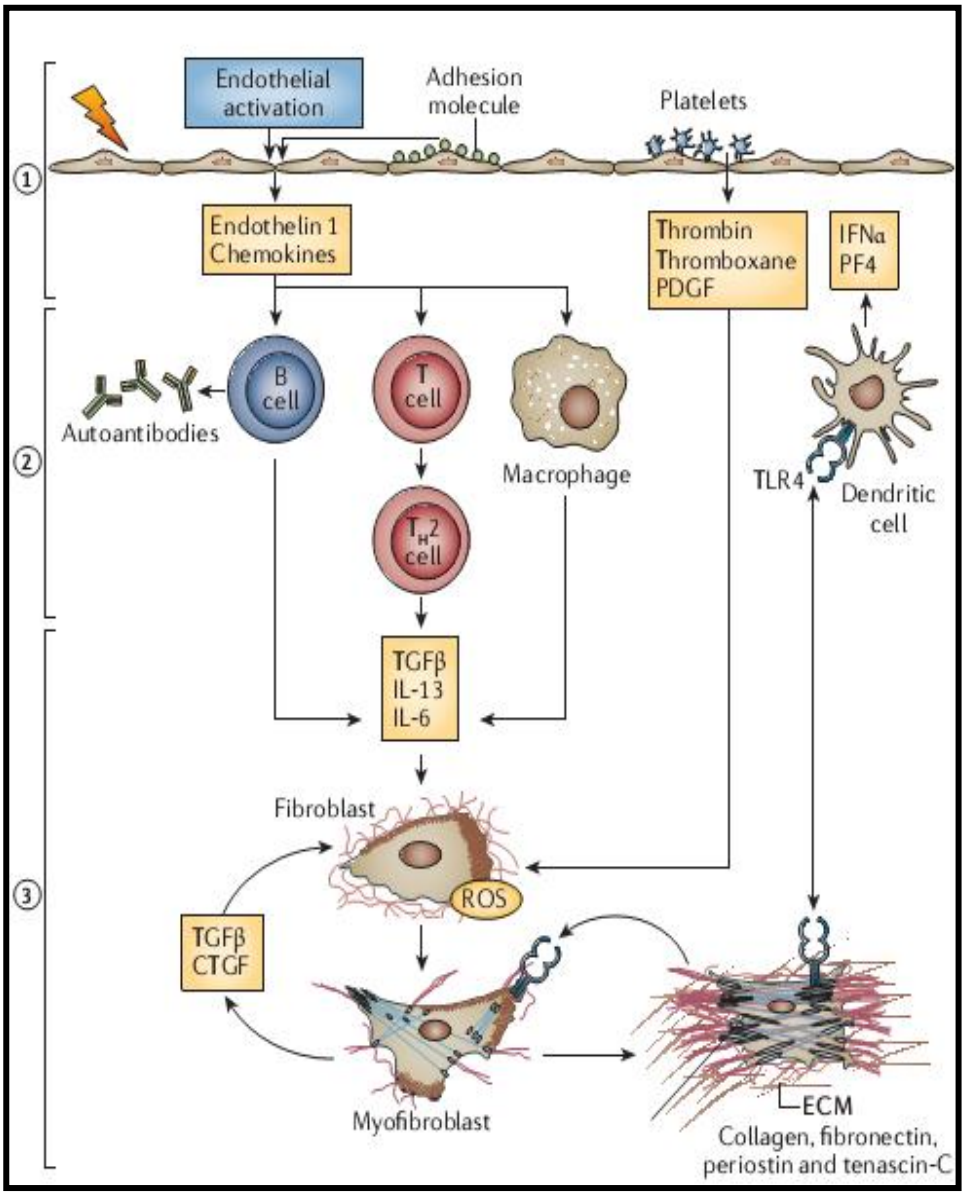

Figure (2): The disease process in systemic sclerosis.

Vascular injury and microangiopathy:

Microvascular injury and endothelial cell activation that results in vascular damage are the earliest, and possibly primary, events in systemic sclerosis. Progressive vascular damage causes a reduction in the number of capillaries (rarefaction), thickening of the vessel wall due to intimal and smooth muscle cell proliferation, and luminal narrowing, which lead to tissue hypoxia and oxidative stress ***(Trojanowska, 2010).***

In addition, activated endothelial cells show increased expression of the adhesion molecules vascular cell adhesion protein 1 (VCAM1), intercellular adhesion molecule (ICAM) and E-selectin, resulting in recruitment of inflammatory cells. They also secrete endothelin 1, connective tissue growth factor (CTGF; also known as CCN2) and other profibrotic factors that stimulate vascular smooth muscle cell proliferation and extracellular matrix production. Inflammatory cell infiltration in the lesions can be prominent in patients with early-stage disease, and inflammatory and immune cells are an important source of TGFβ, PDGF, IL-1, IL-6 and other profibrotic mediators ***(Allanore et al., 2015)*** (Fig. 2).

Inflammation and immune response:

Dysregulation of both innate and adaptive immunity plays a prominent part in systemic sclerosis. Evidence of

autoimmunity includes the presence of inflammatory cells and inflammatory signatures in target tissues such as the skin and lungs; alterations in the number and function of circulating immune cells; the presence of a prominent type I interferon (IFN) signature in circulating and tissue-infiltrating immune cells; and characteristic and distinct serum autoantibodies detected in most patients. Furthermore, genetic studies identified that polymorphisms of IRF5 (interferon regulatory factor 5) and STAT4 (signal transducer and activator of transcription 4), along with several other immune pathway genes, are prominently associated with systemic sclerosis ***(Mayes et al., 2014)***.

Cellular response: Circulating and tissue-infiltrating monocytes and macrophages, plasmacytoid dendritic cells and stromal cells show a type I IFN signature, defined by increased expression of IFN-regulated genes, which reflects activation of Toll-like receptor (TLR)-mediated immune signalling ***(Assassi et al., 2010).***

TLR activation in these cells is thought to be triggered by endogenous ligands, such as nucleic acid-containing immune complexes, as well as by damage-associated molecular patterns (DAMPs), such as variants of extracellular matrix components generated during tissue injury. Fibrotic tissue also displays prominent infiltration of bone marrow-derived immune cells that include CD4+T cells, macrophages, activated B cells, plasma-cytoid dendritic cells and mast cells. Among CD4+T cells,

type 2 T helper (TH2) cells —characterized by secretion of IL-4 and IL-13 predominate over TH1 cells, which primarily secrete anti-fibrotic IFNγ ***(Chizzolini et al., 2006).***

The role of TH17 cells remains to be defined, with some studies implicating IL-17 in fibrosis and other studies indicating an anti-fibrotic effect ***(Brembilla et al., 2013).***

Finally, emerging evidence suggests an important pathogenetic role of tissue macrophages with an 'alternatively activated' M2 phenotype. Levels of soluble CD163, a marker for M2 macrophages, are elevated in the sera of patients with systemic sclerosis, as well as on macrophages in the affected skin and lungs ***(Christmann et al., 2014 and Mathes et al., 2014).***

Cytokines and chemokines: TH2 cytokines, including IL-4 and IL-13, have prominent roles in the pathogenesis of systemic sclerosis. The levels of TH2 cytokines are increased in the serum and fibrotic tissue, and they stimulate fibroblast proliferation and extracellular matrix synthesis in cell cultures ***(O'Reilly et al., 2012).***

These findings are supported by studies in animal models, as illustrated by the attenuation of fibrosis in mice with the genetic deletion of IL13, whereas targeted over-expression of IL13 results in pulmonary fibrosis ***(O'Reilly, 2013).***

Of special interest in systemic sclerosis is IL-6, a multifunctional cytokine produced by T cells and B cells,

fibroblasts, fibrocytes and endothelial cells. IL-6 signals through the widely expressed GP130 receptor that forms a heterodimer with IL-6 receptor subunit-α, which activates the JAK/STAT and mitogen-activated protein kinase (MAPK) pathways and induces TH2-dominant immunity, inflammation and fibrotic responses. High levels of IL-6 in systemic sclerosis correlate with the extent of skin involvement and portend poor long-term outcomes ***(Khan et al., 2012)***.

In vitro, an antibody against human IL-6 reduced type I collagen levels in fibroblasts derived from patients with systemic sclerosis, whereas mice with the genetic deletion of Il-6 had reduced inflammation and fibrosis after a profibrotic challenge (bleomycin). Moreover, administration of an IL-6 receptor-specific antibody in mice prevented development of fibrosis induced either by bleomycin or by immunization with topoisomerase I ***(Kitaba et al., 2012 and Yoshizaki et al., 2011).***

These observations provide the rationale for the clinical trials of IL-6 receptor-specific antibody (tocilizumab) in systemic sclerosis. Chemokines have important roles in angiogenesis, wound healing and fibrosis. Serum and tissue levels of C-C motif chemokine 2 (CCL2; also known as MCP1), CCL3 (also known as MIP1α), IL-8 and CCL18 are increased in patients with systemic sclerosis, correlate with disease severity and can predict progression ***(Hasegawa et al., 2013).***