

## Musculoskeletal Involvement in Systemic Sclerosis

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## Abstract

Systemic Sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs, pronounced alterations in the microvasculature and frequent cellular and humoral immunity abnormalities.

The rheumatic involvement of SSc is polymorphic and can reveal the disease or may appear during the course of its progression. Musculoskeletal involvement is dominated by non specific arthralgia, polyarthritis, and bony resorption especially acro-osteolysis.

The diagnosis of these rheumatic manifestations is generally based on x rays examination. Musculoskeletal involvement in SSc is generally relieved with Non Steroidal Anti-Inflammatory Drugs (NSAID) or low dose of corticotherapy. The immunosuppressive therapy is used in corticoid-resistant or corticoid-dependent forms such as méthotrexate. The aim of our review is to presents an overview of the different osteoarticular and muscular involvement in SSc, their diagnosis and management.

## Introduction

Systemic Sclerosis (SSc) is a connective tissue disease characterized by fibrosis of the skin and internal organs, pronounced alterations in the microvasculature and frequent cellular and humoral immunity abnormalities [1,2].

Rheumatic manifestations are rare. They may include varying degrees of rheumatic complaints ranging from arthralgias to frank arthritis or bony lesions.

Many patients may develop musculoskeletal symptoms as an early sign of the disease or during the course of their illness. Articular and bone involvement contribute to disability and impaired quality of life and reducing the performance of everyday occupation in SSc.

Treatment of rheumatologic disorders often involves with NSAID, corticosteroids and methotrexate.

## Joint Involvement

Joint involvement in SSc affects 46-97% of patients with SSc [3]. Generalized inflammatory arthralgias with pain and stiffness are the usual presentation of articular involvement. All joints may be affected, mainly the fingers (in particular the Metacarpophalangeal (MCP) and Proximal Interphalangeal (PIP) joints), wrists and ankles. Franck arthritis is less common. The onset of this latter may be acute or insidious, and oligoarticular or polyarticular in pattern [4].

In EUSTAR (EULAR Scleroderma Trials and Research) cohort, frequencies of synovitis and joint contractures were 16%, and 31%, respectively [5]. Synovitis was more frequently detected with ultrasonography (46%) than with clinical examination (15%  $P < 0.01$ ) [6].

Rheumatoid factor positivity occurs in up to 30% of SSc patients [7]. This is considered as a non specific reactivity. The search for anti-CCP antibodies might be useful in the identification of the infrequent cases of true SSc-rheumatoid arthritis overlap. The synovial fluid is inflammatory. Its analysis reveals increased leukocyte concentrations of more than 2000 cells/mm<sup>3</sup> and a predominantly mononuclear infiltrate.

Articular involvement was associated with a more severe disease. Inflammatory joint involvement is considered us bad prognosis and at risk of severe organ damage, especially severe vascular (pulmonary hypertension) and muscular (muscle weakness) involvement [6].

The radiologic findings in the joints are non specific. They include diffuse or periarticular osteopenia, soft tissue swelling, joint space narrowing, subluxations and rarely frank erosions. These articular features may be associated with non-articular abnormalities, in particular skin atrophy, subcutaneous calcinosis and digital tuft resorption, which are among the most distinctive radiographic findings in SSc [8]. The power Doppler ultrasonography was found to be significantly higher than the clinical examination to detect effusion and synovial proliferation. MRI is also a very promising tool to detect synovitis [9].

## Soft Tissue Involvement

In the EUSTAR database, the prevalence of tendon friction rubs, defined as a leathery, rubbing sensation detected as the tendon was moved actively or passively, was 11% [5]. These abnormalities are frequent in the tendons of knees, wrists, fingers and ankles, related to fibrinous deposits on the surface of tendon sheaths. In the leg, the tendons of the tibialis anterior and the Achilles tendon are frequently affected than the peroneus muscles [10]. When it occurs in wrist it can be associated with a carpal tunnel syndrome. The data from the EUSTAR database highlighted the independent association in multivariate analysis between tendon friction rubs and digital ulcerations, muscle weakness, pulmonary fibrosis on plain chest X-ray and proteinuria detected with a urinalysis dipstick. Tendon involvement can be considered as a sign highly predictive of bad outcome [11].

Subcutaneous calcifications may be seen as a hallmark of SSc. It can occur in feet, knees and legs. Calcinosis has been strengthened by recent cross-sectional series showing a link between calcinosis, acro-osteolysis and digital ulcerations [12]. Calcinosis and digital ulcers were recently identified as independent predictors of the radiographic progression of acro-osteolysis. These data suggest that patients with severe digital vasculopathy are more at risk to experience radiographic progression of bone resorption and further support the role of vascular injury playing a critical role in such lesions, possibly due to repeated vasospasm.

## Bone Involvement

Bone involvement is dominated by acro-osteolysis, defined as bony resorption of the terminal digital tufts, occurs in about 20% of the patients [13]. Other locations may be concerned such as carpal bones, radius, ulna, ribs, mandible, clavicle, humerus or cervical spine. It is supposed that acro-osteolysis results from impairment of blood supply, although pressure from skin tightening may also play a role [14].

## Muscular Involvement

Myopathy involvement is frequent in SSc. It is seen in 80% of SSc patients. This myopathy is often mild, with minor proximal weakness, and normal or slight elevation of Creatine Kinase (CK).

The overlap between inflammatory myositis and SSc is less frequent. This manifestation is characterized the presence of Anti-PM/Scl antibodies.

## Management of Musculoskeletal Involvement

The management of articular involvement is essentially symptomatic. The joint symptoms respond to simple NSAID treatment or small doses of corticosteroids (<10 mg/day) and do not require more intensive therapy. The risk of renal crisis with the use of corticotherapy should be carefully considered. Corticosteroid can be injected in the joint or under the retinaculum in the case of tenosynovitis.

Methotrexate may be used for the treatment of inflammatory arthritis and sub-cutaneous route is preferred to improve absorption. Other immunosuppressive drugs may be used, such as azathioprine or cyclophosphamide.

Lam and al [15] reported the efficacy of TNF $\alpha$  inhibitors on inflammatory joint symptoms in a retrospective study performed on 18 patients treated with etanercept during a 2-66 month period. Fifteen of these 18 patients had positive responses with a significant decrease in synovitis and complete resolution of joint symptoms in some patients.

Despite these encouraging results, it seems reasonable to avoid TNF $\alpha$  inhibitors in SSc because of some rare cases of fatal exacerbation of fibrosing alveolitis which have been reported in an SSc patient [16]. Controlled trials regarding the efficacy for joint symptoms and safety of TNF $\alpha$  inhibitors in SSc are needed.

Rituximab (RTX), a chimeric monoclonal antibody against the protein CD20 that demonstrated efficacy in RA, could represent an alternative to TNF $\alpha$  inhibitors in SSc. Recent studies suggest a possible promising therapeutic effect of RTX in SSc patients with clinical symptoms, namely the improvement of articular involvement [17].

There is also no actual robust data in favor of the use of tocilizumab and abatacept for the treatment of inflammatory joint disease related to SSc.

SSc related myopathy does not usually require any specific therapy. However, in the case of overlap between SSc and inflammatory myositis, corticosteroids and immunosuppressive may be added to the conventional treatment of SSc.

The surgery of the hand for SSc is sometimes needed. It includes pain relief, repositioning of the digits, arthrodesis and arthroplasty [4].

## Conclusion

Musculoskeletal involvement is frequent in SSc. Although the understanding of osteoarticular pathogenesis has significantly increased in the last few years, optimal treatments of inflammatory joint disease remain to be determined and appear as a major challenge for improving SSc morbidity and patients' quality of life. Despite encouraging preliminary data large randomized controlled trials are mandatory before drawing any conclusion.

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