

# **Musculoskeletal involvement in systemic sclerosis**

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**Abstract:**

Musculoskeletal (MSK) involvement is a very frequent manifestation of patients with systemic sclerosis (SSc). There are several reports about clinical trials assessing musculoskeletal involvement in SSc. However, only few controlled studies have been conducted. The prevalence of musculoskeletal symptoms, clinical and radiographic findings has been assessed.

The most important articular (arthralgia, synovitis, contractures), tendon (tendon friction rubs, tenosynovitis) and muscular manifestations (myalgia, muscle weakness, myositis) should be carefully evaluated during the assessment of SSc patients, because these are not only common, but substantially influence the quality of life and some of them also have predictive value concerning disease activity and severity.

## Introduction

Systemic sclerosis (SSc) is a multi-system disease characterized by vascular damage, autoimmune and fibrotic processes. Involvement of the internal organs – lungs, heart and kidney - is responsible for the high mortality of the disease. Musculoskeletal (MSK) involvement, on the other hand, is one of the main factors of the devastating disability and the dramatically decreased quality of life in scleroderma patients.

MSK involvement altogether is very common in SSc however, there are great differences in the frequency of the various MSK manifestations. It is one of the main factors affecting quality of life in SSc. Although in different pattern and extent, it is present in both the diffuse (dSSc) and limited (lSSc) cutaneous subtypes of SSc. The MSK manifestations are listed organized by complaints, signs and symptoms below in Table I.

**I. Table. Musculoskeletal manifestations in systemic sclerosis**

	Skeletal muscle manifestations	Skeletal manifestations		Tendon manifestations
		Articular	Non-articular	
<b>Complaints</b>	- myalgia - weakness	- arthralgia - joint stiffness	- shortening of digits -loss of digits	- pain over the tendons
<b>Symptoms</b>	- muscle weakness - muscle tenderness	- joint tenderness and/or swelling (arthritis) - joint contractures	- pathological fractures	- tendon friction rubs
<b>Signs (laboratory, imaging, histology)</b>	- elevated creatin kinase and aldolase levels - signs of myopathy, myositis on electromyography - mononuclear inflammation, fibrosis, microangiopathy, necrosis on muscle biopsy	- elevated acute phase reactants - joint space narrowing -marginal erosions - synovial proliferation - synovial effusion	- generalized osteoporosis or osteopenia - acroosteolysis and other localized bone resorption -osteomyelitis	- tenosynovitis - carpal tunnel syndrome

## Muscle involvement

## **Prevalence**

The prevalence of skeletal myopathy in SSc varies from 5% to 96% due to the lack of diagnostic consensus criteria [1-11]. In the published studies most often combinations of clinical, biological, electromyographic (EMG), MRI and/or histological evidence for muscle abnormalities were used [1, 3, 5, 10, 12-15]. Another factor of the varying prevalence may be the inclusion or exclusion of scleroderma-myositis overlap syndromes [7, 16, 17]. There is no consensus whether an inflammatory myopathy in SSc should rather be considered as disease symptom or as scleroderma-myositis overlap. SSc is the most common connective tissue disease associated with inflammatory myopathies, and it was found to account for 42% of patients with myositis overlap [17].

In a study by Medsger et al [5] only 20% of patients reported muscle-related symptoms whereas upon examination 6 (11%) had 'marked', 10 (19%) had 'severe', 18 (34%) had 'moderate', and 9 (17%) had 'minimal' weakness. Proximal muscle weakness was found in 20 of 38 patients (53%).

The role of genetic factors has not yet been systematically investigated. One Japanese study reported a prevalence of myopathy of 14% in SSc patients [13]. Afro-American scleroderma patients were found to have a higher prevalence of myositis and severe skeletal muscle involvement was also more often encountered compared to white SSc patients [18, 19] and another study has shown a prevalence of 37% of myositis in black South Africans with SSc [14]. In another study, important sociodemographic, clinical, and serologic differences were found between whites, African Americans, and Hispanics, however, the frequency of myositis was not significantly different among these patient groups [20].

## **Clinical symptoms**

The most frequent clinical symptoms are muscle pain and weakness. The frequency of muscle pain varies from 20% to 86% [5, 21] in SSc patients. Scleroderma patients with myopathy have usually symmetric proximal limb weakness that is indistinguishable from that seen in patients with idiopathic inflammatory myositis. Distal weakness may be also present [2, 5] but sometimes it can be difficult to distinguish myopathic weakness from the limitation of movement due to skin sclerosis, articular changes in proximity to the assessed muscles or fibrosis of underlying tissues.

Muscle weakness reported by the treating physician was 18.9% in the ISSc and 33.5% in the dSSc subset in patients fulfilling the ACR classification criteria, and 36.5% in the 'other' subgroup, consisting of patients with skin sclerosis distal to metacarpophalangeal (MCP) joints in the EUSTAR database comprising data of 9165 SSc patients [22]. This latter group included most probably patients with early SSc as well as cases with overlap syndromes. In other studies, the prevalence of abnormal muscle strength tested manually varied widely, from 10% up to 96% [1, 5, 23-25]. The lower prevalence of self-reported muscle weakness in the majority of the studies may suggest that muscle involvement in SSc patients is frequently rather mild and/or that the level of physical activity of SSc patients is reduced due to other reasons such as malaise, synovitis, and heart or lung disease. However, in a study by Clements et al the prevalence of self-reported muscle weakness was higher (26-40%) if compared to decreased muscle strength by manual muscle testing (MMT) (10%) [23]

indicating that sometimes muscle weakness may not be due to a primary myopathy but due to other scleroderma-associated disease symptoms such as joint involvement, skin contractures or fatigue.

Apart of the muscles of the limbs, other muscles might be also affected in SSc, e.g. head extensor muscles [7, 26-28] described in several recent case reports. There are no data about the involvement of respiratory muscles in SSc, however in patients with SSc-polymyositis/dermatomyositis overlap syndrome, respiratory muscles may also be affected [29].

Clinical association of myopathy was found with tendon friction rubs (TFR) in both SSc subsets in a recent EUSTAR study, where TFR was positively associated with muscle weakness. However, whether this was due to a generally increased disease activity or secondary due to affection of joints and tendons cannot be answered [30].

The presence of myositis was also found to be associated with myocarditis in SSc patients [4, 10]. In accordance with previous studies [13, 14], recent case-control studies confirmed myopathy as independent risk factor for cardiac involvement and left ventricular dysfunction in SSc [3, 31]. Patients who developed cardiac disease in the aforementioned studies had more frequently inflammatory myositis with marked increase of creatine kinase (CK) levels.

## **Evaluation and examination**

As myopathy is relatively frequent in SSc patients and may be an early disease manifestation, all patients should be screened for muscle involvement at disease onset and regularly later on. However, it can be difficult to distinguish primary myopathic weakness from the limitation of movement due to skin thickening, articular changes in proximity to the assessed muscles or fibrosis of underlying tissues, and whether it is due to inflammation or muscle damage. Other secondary causes of myopathy are muscle weakness due to disuse (fatigue, joint involvement, pulmonary/heart involvement), atrophy because of weight loss or due to side-effects of drugs (steroids, statins, antimalarials) [32]. Therefore, when the history or physical exam (MMT) suggests the possibility of proximal muscle weakness, additional testing is indicated including laboratory testing of muscle enzymes and respective auto-antibodies, EMG, MRI and muscle biopsy.

Laboratory testing includes creatine kinase and aldolase levels, as elevation of one or both are characteristic of underlying myopathic process. However, a normal value does not exclude inflammatory myopathy, as it was demonstrated in the study by Ranque et al, where 82% of patients with biopsy proven myositis had increased CK and 76% had increased aldolase levels [21].

Several autoantibodies have been demonstrated to be associated with skeletal muscle disease in SSc patients. The anti PM/Scl antibody was described in patients with scleroderma and polymyositis overlap. In a meta-analysis, 31% of patients with SSc and either polymyositis or dermatomyositis were anti-PM/Scl positive [33]. The PM/Scl positive patients from the Pittsburgh Scleroderma Databank had inflammatory changes on muscle biopsy in the majority of cases (58%) [34]. Other commercially available autoantibody that may be useful to identify the risk of muscle involvement in the individual patient is the anti-Ku antibody, which was associated with muscle weakness, CK elevation and myopathic EMG features compared to anti-Ku negative patients [35]. Both the PM/Scl positive and anti-Ku antibody positive SSc

patients have limited cutaneous rather than diffuse scleroderma. On the contrary, the presence of anti-centromere antibody (ACA) has been found to be 'protective' for myositis [3, 4, 34]. A recent EUSTAR analysis showed that in anti-Scl70 (=anti-topoisomerase I) positive patients muscle involvement occurred more often (muscle weakness in 32%, muscle atrophy in 16% and CK elevation in 8.7%) compared to ACA positive patients [9]. The presence of anti-U3-RNP (fibrillarin) was also associated with myopathy [34, 36, 37] in SSc patients. In a large SSc patient cohort, 4.1% of patients were found to have anti-U3-RNP positivity (38% having lSSc and 62% having dSSc). 54% of anti-U3 RNP positive dSSc patients developed myositis [38]. Anti-PL7 and anti-PL12 were found to be positive in patients with myositis-overlap syndromes but at a low frequency. Anti-Jo1 autoantibodies occur in scleroderma-myositis overlap syndromes in 8-24% [7, 17] of patients who have myositis. Anti-SRP positivity occurs most often in "pure" myositis [39] and in patients with scleroderma-myositis overlap syndromes [17] and is associated with severe muscle weakness and atrophy [39]. The EMG displays pathologic findings in the vast majority of SSc patients (>90%) [1, 2, 21] regardless of clinical muscle involvement, laboratory features or disease duration. The electromyographic features are similar to those of patients with polymyositis [1, 2]. The overall sensitivity to detect myopathy is higher with EMG compared to MRI [21] or muscle biopsies [1, 5, 21, 32].

The role of MRI in diagnosing muscle involvement in SSc has not been defined and up to now there are only a few studies assessing its use in this patient cohort. In a recent study, 12 patients underwent MRI of whom 8 (67%) showed inflammation of girdle muscles with muscle atrophy and fatty infiltration in three cases [21]. Another study performed with 18 SSc patients with musculoskeletal complaints showed MRI findings compatible with myopathy or myositis in 14 (78 %) patients, but no correlation was seen with the CK levels [40]. In clinical practice, MRI can be an important aid in the identification of biopsy sites.

New imaging methods for the assessment of inflammatory myopathies include contrast enhanced muscle ultrasound (US) to differentiate atrophic from inflamed muscles and specialized MR techniques such as T2 mapping, diffusion-weighted imaging and blood oxygenation level-dependent imaging, which can provide information on muscle recruitment, myofibrillar structure and can functionally evaluate the microcirculation [41, 42].

The histological findings of muscle biopsies in SSc patients with myopathy are heterogeneous and non-specific. They include mononuclear inflammation, interstitial fibrosis in the perimysium and epimysium, microangiopathy, atrophy, myofiber necrosis and regeneration of variable degree [5, 6, 10, 21]. These histological findings were indistinguishable from patients with poly-/dermatomyositis [1, 7, 10, 43, 44]. Only few data are available about the characterization of the cellular infiltrates in patients with SSc myopathy. In one study of 11 scleroderma muscle biopsy specimens, CD8<sup>+</sup> and CD4<sup>+</sup> cells were found in roughly equal proportion in perivascular cellular infiltrates, whereas CD8<sup>+</sup> cells predominated in the perimysium [45]. In the recent study by Ranque et al overexpression of MHC I, complement deposits on vascular walls with predominance of CD4<sup>+</sup> T cells similar to dermatomyositis or absence of complement deposits with predominance of CD8<sup>+</sup> cells like in polymyositis were observed [21].

One of the most important problems when assessing myopathy in SSc is the absence of definite criteria for diagnosis. At present, there is no consensus whether an inflammatory

myopathy in SSc should rather be considered as disease symptom or as scleroderma-myositis overlap. Usually the myopathy is considered as being overlap when a patient with definite SSc also satisfies the published diagnostic criteria for polymyositis/dermatomyositis [46].

Clements et al suggested two principal patterns of muscle involvement based on manual muscle strength testing, muscle enzyme levels and EMG findings [1]. The 'simple myopathy' was a mild form that appears more frequently in SSc patients. These particular patients present with proximal muscle weakness, normal or mildly increased CK and aldolase levels, and polyphasic motor unit potentials on EMG, but without the insertional irritability and fibrillation that characterise classic polymyositis. The muscle involvement is typically refractory to corticosteroids. "Complicated myopathy" is far less common and represents a true overlap between scleroderma and polymyositis. This form is characterized by muscle weakness, highly increased muscle enzymes, polyphasic motor unit potentials of short duration and small amplitude, fibrillations, positive sharp waves and increased insertional irritability on EMG [1]. Several studies have supported both the presence of a rather mild form of proximal myopathy [2, 25, 43, 44] and of myositis in patients with SSc.

However, this previously suggested classification into a simple and complicated myopathy to predict the clinical course and response to therapy may not be further sustained since an increasing number of studies do not support this classification [3-6, 16, 47].

When assessing the results of muscle biopsies, no clear-cut classification criteria have emerged either. However, these studies have not included immunostaining studies, therefore further assessment on the immunopathological nature of muscle involvement are needed before any new classification criteria are proposed [48].

## **Prognosis**

Scleroderma patients with skeletal myopathy do not seem to have worse prognosis compared to those patients without myopathy [49-51]. However, it is associated with an increased risk of myocardial involvement, which might lead to the development of late-stage late-onset life-threatening conduction defects [3, 4, 10, 13].

## **Treatment**

To date, there are no generally accepted treatment recommendations regarding SSc associated myopathy. Based on the results of retrospective studies, patients with inflammatory myopathy with elevated CK levels, inflammation on MRI or inflammatory infiltrates in muscle biopsies are treated with varying doses of corticosteroids [1, 10, 21] with or without immunosuppressive drugs such as methotrexate [43, 44, 52] whereas myopathy in patients with normal or mildly elevated CK levels and absence of inflammation in MRI or biopsy often remains untreated [1, 10]. These latter patients appeared to have a relatively stable disease course even when left untreated. In SSc patients unselected for myopathy, treatment with D-penicillamine [23] or oral cyclophosphamide [52, 53] had no impact on muscle involvement. A recent retrospective study of 35 SSc patients showed that corticosteroid therapy was associated with no biochemical parameter in the multivariate analysis [21]. Distinction between good and poor responders to immunosuppressive therapy could be made only based on histopathological findings of the muscle biopsy: in patients without

inflammation or necrosis on biopsy, only 13% had a favorable response to the treatment, whereas patients with necrosis, inflammation, or necrosis and inflammation on muscle biopsy had a 89%, 90%, and 100% chance of favorable treatment response, . This finding was in accordance with previous studies [1, 10]. However, there should be awareness for the risk of scleroderma renal crisis in patients on glucocorticoid treatment (independently of the dose used), especially in patients with early diffuse disease and poor prognostic factors [21, 54, 55]. High doses of corticosteroids should probably only considered in severe biopsy-proven myositis [21], whereas in less severe cases low-dose corticosteroids might be sufficient.

Regarding the use of biological therapies in SSc-associated myopathy, only a few case histories are available. In a recent study, diffuse SSc patients with progressive skin disease refractory to oral cyclophosphamide were treated with rituximab. One patient who additionally suffered from a severe myositis which did not respond to the combination of cyclophosphamide with MTX, treatment with rituximab led to the improvement of clinical symptoms and the normalization of CK levels [52]. In another study, which tested the effect of abatacept in refractory myopathy in 7 SSc patients, abatacept did not improve muscle outcome measures, although a tendency of improvement could be observed [56].

Patients with scleroderma-myositis overlap syndromes are usually treated similarly with a good response to corticosteroids in 89-100% [1, 10, 17, 21].

**In summary**, the musculoskeletal muscle involvement is a relatively common manifestation in SSc. The evaluation of myopathy in SSc patients includes the testing of muscle enzymes, specific autoantibodies, manual muscle testing, EMG and muscle biopsy. With respect to auto-antibodies, anti-U1-RNP, anti-U3-RNP, anti-Scl70, anti-Pm-Scl, anti-Ku, anti-Jo are found to be associated with myopathy in SSc and scleroderma-myositis overlap syndromes. EMG is currently probably the most reliable and sensitive diagnostic tool to detect SSc-associated myopathy. The muscle biopsy helps to identify those patients who might have beneficial therapeutic response to immunosuppressive agents. SSc patients with myopathy should be carefully screened for cardiac involvement even in the absence of cardiac complaints.

## **Skeletal involvement**

Skeletal involvement of the SSc can be divided into articular and non-articular involvement. Articular involvement can be present in many different forms in SSc. The most common manifestations are arthralgia and joint contractures. Arthritis is less frequent, but also relatively often present in SSc [30, 57]. Joint involvement can be the initial manifestation of SSc. Its onset can be acute or insidious with an intermittent, chronic remittent, slowly progressive or rapidly progressive course which can be present in monoarticular, oligoarticular, or polyarticular pattern.[58] Though involvement of the hands is more prominent and frequent in SSc than the feet, foot involvement should also be taken into consideration [59-63]. The involvement of the temporomandibular joints in SSc has also been reported in a few studies [63-65].

The main forms of non-articular involvement in SSc are generalized and localized osteoporosis, digital tuft resorption and osteolysis at other body regions.

Many studies have established an increased risk of bone loss and fracture in individuals with chronic inflammatory conditions. Patients with SSc may have an increased risk of osteoporosis (OP) because of a chronic inflammatory state, premature menopause, occult malabsorption or malnutrition, low weight, major disability, immobilization, and use of corticosteroid therapy. However, results regarding the risk of osteoporosis in SSc are still conflicting in SSc, since studies involved different SSc populations, study design, and generally a relatively small sample size [66-72]. A recent study has found that the prevalence of osteoporosis and fracture in a cohort of patients with SSc (n=71) was increased compared to the investigated healthy controls and RA control group, highlighting an increased risk of OP and fracture in SSc [73]. They have identified age and vitamin D deficiency as independent risk factors of fracture. The prevalence of OP in their SSc population was 30%. This result was in accordance with a recent review analyzing data of 19 relevant papers, where the prevalence of low bone mineral density and osteoporosis was 27%-53.3% and 3%-51.1%, respectively [74]. The prevalence of OP in women with SSc was similar to a large group of age-matched women with rheumatoid arthritis [73]. No difference in OP has been reported between patients with the limited cutaneous or diffuse cutaneous subset [70, 72, 73]. Corticosteroid therapy did not influence the outcome of the diagnosis of OP [73]. The similar frequency of fracture in SSc and RA population found in this particular study underlines the high risk of fracture in SSc and supports the need for systematic screening for this complication. O'air et al also demonstrated in their recent review, that patients with SSc are at risk of low BMD and fracture, especially when other risk factors for OP are present. As studies examining the risk factors for low BMD were conflicting, they suggested the need for further research for clarifying the true risk factors in SSc [74].

### **Prevalence of articular involvement**

Articular involvement is very common in SSc. However, only the average frequency can be estimated, partly because of the difficulties of physical examinations, partly because of the lack of consensus on assessment techniques. In the EUSTAR database frequencies of synovitis, tendon friction rubs, and joint contractures were 16%, 11%, and 31%, respectively [30].

The prevalence of arthralgia in consecutive SSc patients differs greatly, from 23 to 81%, among the studies of different institutes. However, it is mainly reported in about 70% of the patients [24, 57-61, 75-81].

The frequency of synovitis in SSc by clinical assessment is around 15-20% [30, 58-61, 75-77]. In consecutive SSc patients the mean number of tender joints is around 3; the mean number of swollen joints is between 0 and 2 according to most studies on this issue, except for the study of Blocka et al, where this number was much higher [53, 59, 82-85]. According to a recent metaanalysis of 7 studies the prevalence of radiologically detectable arthritis is 26% in SSc [86].

There is no consensus on what degree of range of motion decrease should be called a joint contracture. Therefore, the prevalence of contractures assessed by physical examination in different studies varies between 24 and 56 % [23, 87].

## **Clinical symptoms**

Synovitis can be present in patients with SSc in all disease stages, but it is most frequent in the early stage of the disease. The frequency of synovitis is higher in patients with the diffuse cutaneous subset compared to the limited cutaneous subtype, but only in early disease [30, 85, 88]. Arthritis-related pain is closely associated with SSc patients' health related quality of life [89]. According to Baron et al arthritis can be detected most often in the metacarpophalangeal joints (MCP), wrists, knees, distal interphalangeal joints (DIP), and proximal interphalangeal joints (PIP), in decreasing order [58].

Arthralgia and hand stiffness were among the four highest rated symptoms in terms of frequency and impact on daily activities in the Canadian National Survey. [57]. Arthralgia was found to be significantly more common in patients with dSSc, than with lSSc [77]. Moreover, Skare et al reported that pain and stiffness were the symptoms that most affected functionality [81].

Contractures are one of the main sources of disability in SSc. They are frequent in both subtypes; however, the prevalence of joint contracture is higher in dSSc, than in lSSc. Moreover, diffuse cutaneous subset is an independent predictor of the progression of flexion contractures. Though the development of contractures is relatively slow and gradual, it can be present in the early stages of the disease, too [53, 76, 77, 88, 90].

## **Rheumatoid arthritis-scleroderma overlap**

The patients who fulfill the classification criteria of both the SSc and RA are considered as SSc-RA overlap patients. Since SSc by itself can cause significant articular damage, the determination of SSc-RA overlap is difficult. Similar changes, resembling those seen in RA, are noted in the hand joints of SSc patients [58, 63]. Thus exact prevalence of true SSc-RA overlap is hard to determine, it was found in 4,6%-5.2% of SSc patients [91, 92]. In the study of Misra et al., 21% of the SSc patients with articular symptoms also had RA-overlap [93].

Szűcs et al reported that SSc-RA overlap patients carried the SSc-associated HLA-DR3 and HLA-DR11 alleles, as well as the RA-related HLA-DR1 and HLA-DR4 alleles in the genetic study of 22 SSc-RA overlap patients [91].

Many studies have confirmed that there is no significant difference between patients with and without erosive arthropathy on radiography in terms of rheumatoid factor (RF) [58, 62, 88, 90]. Furthermore, synovitis detected by US does not correlate with the presence of the RF [94]. In contrast, in the study of Jinnin et al., elevated RF was seen in SSc-RA overlap patients significantly more frequently, than in those without RA [92].

Anti-CCP antibodies can be detected also in patients with SSc, but they are generally less commonly present than in adults with rheumatoid arthritis (RA) [95]. In a few studies significant association has been detected between anti-CCP positivity and the presence of arthritis and marginal erosions. Thus, it has been suggested that high titers of anti-CCP antibodies may help to define the diagnosis of SSc-RA overlap syndrome [75, 96-98]. In contrast, Avuac et al., found no significant difference between patients with and without arthritis or erosions in terms of presence of anti-CCP2 antibodies [88]. Generini et al did not find significant association between anti-CCP positivity and articular involvement either, though it must be noted, that they had a small number of anti-CCP positive patients (n=3)

[99]. Ueda-Hayakawa et al suggested the combined use of anti-CCP, RF and anti-agalactosyl IgG antibodies, because 91% of their SSc-RA overlap patients were positive for two or more of these RA-related antibodies [100].

In conclusion, RF and anti-CCP antibodies might be more common in SSc-RA overlap patients than in SSc patients without RA; however, the presence of RF or anti-CCP by itself does not give sufficient help in the establishment of RA diagnosis in SSc patients, though their combined presence with anti-agalactosyl IgG antibodies might give further help.

## **Evaluation and examination**

The assessment of arthritis is very difficult in SSc due to certain characteristics of the disease: skin oedema, thickening and tethering, digital ulcers, subcutaneous calcinosis and contractures [84]. It has also been pointed out that physical examination is not sensitive enough to assess arthritis in SSc [84, 101, 102]. So far, there is no fully validated and universally accepted assessment technique for assessing arthritis in SSc by physical examination. The 8 joint count has been used in a few studies [24, 53, 82, 83, 85, 103]. This assesses swelling and tenderness of the MCPs (as a whole on each hand) the wrists, elbows, and knees as absent or present. The 28 joint swelling and tenderness count – as part of the DAS28 disease activity index – is a worldwide accepted tool for assessing arthritis in rheumatoid arthritis (RA) [104, 105]. This particular instrument has also been used in SSc in two studies [56, 103], although its validity has not been proved in scleroderma. Its adaptation to SSc may be considered, because the joint involvement pattern of SSc may differ from that of RA. Unlike RA, the DIP joints are often involved in SSc, as erosions and joint space narrowing are frequently seen on hand X-ray. However, the presence of concomitant osteoarthritis cannot be excluded, either [58, 88, 90]. Besides DAS28, the adaptation of other articular indexes – used in RA – may be considered for joint assessment in SSc, eg. the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI).

The association of acute phase reactant elevation - indicating systemic inflammation - and the arthritis detected by physical evaluation, radiography, MRI, US and Doppler US have been reported by a number of studies [30, 40, 84, 88, 90, 94]. Moreover, in the study of the EUSTAR cohort of more than 6000 patients, clinical synovitis had the highest strength of association with elevated acute-phase reactants taken as the dependent variable. This was true in both the lSSc and dSSc subsets, and in all disease stages [30]. The radiographic signs of joint inflammation are also associated with an increased CRP [90]. However, it must be noted, that CRP elevation is a marker of current inflammation, while marginal erosions, juxtaarticular osteoporosis and joint space narrowing are signs of long term inflammation that is not necessarily present at the moment [62].

Articular involvement was assessed also by imaging in a number of studies. Radiographic studies are the most common, but there are also a few studies about ultrasound imaging, magnetic resonance imaging, thermography and bone scan [58-63, 75, 86, 88, 90, 93, 94, 101, 102, 106-111]. The most frequent articular findings by imaging were joint space narrowing (JSN), erosions, and contractures.

In the study of Blocka et al all radiographic findings showed progression, although isolated reversibility was also noted [59]. In the longitudinal study of Avouac et al radiographic

progression of erosive arthritis was seen in 24%, of acroosteolysis in 22% and of flexion contracture in 18% of the patients over a median of 5-year follow-up period [107].

Though joint space narrowing can be a sign of previous synovitis, it can also be the consequence of osteoarthritis. JSN in SSc is most frequently seen in the DIPs, but it is also common in the other joints of the hand. It is not clear, whether the high frequency of JSN in the DIPs in SSc patients is part of the articular manifestations of scleroderma or if it is caused by concomitant osteoarthritis of the hands [58, 90]. In the US study of Cuomo et al., SSc patients displayed significantly lower prevalence of JSN than patients with RA [94]. In terms of SSc cutaneous subsets, Erre et al. found no significant differences in the prevalence of JSN [90].

Erosions in SSc are often similar to those seen in rheumatoid arthritis, however they are less frequent [63, 94]. However, in SSc well-circumscribed foci of osseous resorption or erosions on the dorsal aspects of metacarpal or proximal phalangeal heads can be also found. [59] Erosions are most frequently detected in PIP and MCP joints; however erosions can be present in the DIPs, too [58, 84, 88, 90]. Avouac et al reported that 72 % of the patients with erosions had erosive changes in the DIP joints. Of note is, that most of their patients were post-menopausal women, thus the possibility of an arthropathy, unrelated to SSc could not be ruled out. [88]. In contrast to this, Block et al found no erosions in the distal interphalangeal joints in their study [59].

Cuomo et al reported that the prevalence of joint effusions did not differ between SSc and RA patients, but SSc patients displayed a significantly lower prevalence of synovial proliferation and power Doppler signal. They found joint effusions and synovial proliferation in 22%; while synovial proliferation altogether in 42% of 45 consecutive SSc patients [94]. Elhai et al detected inflammatory synovitis by US in more than half of the 52 consecutive SSc patients. Synovitis by US was found in the wrists and hand joints of SSc patients without a statistically significant difference when compared to the RA patients. They have also reported that SSc patients with disease duration of 3 years or less had significantly more clinical synovitis than those whose disease duration was more than 3 years; however, the prevalence of US synovitis was not significantly different between the early and the late disease stage groups [84].

Flexion contractures emerge as the most frequent articular abnormality on radiographs in SSc, they are present in nearly 90% of all patients [59]. The prevalence of finger flexion contractures is significantly higher in patients with dSSc compared with lSSc [61, 88].

Calcium deposits most often occur in the subcutaneous soft tissues; however, they may also develop in the tendons, peritendinous or periarticular areas [108]. In the study of Cuomo et al osteophytosis was detected in 58 %, and periarticular calcinosis in 27% of SSc patients by US. They found no difference in the prevalence of osteophytes in SSc and RA patients [94]. Erre et al – in agreement with Avouac et al – reported association between calcinosis and erosions; nevertheless, they were not able to demonstrate a complete topographic overlapping of these lesions. Thus, the pathogenic role of calcinotic deposits on the occurrence of erosive arthritis is not completely sustained by these results [88, 90].

Similarly to erosions and joint space narrowing, juxtaarticular osteoporosis and osteopenia are periarticular signs of long term joint inflammation. The prevalence of juxtaarticular osteoporosis detected by radiography is between 4 and 42% [58, 59, 61, 75, 90, 112]. No significant difference was detected in the frequency of juxtaarticular osteoporosis between

ISSc and dSSc [90]. Though clinical sign of arthritis is more common in dSSc, than in ISSc, the similar prevalence of juxtaarticular osteoporosis in the two subsets indicate that subclinical inflammation of the joints is as frequent in ISSc, as in dSSc.

The resorption of the distal phalanges, also called as acroosteolysis, is quite common in SSc, with a frequency of 9-63%. Although it is mostly progressive, there is evidence of improvement in a few cases [63]. It is not clear whether its frequency differs among the limited and diffuse cutaneous forms of the disease or not [75, 77, 90, 110]. It is usually studied by radiography; however, Freire et al recently reported that sensitivity of US was similar to radiography in acroosteolysis detection. In their study, the majority of patients with tuft resorption also exhibited power Doppler US signal adjacent to the acroosteolysis bed, in some cases even when distal vascularization was not detected. They suggested this might be secondary to granulation tissue to induce bone formation in an attempt to repair the osteolysis. [108].

While resorption of distal phalanges is the most common, osteolysis in other sites including feet, ribs, and mandibles may also occur. In the study of Bassett et al 7 of 55 patients exhibited partial destruction of ribs 2-6, and 6 of the 35 patients presented with osseous resorption around the mandibular angles [63]. Resorption of the distal ulna was reported in 2% of the patients in four studies, while previously it was found in 8% of the patients in the study of Baron et al. [58, 60, 84, 88].

## **Prognosis**

The presence of arthritis was also found to be associated with markers of severe vascular (elevated SPAP > 40 mm Hg) and muscular (muscle weakness) involvement and with increased HAQ disability score [30, 88]. In contrast, US detected synovitis did not correlate with HAQ-DI [94]. This disagreement can be explained by the fact, that US might detect not only painful and disabling synovitis, but also subclinical synovial effusions as well.

The resorption of distal phalanges is significantly associated with digital ulcers and extraarticular calcification, interstitial lung disease, reduced forced vital capacity (FVC), oesophagus involvement, and more severe disease [88, 90, 109].

SSc patients with joint contractures are more likely to experience severe vascular and muscular disease, as well as to have elevated acute-phase reactants [30]. Flexion contractures detected by radiography are reported to be associated with interstitial lung disease, reduced FVC, oesophagus involvement and high HAQ disability score [88, 90].

According to a study of Avouac et al., the presence of digital ulcers independently predict progression of acroosteolysis [107]. In multiple logistic regression analysis calcinosis, and PAH were associated with acroosteolysis as dependent variable [88].

## **Treatment**

There have been very few studies assessing the therapy of synovitis in SSc. In analogy to rheumatoid arthritis, SSc patients with arthritis are usually treated with DMARDs and corticosteroids. Only limited information is available concerning the efficacy of methotrexate, azathioprine, and mycophenolate mofetil. Su et al have found that methotrexate did not decrease significantly the mean of tender joint count and number of areas affected by tendon

friction rubs over the 48-week study. They have observed similar results with rapamycin, an IL-2 inhibitor [85].

According to the EULAR recommendations consistent with expert opinion, low dose of steroids is commonly used for the treatment of inflammatory arthritis in patients with SSc, however its efficacy has not been proved in any randomized controlled trial [113]. Corticosteroids should only be given in low dose ( $\leq 10\text{mg}$ ) and with great precaution due to the risk of inducing renal crisis [114].

A pilot study conducted by Nacci et al. suggested that intravenous immunoglobulins (IVIG) might reduce joint pain and tenderness, with a significant recovery of joint function in patients with SSc with severe and refractory joint involvement [103]. However, the high cost of IVIG will probably not allow its extensive use among SSc patients with arthritis. D-penicillamine has been found to be ineffective in the treatment of SSc arthritis in a two-year, double blind, randomized, controlled clinical trial [24].

Cyclophosphamide was reported by two randomized, controlled clinical trials to be effective in the treatment of SSc related interstitial lung disease [115, 116]. However, there were no differences in musculoskeletal measures (joint swelling, joint tenderness, large joint contractures, muscle tenderness, muscle weakness, fist closure) between the cyclophosphamide and placebo groups at baseline, 12 and 24 months in the Scleroderma Lung Study [53].

In a pilot study of a small group of patients, tocilizumab and abatacept appeared to be safe and effective on joints, in patients with refractory SSc [56].

Recombinant relaxin was also tested in the treatment of SSc articular involvement, however it turned out to be of no help in reducing functional disability in patients with dSSc, moreover it was associated with serious renal adverse events [83].

Tumor necrosis factor alpha inhibitors appeared to be efficient in the treatment of SSc joint involvement in two small studies [117, 118], but did not show clear benefit in a third study [119]. However, according to the consensus of the EUSTAR experts their use should be limited to clinical trials due to the potential danger of severe exacerbation of pulmonary fibrosis [120].

In cases of marked damaged hand function may be significantly improved by surgery in some patient. Pain reduction can also be a surgical goal in some cases [121].

There are no drugs available so far that have been proven to improve calcinosis [113].

**In summary**, skeletal involvement is frequent in SSc. Patients with SSc have an increased risk for developing osteoporosis, thus patients should be regularly screened. Patients with early disease, diffuse subset, joint complaints or elevated acute phase reactants should be evaluated for arthritis and contractures. Since joint involvement can be the initial manifestation of the disease, SSc should be considered in the differential diagnosis of patients with arthritis, especially in those with other SSc-related features eg. puffy fingers, ANA positivity, nail fold capillaroscopy changes. Contractures start to develop in the very early stage of the disease, thus range of motion should be assessed regularly from the first visit of the patients. Patients with joint contractures should be monitored closely for development or deterioration of vascular or muscle involvement.

In case of articular complaints, symptoms or signs, imaging and laboratory examinations (X-ray, US, acute phase reactants) are also needed. Arthropathy in SSc appears to be progressive in most of the cases. We are still lacking evidence based therapeutic and preventive strategies for musculoskeletal involvement of SSc. Besides low doses of corticosteroids, methotrexate, leflunomide, azathioprine, mycophenolate mofetil are given as off-label drugs in SSc, as we are lacking large, controlled studies assessing these drugs in the treatment of SSc related arthritis.

## **Tendon involvement**

Tendon friction rubs and tenosynovitis are the major kind of tendon involvement described in SSc. Tendon friction rubs (TFRs) are characterized by a leathery crepitus felt above the tendons [122]. This does not necessarily mean the inflammation of the tendon sheath.

### **Prevalence**

According to the EUSTAR database, the prevalence of TFRs in SSc is about 11%. It can be found in both subsets and in all disease stages; however it is more common in patients with dSSc, early disease and in the Caucasian race [30, 77, 82, 123]. In the study of Elhai et al. tendon friction rubs were only found in those patients, who also had tenosynovitis detected by US [84].

Only few data are available concerning the frequency of true tenosynovitis in SSc. By clinical assessment, tenosynovitis was diagnosed in 16% of 38 consecutive SSc patients and in 12% of SSc patients with a history of hand or wrist joint pain and/ or swelling [101, 106]. The frequency of tenosynovitis detected by US or MRI is approximately 27% among consecutive SSc patients [84, 108]. Stoenoiu et al reported similar frequency in consecutive dSSc patients [124]. Tenosynovitis by MRI was found in 47-88% of SSc patients with a history of articular involvement [40, 101, 102]. A study among consecutive SSc patients has also been conducted, where tenosynovitis was found in 11% of the patients by MRI [106].

### **Clinical symptoms**

Some patients are not only aware of the friction rubs, but also complain about accompanying pain [123]. Pain along the tendon, that is not restricted to the nearby joints, can also be a sign of true tenosynovitis.

### **Evaluation and examination**

TFRs can be rapidly assessed during routine physical examination by an experienced examiner. According to Steen et al, the best way of evaluating the presence of TFR is by placing ones digits with palmar aspect across the examined tendon, and asking the patient to move the underlying joint through the possible range of motion. In case tendon friction rubs are present, a leathery, rubbing, “squeaking” sensation will be noted by the examiner and sometimes by the patient, too. Rubs may be present in numerous areas, however the following tendons are most frequently involved: extensor and flexor tendons of the fingers and wrists, and tendons over the elbow (triceps), knees (patellar), and ankle (anterior and posterior tibial, peroneal, and Achilles). Shoulder, scapular, trochanteric or toe rubs can also be noted, but less

commonly. Most often TFR are easily reproducible, however they might be intermittent or disappear with repeated movements. Usually patients have rubs in more than one body region, thus the presence of TFR can be unequivocally determined. [123]

When pain and tenderness on palpation of a certain tendon raises the suspicion of tenosynovitis, the diagnosis can be confirmed by US examination. Elhai et al detected a power Doppler signal corresponding to an inflammatory activity in 54% of tendons with tenosynovitis, and hyperechoic tendon sheath thickening, a pattern considered as sclerosing in 43% of the tendons with US tenosynovitis. This pattern appeared to be specific to SSc patients as compared to RA [84].

## **Prognosis**

Steen et al have pointed out the predictive value of TFRs in establishing the diagnosis of dSSc in an early stage [123]. This was confirmed in the study of Ostojic et al [77]. Khanna et al has assessed the significance of TFRs in early dSSc in a randomized controlled trial and found that the presence of TFRs was associated with a higher HAQ-DI. They have also observed that changes in TFR predicted changes in MRSS and HAQ-DI, thus the appearance of TFRs was associated with active disease [82]. Moreover, patients with TFRs have a more than 2-fold risk of developing renal crisis and cardiac and gastrointestinal disease complications compared to patients without this finding. Patients with TFRs also have reduced survival rates [125]. In the EUSTAR cohort significant associations have been found between the presence of TFRs and digital ulcers, muscle weakness, pulmonary fibrosis on plain chest X-ray, and proteinuria. The presence of TFRs may indicate the existence of a severe vascular, interstitial lung, and renal involvement, regardless of the disease stage [30].

Elhai et al. evaluated the correlations of tenosynovitis detected by US. They found that US tenosynovitis was associated with joint space narrowing in the wrist, radiologic demineralization, higher modified Rodnan skin score, presence of anti-Scl-70 antibodies, more active and severe disease. US tenosynovitis was more likely to occur in patients with tendon friction rubs, in those with a higher finger to palm distance, and in those with higher number of painful and swollen joints. Moreover, the presence of anti-Scl-70 antibodies and radiologic demineralization were independently associated with tenosynovitis in multivariate analysis [84].

**In summary**, it is very important to search for TFRs, particularly in the first years of SSc, however appropriate assessment requires some experience. Tendon friction rubs can be regarded as a marker of severity of SSc and patients presenting with TFRs should be carefully monitored for serious internal organ involvement. Tenosynovitis characterized by true inflammation of the tendon, pain and sometimes swelling can also be present in SSc. In case suspicion is raised by clinical evaluation, further examination by US might be needed.

## **Disability and quality of life**

Johnson et al found that joint involvement in SSc is more disabling than joint involvement in psoriatic arthritis; and patients with SSc experience more severe pain than patients with RA. Physical health relating to quality of life is adversely affected in patients with SSc and

disability is associated with the joint involvement [126]. Skin and musculoskeletal involvement in SSc is usually most prominent on the hands, thus hand function can be dramatically reduced. In the Canadian National Survey among more than 400 SSc patients, complaints related to decreased hand function were frequently endorsed (67% of the patients), and were commonly associated with remarkable impact on daily activities [57]. In the diffuse subset of SSc patients the development of functional impairment is quite rapid: significant functional impairment is present in about half of the patients within the first 18 months after onset of the disease [87].

Health related quality of life (HRQOL) perceived by SSc patients is significantly impaired compared with healthy individuals. Moreover, Hyphantis et al. found that SSc patients have impaired HRQOL in comparison with RA, SLE, and Sjögren patients, when age, pain, psychopathology, and coping strategies were taken into account [89].

Many different tests and questionnaires have been developed in order to measure hand function, quality of life and global disability in rheumatic patients. Some of these have been primarily developed for SSc, others have been adapted to SSc or validated for SSc without any changes from another disease. Clements et al. recently evaluated the validity of various potential outcome variables for the assessment of articular involvement according to the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) filter [127]. Thus, we will only briefly introduce the Health Assessment Questionnaire; which is undoubtedly the most important instrument in measuring disability in SSc. It is a patient questionnaire that has been fully validated in SSc and translated into many languages [128, 129]. In the high-dose versus low-dose D-penicillamine study it has also been shown, that HAQ is a predictor and correlate of outcome in SSc [87]. Rannou et al. showed that hand disability was the far most important determinative of disability measured by HAQ in SSc [79].

## **Disease activity**

The European Scleroderma Study Group (EScSG) developed preliminary disease activity indices to be used in SSc patients [130, 131]. However, these criteria await further validation, as further work is requested to prove their responsiveness. In this particular index, musculoskeletal involvement is represented by the presence of bilateral arthritis.

Based on clinical observations, additional clinical parameters that could indicate the activation of musculoskeletal system might be the worsening in the musculoskeletal symptoms, active myositis, symptoms corresponding to carpal tunnel syndrome and the presence of tendon friction rubs [30, 82, 125]. Definition criteria and consensus assessment methods of these types of involvements are still lacking, therefore it is difficult to define their precise role in the assessment of disease activity.

Attempts were made to improve the EScSG activity index [132]. Regarding the musculoskeletal component of the disease, the value of HAQ-DI, and the change in HAQ-DI was incorporated into the so-called 12-point activity index. The number of contractures was also found to be correlated to both the EScSG activity index and the 12-point activity index. CRP has shown the same association with these two indices [132]. Of note is that in the study of the EULAR cohort of more than 6000 patients, clinical synovitis had the highest strength of association with elevated acute-phase reactants taken as the dependent variable. This was

true in both ISSc and dSSc subsets [30]. The radiographic signs of inflammation (occurrence of marginal erosions with the exception of DIP joint erosion and/or juxtaarticular osteoporosis in association to space narrowing of proximal interphalangeal joints) were also associated with an increased CRP in another study [90]. CRP also correlated with the HAQ-DI [133]. Therefore, the elevation of CRP might reflect an underlying musculoskeletal activity in SSc.

## **Musculoskeletal rehabilitation**

There have been a few small studies investigating different musculoskeletal rehabilitation techniques in SSc. The main techniques that have been proved to have beneficial effect on hands are hand range of motion exercises, paraffin wax bath, connective tissue massage, manual lymph drainage and patient education [134-140]. Splinting was also studied, however did not turn out to be useful [141]. Recently studies are not only focused on the rehabilitation of the hands, but also on orofacial rehabilitation and overall rehabilitation programs – consisting of specific and global techniques[134-140].

Mouth opening, functional ability, hand function and mobility can be improved by overall rehabilitation. The advantages of overall rehabilitation in SSc have been studied in two recent studies with similar results. However, with a few exceptions – e.g. hand mobility, grip strength – these results tend to disappear over a relatively short period of time, within a few months after the end of the rehabilitation programs. Thus these programs should be either continuous or regularly repeated in order to sustain their benefits [142, 143].

**The overall summary** is that musculoskeletal involvement:

- is very frequent in SSc,
- is often among the initial manifestations of the disease,
- causes significant disability hence decreases quality of life,
- if present, may predict more severe internal organ involvement.

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