INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by different degrees of skin fibrosis and visceral organ involvement. The etiology of SSc remains obscure; the disease appears to be the result of a multistep and multifactorial process, including immune system alterations, under the influence of genetic and exogenous (toxic or infectious) factors ***(Giuggioli et al., 2018).***

Vitamin D have been the focus of a growing number of studies in past years, demonstrating their function not only in calcium metabolism and bone formation, but also their interaction with the immune system since vitamin D receptors expressed in different tissues. Numerous studies have been conducted to study whether vitamin D is associated with SSc; however, they produced varying results ***(Dankers et al., 2017)***

Vitamin D deficiency identified to be frequent in SSc patients and associated with disease activity or phenotype characteristics such as pulmonary hypertension, lung involvement, and extensive cutaneous forms ***(Laura et al., 2016).***

Vitamin D deficiency may change the balance of cartilage metabolism via reducing the synthesis of proteoglycan and/or increasing the metalloproteinase activity, leading to cartilage loss ***(Malas et al., 2013).***

Patients with SSc had thinner femoral cartilage. The underlying possible mechanisms of thin FCT may be multifactorial, and there may be many influencing factors like immune activation, vasculopathy, oxidative stress and synovial fibrosis or markers of cartilage degradation. The possible factors influencing the change in cartilage thickness or metabolism in patients with SSc require further research ***(Gamze et al., 2014)***.

AIM OF THE WORK

To study levels of vitamin D in relation to the femoral cartilage thickness (FCT) in patients with SSc and to analyze the associations between the (FCT), vitamin D levels, SSc- disease severity score.

Chapter 1

SYSTEMIC SCLEROSIS

Scleroderma or systemic sclerosis (SSc) is an autoimmune disorder of unknown aetiology, characterised by fibrosis and microvascular injury in affected organs. The hallmark of the disease is thickening and tightness of the skin and of subcutaneous tissue ***(Pelechas et al., 2019)***.

Hippocrates was the first to describe the illness as "thickened skin". The first detailed description of the disease was by an Italian doctor named Carlo Curzio in the mid 1700s, but the term "scleroderma" was first coined by Giovambattista Fantonetti in 1836 ***(Pelechas et al., 2019)***.

1) Epidemiology:

SSc is present throughout the world and is represented in all ethnic groups. Incidence and prevalence figures vary widely and there appears to be a large geographical variation.Around the world, prevalence is reported to vary from 30-240 per million) as It seems to be more common in North America and Australia than in Europe ***(Denton et al., 2016)***.

SSc represents 5.8% of patients with rheumatologic diseases in Egypt ***(Goma et al., 2016)***.

The risk of systemic sclerosis is 4-9 times higher in women than in men. However, the mechanisms responsible for the disproportionately higher frequency in females have not been elucidated ***(Barnes and Mayes, 2012)***.

The peak age of onset is 40-50 years but it can affect any age group. It is rare in children ***(Ranque and Mouthon, 2010)***.

2) Etiology and Risk Factors:

The exact etiology of systemic sclerosis is unknown. Systemic sclerosis is not inherited, although a genetic predisposition plays an important role in its development. Environmental factors (e.g, triggers or accelerators) may contribute to the development of systemic sclerosis in the proper genetic background ***(Rubio et al., 2017)***.

The strongest genetic association for SSc lies within the MHC region, with loci in *HLA-DRB1*, *HLA-DQB1*, HLA-DPB1, and *HLA-DOA1* being the most replicated. The non-HLA genes associated with SSc are involved in various functions, with the most robust associations including genes for B and T cell activation and innate immunity ***(Tsou and Sawalha, 2017)***.

- **Possible risk factors which have been implicated include:**

1. Infectious agents. Various agents, including *Helicobacter pylori*, hepatitis B virus, Epstein - Barr virus, *Toxoplasma gondii* and chlamydia have been implicated as possible triggers.

2. Chemicals (such as polyvinyl trichloroethylene, some pesticides, organic solvents, hair dyes and silica).
3. Drugs (such as cocaine, pentazocine, bleomycin, penicillamine and vitamin K).
4. Radiation therapy.
5. Physical trauma.
6. Vitamin D deficiency. There is a strong association and many people with SSc have documented vitamin D deficiency. ***(Pattanik et al., 2015)***

Case reports describe the development of scleroderma in patients treated with the immune checkpoint inhibitor pembrolizumab for metastatic melanoma ***(Barbosa et al., 2017)***.

3) Pathogenesis:

The clinical and pathologic manifestations of the disease are the result of three distinct processes:

1) Innate and adaptive immune system abnormalities leading to production of autoantibodies and cell-mediated autoimmunity.
2) Microvascular endothelial cells (MVEC) and fibroproliferative vasculopathy of small vessels.
3) Fibroblast dysfunction leading to excessive collagen (CI) and other matrix components accumulation in skin, blood vessels, and internal organs ***(Jimenez, 2013)***.

All three of these processes interact and affect each other. The disease is heterogeneous in its clinical presentation that likely reflects different genetic or triggering factor (i.e., infection or environmental toxin) influences on the immune system, vasculature, and connective tissue cells ***(Pattanaik et al., 2015)***.

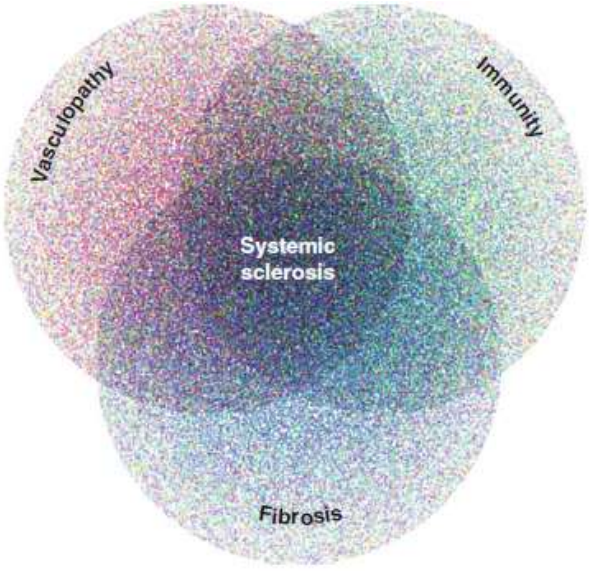

Fig. (1): The triad of pathogenesis of SSc. Adapted from ***(Varga and Hinchcliff, 2014).***

4) Types of systemic sclerosis:

SSc is classified according to the extent of skin involvement. Classification is important as early management will depend upon which type is diagnosed.

1. **Limited cutaneous systemic sclerosis (lcSSc), or limited scleroderma**

- Areas of skin affected include only the face, forearms and lower legs up to the knee.
- The older term for limited scleroderma is CREST syndrome (**C**alcinosis, **R**aynaud's disease, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasia).

2. **Diffuse cutaneous systemic sclerosis (dcSSc), or diffuse scleroderma**

- Skin areas involved include also the upper arms, thighs or trunk.
- Severe internal organ fibrosis, and aggressive course with a poor prognosis.
- Prevalence of lung fibrosis, renal crisis, and cardiac complications is high in this subset of the disease.

3. **Systemic sclerosis sine scleroderma**, in which there is internal organ involvement without the skin changes.

(Denton et al., 2016)

4. Other types:

- Paraneoplastic scleroderma: Scleroderma associated with neoplasia is rare, with only a small number of cases reported ***(Jedlickova et al., 2015)***.

- Scleroderma mimickers: there are patients who present with features considered to be typical of scleroderma, such as Raynaud's and skin thickening, and who may have a syndrome mimicking scleroderma as nephrogenic systemic fibrosis, scleredema, scleromyxedema and eosinophilic faciitis ***(Hummers and Tyndall, 2016)***.

- Overlap SSc is thought to account for up to 20% of cases ***(Denton et al., 2016)***.

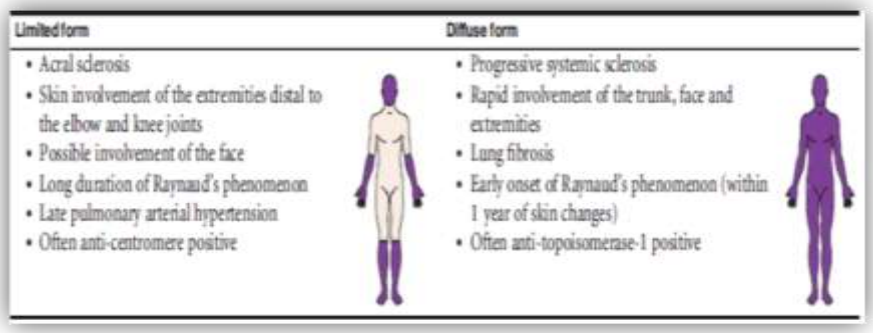

Fig. (2): Subclassification of scleroderma. Adapted from ***(Knobler et al., 2017).***

5) Clinical Features:

In general common presenting symptoms are Raynaud's phenomenon (which may precede other symptoms by some years), skin hardening in hands or face and oesophageal symptoms. Both limited and diffuse scleroderma can involve internal organs; the severity of skin changes does not necessarily reflect the severity of internal organ involvement ***(Van Den Hoogen et al., 2013)***.

1. Skin Manifestations:

Skin involvement is the earliest, most frequent and characteristic manifestation of SSc. The 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc, assign the highest scores to skin involvement ***(Van Den Hoogen et al., 2013)***.

Raynaud's phenomenon (RP), and cutaneous sclerosis are almost constant in SSc, affecting respectively 95 and 75%of SSc patients ***(Jaeger et al., 2016)***.

Other cutaneous signs include nailfold and fingernail alterations (80%), cutaneous ulcerations (40%), telangiectasia (75%), hyperpigmentation of thickened skin (30%), and cutaneous calcifications affecting soft tissues, fingers, forearms, elbows and knees (25%). Less frequently, patients may present achromicmaculae or patches ***(Desbois and Cacoub, 2016)***.

The extension and degree of sclerosis is quantified using the modified Rodnan skin score (mRSS) ***(Brennan et al., 1992)***, which remains the most widespread method, both in clinical practice and in research settings ***(Barsotti et al., 2015)***.

At an early stage, cutaneous and soft tissue sclerosis affects the face. Facial skin hardens, mimic folds disappear, lips become thinner and the nose sharper, and facial hair falls (Fig. 3) ***(Salem et al., 2013)***.

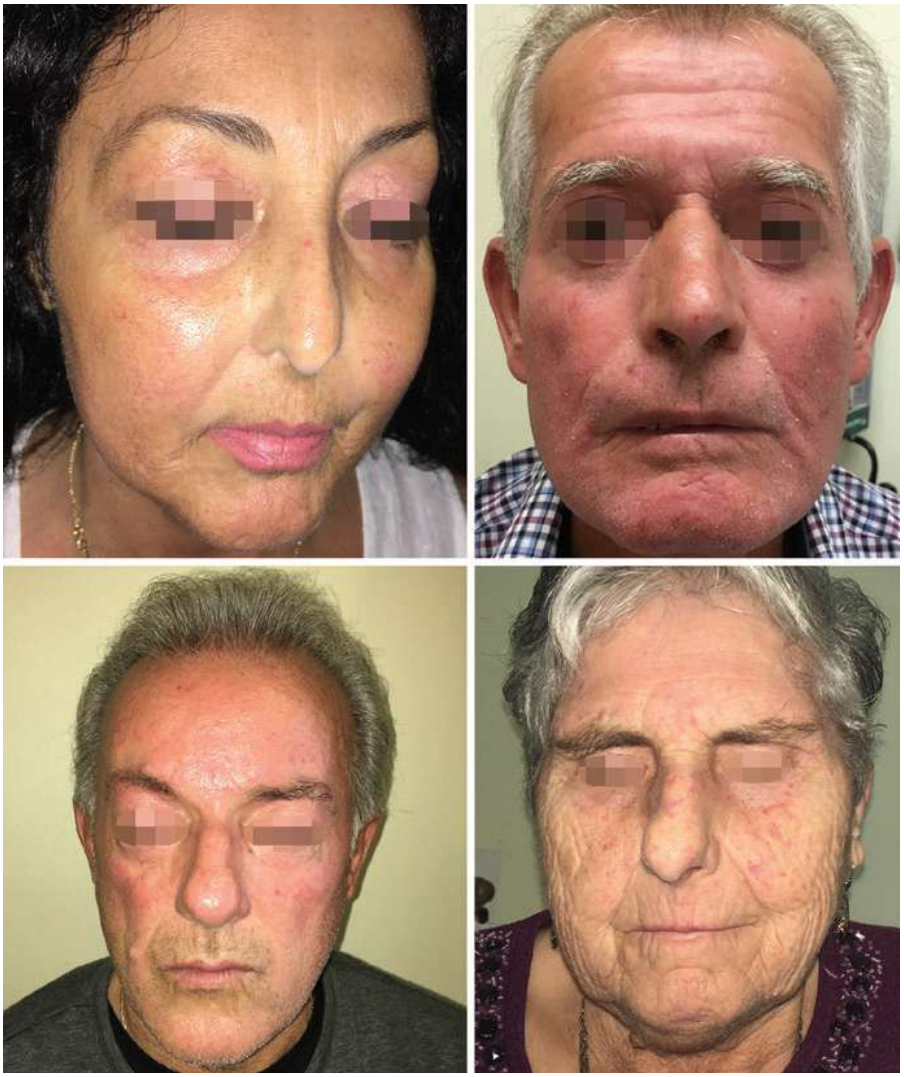

Fig. (3): Early manifestations of sclerodema facies, microstomia and fissures radiating from the mouth with a few telangiectasias on the face. Adapted from ***(Pelechas et al., 2019).***

Microstomia, namely reduction of mouth opening, due to sclerosis of perioral soft tissue is the main oral manifestation of SSc, occurring in 52–80% of the SSc (Fig. 5) ***(Bajraktari et al., 2015)***.

It may impair social relationships, mastication, mandibular movements, and proper oral hygiene. Consequently, it may determine a higher incidence of oral diseases such as dental caries, periodontal diseases, or other types of oral infections ***(Silvestre-Rangil et al., 2015)***.

Recently, fingernail changes, comprising thickened nails, parrot beaking, brachyonychia, hyponychium hyperkeratosis, pterygium inversum unguis, splinter hemorrhage, and thickened/enlarged cuticles were reported to be associated with ulcers in SSc ***(Marie et al., 2016)***.

Various cutaneous pigmentary alterations have been described in SSc, including a diffuse, generalized hyperpigmentation with accentuation in sun-exposed areas, a vitiligo like depigmentation with perifollicular hyperpigmentation, and a combined hyper- and hypopigmentation in the areas of sclerosis ***(Vachiramon, 2011)***.

The most characteristic skin pigmentation change is a diffuse hyperpigmentation with sparing of the perifollicular areas, with a "salt-and-pepper" appearance (Fig. 6) ***(Ee and Tan, 2005)***.

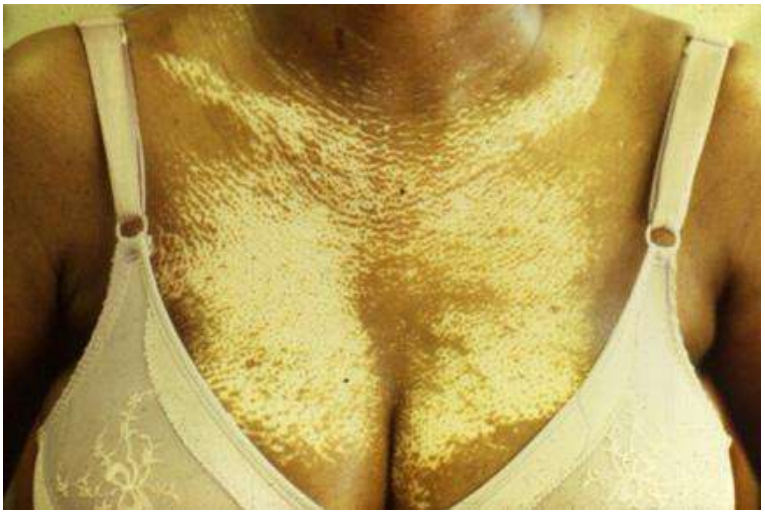

Fig. (4): Anterior chest demonstrating salt-and-pepper hypopigmentation and diffuse hyperpigmentation in a white woman. Adapted from ***(Abignano and Del Galdo, 2014).***

Calcinosis cutis is a disorder characterized by calcium deposition in the skin and subcutaneous tissues (Fig.5) ***(Chander and Gordon, 2012)***.

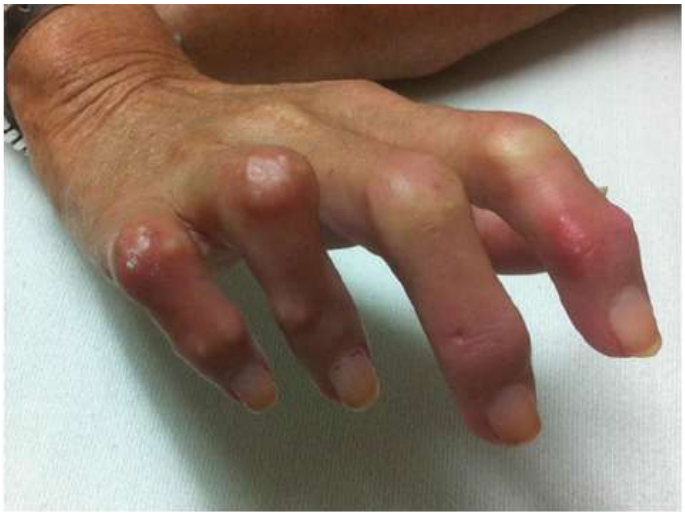

Fig. (5): Calcinosis of the fingers. Adapted from ***(Chander and Gordon, 2012)***.

It is associated with autoimmune connective tissue diseases (ACTDs) including "systemic sclerosis (SSc), dermatomyositis (DM), mixed connective tissue diseases (MCTDs), and, more rarely, systemic lupus erythematosus (SLE)" ***(Gutierrez and Wetter, 2012)***.

Calcinosis is not uncommon in SSc, especially in the limited cutaneous SSc (lcSSc) subtype. Calcinosis is known to be a long-term complication in SSc and presents after a mean disease duration from the first non-Raynaud's symptom of 9–13 years ***(Valenzuela et al., 2013)***.

2. Vascular manifestations:

Raynaud phenomenon results in characteristic color changes of pallor, cyanosis, and then erythema (white, blue, red) in the fingers (Fig.6), toes and other acral body parts, and is usually accompanied by numbness, tingling, or pain. These events are triggered by cold exposure, smoking, or emotional stress ***(Prete et al., 2014)***.

Fig. (6): Phases of Raynaud's phenomenon. Adapted from ***(Pelechas et al., 2019).***