Cartilage Oligomeric Matrix Protein (COMP) in systemic sclerosis (SSc): Role in disease severity and subclinical rheumatoid arthritis overlap

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Abstract

Objective: The aim of the present study was to compare the serum level of COMP in both subsets of Systemic sclerosis (SSc) as a marker of arthritis and reveal an associated subclinical RA overlap and a relation to clinical, laboratory and radiological findings in SSc.

Methods: Forty adult SSc patients were included in the study and grouped into the two subsets diffuse (dSSc) and limited (lSSc) SSc. Their mean age was 40 ± 9 years. Thorough history taking and clinical examination were performed to all patients. Skin thickness was scored according to the modified Rodnan skin score method (MRSS). The disease activity was assessed by measuring the Medsger severity score. The joints were extensively examined and the tenderness counted according to the Ritchie articular index (RAI). Relevant laboratory and radiological investigations were carried out. The serum COMP level was determined by ELISA.

Results: The serum COMP was significantly higher in the SSc patients compared to the control and obviously higher in the dSSc compared to the lSSc patients. The level of COMP was higher in the females and significantly higher in the SSc patients with arthritis (56.5 ± 6.8 μg/ml) compared to those without (34 ± 8.3 μg/ml) \( P < 0.000 \).

Conclusion: The COMP level may become a nonspecific but useful marker for joint involvement in SSc patients to identify patients at risk of joint damage and developing SSc-RA overlap syndrome even with mild arthritis.

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1. Introduction

Systemic Sclerosis (Scleroderma [SSc]) is a multisystem rheumatic disease of unknown etiology characterized by widespread vasculopathy and extracellular matrix deposition leading to fibrosis and autoimmune processes \([1,2]\). Although the pathogenesis of SSc remains unknown, cytokine production and release are key events, characterized by T cell activation and autoantibodies production \([3]\).

It is highly valuable to find easily measurable biomarkers that may represent ongoing disease activity or treatment response \[1\]. Numerous biomarkers reflecting the three main pathogenetic mechanisms in SSc have been expressed, however, there is an unmet need for validated biomarkers for diagnosis, disease classification, and evaluation of organ involvement and therapeutic response \[4\].

Cartilage oligomeric matrix protein (COMP), primarily found in cartilage, is thought to be an important regulator of assembly and maintenance of the fibrillar collagen I and II networks. It accumulates with a striking deposition in the dermis of SSc patients and is produced by the skin fibroblasts possibly due to autocrine TGF-beta stimulation and no reactivity was detected in normal skin. COMP overexpression is sufficient to stimulate excess pathogenic matrix deposition and is involved in the development of fibrosis. Serum COMP shows promise as a new biomarker in SSc \([5,6]\). Serum COMP reflects clinical disease activity of RA and is a valuable serologic marker to identify the subset of patients achieving remission during treatment with anti-TNFs \([7]\).

A preclinical scleroderma-related internal organ involvement was detected in patients with early or probable SSc or undifferentiated connective tissue disease (UCTD) \[8\]. The prognosis for patients with SSc has improved in the past three decades, with fewer patients succumbing to renal-crisis-related death. While pulmonary fibrosis and hypertension are currently the most frequent causes of death, there is evidence that cardiovascular disease will have an important role in the long-term prognosis of SSc in the future \[9\]. Musculoskeletal involvement is more frequent than expected in patients with SSc and is a major cause of disability.
even if the prognosis of the disease largely depends on visceral involvement [10].

Arthropathy, particularly synovial inflammation in SSc, is not well characterized [11]. A rheumatoid arthritis-like arthropathy can be observed in SSc patients [12]. Joint involvement most commonly includes arthralgias, while a true arthritis is less frequent. The development of RA and its diagnosis may be misled by concomitant joint contracture or tendon sheath involvement due to SSc [13,14]. The overlap between SSc and RA is rather uncommon overlap syndrome which should be considered as a distinct clinical and genetic entity [15].

Joint involvement is common in SSc patients during the course of the disease or at disease onset. Besides, arthralgias, stiffness and tendon sheath involvement constitute the most common clinical findings affecting all joints, predominantly the fingers, wrists and ankles. The most common radiographic abnormalities in SSc patients are subcutaneous calcinosis and digital tuft resorptions, which are frequently observed at the hands. Juxtaarticular deminerisation, joint space narrowing and erosions also occur and are diagnostic challenges with RA. Arthritis/arthralgias and radiographic abnormalities similarly affect patients with diffuse or limited subtypes [16].

The aim of the present study was to compare the serum level of COMP in both subsets of SSc as a marker of arthritis and reveal an associated subclinical RA overlap and a relation to clinical, laborato-ry and radiological findings in SSc.

2. Methods

Forty adult systemic sclerosis patients recruited from the Rheumatology outpatient clinic, Cairo University hospitals were included in the study. All patients fulfilled the American College of Rheumatology criteria for PSS [17] and were grouped into patients with limited or diffuse skin involvement according to a proposed classification system [18]. Patients with limited SSc were considered for the presence of CREST syndrome; Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia. Patients with full expression of any other associated rheumatic disease according to their classification criteria were excluded. The SSc patients were not fulfilling the 2010 ACR/EULAR classification criteria for RA [19]: none had prolonged morning stiffness or rheumatoid nodules while patients presenting with major features as arthritis were included. Moreover, none of the patients had mixed connective tissue disease (MCTD) [20], systemic lupus erythematosus (SLE) [21] or polymyositis/dermatomyositis (PM/DM) [22] Their mean age was 40 ± 9.04 years (range 23–54 years). Twenty age and sex matched normal subjects were included as control. Through history tak-ing and clinical examination were performed to all patients. Skin thickness was scored according to the modified Rodnan skin score method (MRSS) [23]. The disease activity was assessed by measuring the degree of severity of involvement of major organs using the Medsger severity score [24]. The joints were extensively examined and the tenderness counted according to the Ritchie articular index (RAI) [25].

Relevant laboratory investigations including antinuclear ant-i-bodies, anticientromere, anti-Scl70, rheumatoid factor and anti-CCP were performed to patients. Furthermore, plain X-rays of the hands and wrists, high-resolution chest CT, Forced vital capacity (FVC), echocardiography and barium swallow were carried out to all patients. Suspicious cases of arthritis by clinical examination or X-ray were confirmed by Doppler ultrasonography (echography) scanning using Philips Hdl 5000 (USA) using 7.5–12 MHS probe.

The serum COMP level was determined by the ELISA technique using a kit supplied from the AnaMar medical AB, Lund, Sweden.

3. Statistical analysis

Statistical Package for Social Science (SPSS) program version 15 was used for analysis of data. Data was summarized as mean ± SD. Mann-Whitney test was used for comparing and analysis of two quantitative data. Pearson’s correlation was used for detection of the relation between two variables. P-value was considered significant if < 0.05.

4. Results

The study included 40 SSc patients and were 19 (47.5%) diffuse subtype and 21 (52.5%) limited subtype. Their mean age was 40 ± 9.04 years, 35 female and five males (F:M 7:1). The males were one of diffuse and four limited subtype. The mean age of control was 40.7 ± 10.38 years and they were 17 females and three male. Arthritis was present in 15 (37.5%) of SSc patients being mild in 12 and moderate in three with a diffuse subtype. None of the patients had morning stiffness of the hands. The COMP level was significantly higher in the diffuse and limited SSc patients compared to the control (6 ± 1.7) (P < 0.001). The mean age (40 ± 8.6 vs 39.9 ± 9.5 years) and age at disease onset (31.8 ± 7.3 vs 35.8 ± 9.1 years) were comparable between the diffuse and limited subtypes. However, the disease duration was significantly longer in the diffuse SSc subtype (8.1 ± 4.4 years) compared to those with limited SSc (4.1 ± 2.2 years) (P < 0.001). Table 1 shows the clinical manifestation of the diffuse and limited SSc subtypes patients. Table 2 shows the results of the RAI, MRSS and the Medsger total severity score for the SSc patients.

There was a significantly higher mean corticosteroid dose received by the diffuse SSc subtype (46.1 ± 28.5 mg) compared to that of the limited (19.3 ± 15.09 mg/day) (P < 0.001). The duration of steroid intake was comparable in both groups (10 ± 4.4 vs 7.7 ± 5.3 years). The mean methotrexate dose was similar in both subtypes (27.5 ± 30.8 vs 14.5 ± 15.6 mg/day). The laboratory investigations of the diffuse and limited SSc patients are shown in Table 3.

The U1RNP antibodies were negative in all the patients. Pulmonary function tests (PFT) showed moderately reduced FVC (64.5% of the predicted values) in the diffuse subtypes and mild affection of the limited subtypes (66.4%) and the difference was not significant (64.5% of the predicted values) in the diffuse subtypes and mild pulmonary function tests (PFT) showed moderately reduced FVC (64.5% of the predicted values) in the diffuse subtypes and mild affection of the limited subtypes (66.4%) and the difference was not significant (P = 0.61). Interstitial pulmonary fibrosis (IPF) was present in 16 (84.2%) diffuse subtypes and 11 (52.3%) limited SSc patients. The X-ray hands showed bone resorption in 14 (73.6%) in those with diffuse SSc and in 14 (66.6%) of those with limited SSc while erosions were seen in five diffuse SSc (26.3%) and 3 limited (14.2%). Acrosteolysis was present in 10 diffuse (52.6%) and seven limited (33.3%) of the SSc patients. Of the 15 cases with arthritis, five were doubtful and confirmed by Doppler ultrasonography showing arthritis with mild effusion, erosions and mild synovial thickening.

The serum COMP level significantly correlated with the MRSS (r = 0.53, P = 0.000), severity score (r = 0.41, 0.009), RAI (r = 0.96, P = 0.000) as graphically presented in Fig. 1 and further correlated with the disease duration (r = 0.35, P = 0.03), methotrexate dose (r = 0.36, P = 0.024), ESR (r = 0.4, 0.011), urea (r = 0.48, P = 0.002), creatinine (r = 0.34, P = 0.04). The total severity score negatively correlated with the FVC (r = 0.38, P = 0.015) and the MRSS correlated with the creatinine level (r = 0.35, P = 0.027). Correlation of the COMP with the studied autoantibodies revealed a positive correlation with the Anti-CCP (P = 0.012) and anti-Scl-70 (P = 0.41) and was insignificant with anticientromere (P = 0.7), ANA (P = 0.69) and RF (P = 0.07).

The level of COMP was higher in the females (43.5 ± 13.7 ug/ml) compared to the males (33.4 ± 5.8 ug/ml) (P = 0.014). In the control, there was no obvious gender difference in the level of COMP (females 6.04 ± 1.79 ug/ml vs males 6.02 ± 1.39 ug/ml; P = 0.98). The serum COMP was significantly higher in the SSc
Table 1
Clinical manifestation of the diffuse and limited (CREST syndrome) SSc subtypes patients.

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>No. (%)</th>
<th>Systemic sclerosis patients</th>
<th>Limited (21) (CREST syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>16 (84.2)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (84.2)</td>
<td>14 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>9 (47.3)</td>
<td>4 (19)</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>13 (68.4)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>19 (100)</td>
<td>19 (90.4)</td>
<td></td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>19 (100)</td>
<td>19 (90.4)</td>
<td></td>
</tr>
<tr>
<td>Hypo/hyperpigmentation</td>
<td>18 (94.7)</td>
<td>19 (90.4)</td>
<td></td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>3 (15.7)</td>
<td>8 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>13 (68.4)</td>
<td>12 (57.1)</td>
<td></td>
</tr>
<tr>
<td>Pitting scars</td>
<td>11 (57.8)</td>
<td>11 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Digital gangrene</td>
<td>8 (42.1)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Calcinosis</td>
<td>2 (10.5)</td>
<td>10 (47.6)</td>
<td></td>
</tr>
<tr>
<td>Articular</td>
<td>15 (78.9)</td>
<td>19 (90.4)</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>15 (78.9)</td>
<td>19 (90.4)</td>
<td></td>
</tr>
<tr>
<td>Arthritis</td>
<td>9 (47.3)</td>
<td>6 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Tendon friction rubs</td>
<td>9 (47.3)</td>
<td>5 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Hand deformities</td>
<td>5 (26.3)</td>
<td>6 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Neurological</td>
<td>12 (63.1)</td>
<td>8 (38.1)</td>
<td></td>
</tr>
<tr>
<td>CTS</td>
<td>8 (42.1)</td>
<td>4 (19)</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>7 (36.8)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td>3 (15.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Myalgia/weakness</td>
<td>12 (63.1)</td>
<td>8 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>16 (84.2)</td>
<td>16 (76.1)</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>16 (84.2)</td>
<td>16 (76.1)</td>
<td></td>
</tr>
<tr>
<td>Esophageal hypomotility</td>
<td>11 (57.8)</td>
<td>14 (66.6)</td>
<td></td>
</tr>
<tr>
<td>Esophageal dilatation</td>
<td>4 (21)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>17 (89.4)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Dry cough</td>
<td>13 (68.4)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (89.4)</td>
<td>15 (71.4)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>6 (31.5)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td>6 (31.5)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Valve involvement</td>
<td>3 (15.7)</td>
<td>7 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1 (5.2)</td>
<td>2 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>9 (47.3)</td>
<td>8 (38.1)</td>
<td></td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>4 (21)</td>
<td>10 (47.6)</td>
<td></td>
</tr>
</tbody>
</table>

CREST: Calcinosis, Raynaud’s, Esophageal dysmotility, Sclerodactyly, Telangiectasia; CTS: carpal tunnel syndrome.

patients with arthritis (56.5 ± 6.8 ug/ml) compared to those without (34 ± 8.3 ug/ml) (P < 0.000).

5. Discussion

Upregulation of COMP expression contributes to different pathways of fibrosis and may serve as a biomarker for the degree of SSc skin involvement [26]. In the present study, 47.5% of the patients had diffuse subtype (dSSc) and 52.5% limited (lSSc). This is in harmony with other studies that found that lSSc represents 58% [14], 70% [27] and could be even higher (77%) [15].

In the present study, cutaneous manifestations were present in 95% of patients, being more frequent in dSSc, while telangiectasia, calcinosis and esophageal hypomotility were more in lSSc. The FVC was reduced in both subtypes. In another study digital ulcers, interstitial lung fibrosis, decreased FVC, esophageal hypomotility, musculoskeletal impairment and heart involvement were more common in dSSc whereas, fingertip osteolysis, telangiectasia, and arthritis were equally frequent in both subsets [28].

The MRSS was higher in dSSc patients. In a comparable study, the MRSS values ranged from 3–32 (median 14) [27]. The current work showed a significant correlation of the COMP level with MRSS. Similarly, COMP was found to accumulate in SSc skin and moderately

Table 2
The Ritchie articular index, Modified Rodnan Skin Score and the Medsger total severity score.

<table>
<thead>
<tr>
<th>Index/score mean ± SD</th>
<th>Diffuse (19)</th>
<th>Limited (21) (CREST syndrome)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAI</td>
<td>11.8 ± 6.8</td>
<td>7.2 ± 5.4</td>
<td>0.02</td>
</tr>
<tr>
<td>MRSS</td>
<td>25.8 ± 10.9</td>
<td>18.8 ± 6.9</td>
<td>0.02</td>
</tr>
<tr>
<td>Medsger severity</td>
<td>14.6 ± 5.2</td>
<td>12 ± 3.3</td>
<td>0.07</td>
</tr>
</tbody>
</table>

CREST: Calcinosis, Raynaud’s, Esophageal dysmotility, Sclerodactyly, Telangiectasia; CTS: carpal tunnel syndrome, RAI: Ritchie articular index, MRSS: Modified Rodnan Skin Score.

Fig. 1. Correlation of serum COMP with the articular index, MRSS and the total severity in systemic sclerosis patients. RAI: Ritchie Articular Index; MRSS: Modified Rodnan Skin Score.
correlated well with the MRSS [6,29] and changes closely paralleled those in MRSS [6].

Articular manifestations were seen in 85% with arthralgias being more often in ISSc followed by arthritis and friction rub being more in dSSc. Gastrointestinal tract and pulmonary involvement including dysphagia, esophageal hypomotility and dyspnea occurred in 80% and cardiac involvement in 32.5% of the cases. Several other studies described the distribution of clinical manifestations among the SSc patients. Pulmonary fibrosis was seen in 77%, esophageal dysmotility in 55% and cardiac involvement in 50% [15].

Similarly, Raynoud’s phenomenon was found in 100% of the patients, telangiectasia in 94%, calcinosis in 40%, digital scars in 66% and ischemic ulcers in 58% [27]. Digital ischemic ulcers are the hallmark of SSc-related vasculopathy and characterized by endothelial dysfunction leading to intimal proliferation and thrombosis which is associated with significant morbidity [2] and impact on activities of daily living and work disability [30].

Peripheral arthropathy seen in SSc is usually persistent inflammatory and erosive similar to that seen in RA. However, arthralgia without overt inflammatory joint disease are more common [11]. The present results highlight the striking level of articular involvement in SSc, as evaluated by systematic examination. In accordance are the results that show that synovitis and tendon friction rubs are associated with a more severe disease and systemic inflammation and were more prevalent in dSSc [14].

In the present study, the COMP was significantly higher in the SSc patients with arthritis. Furthermore, anti-CCP was detected in 17.5% being obviously higher in dSSc. In agreement was the study that found anti-CCP in 12% SSc patients being higher in SSc-RA overlap. Elevated anti-CCP Abs may help to define the diagnosis of SSc-RA overlap. On the other hand, matrix metalloproteinase-3 (MMP-3) might be a better marker to assess skin rather than joint involvement in SSc patients; as it did not correlate with the presence of arthritis or arthralgia but was significantly associated with MRSS [31]. Almost all SSc-RA and SSc patients with elevated anti-CCP exhibited arthralgias and interstitial pneumonia and only correlated with the presence of arthritis [32,33]. According to our results, COMP could be considered a more reliable marker for SSc patients with joint involvement who may be at risk of developing SSc-RA overlap.

Arthritis in the present study was mostly mild, though we believe that a subclinical RA association would exist. Overlap with RA was present in 10% of SSc patients with anti-CCP detected in 83% and RF in all. However, anti-CCP antibodies had a much higher specificity than RF for RA. Anti-CCP is useful to identify SSc/RA overlap and is crucial in the management of SSc allowing an adequate therapy of RA to prevent further joint damage in patients who already have a poor quality of life [13,34]. Another study found that SSc-RA overlap was present in 4.6% of SSc patients with the onset of SSc preceding RA in most cases and characterized by a distinct mixed serological pattern resembling both [15].

The prevalence of SSc-RA overlap is 4.3–5.2% among SSc patients, which is higher than in the general population. Thus, it is clinically important to check for the occurrence of RA in patients with established SSc. The early diagnosis of RA is often difficult in patients with SSc because symmetric polyarthritis may be commonly present in both diseases [15]. Similarly, the SSc-RA patients were mostly dSSc, with severe seropositive polyarthritis, pulmonary fibrosis and more associated with anti-Scl70 [35]. Conversely, 23% of SSc/RA overlap patients had dcSSc and 77% had lcSSc [15].

In the present study, the ANA antibodies were detected in 66.7% of cases, Anti-Scl70 in 20%, RF in 22.5% and anti-CCP in 17.5%, all being obviously higher in dSSc subset. On the other hand, Anti-centromere was exclusively detected in the ISSc subset. Rheumatoid factor was present in 29.1% and anti-CCP in 7.27% of SSc patients which was associated with an erosive aspect [36]. In another study on SSc/RA overlap patients, ANA, anti-Scl70, RF and anti-CCP antibody positivity were detected in 100, 23, 73 and 82 of patients, respectively [15].

Bone resorption was present in 70% of SSc patients and erosions in 20% being higher in dSSc. Acroosteolysis was present in 42.5 and 27.5% had joint deformities. There is a burden of hand radiological damage in SSc patients. Tuft acro-osteolysis were the most common findings observed and were associated with a more severe disease and erosions present in 14.55% of SSc patients [36]. Rare
SSc-associated arthropathy with an RA-like pattern, characterized by marginal erosions was present in 4.19% of cases [12], however, hand joint destruction was observed in 82% of SSc patients [15]. The radiological features of arthropathy in SSc patients with polyarthritis showed abnormalities in 80% with erosions in 43%. Conversely, there was no significant difference between patients with and without erosive arthropathy in terms of the subtype, organ involvement, calcinosis presence of RF, ANA or Anti–ScI70 [37].

Sicca (Sjögren’s) syndrome was frequently present in the studied SSc patients (35%) being much more prevalent in ISSc. Primary Sjögren’s syndrome is a chronic autoimmune disorder of the exocrine glands and has been occasionally reported with anticitrulline antibodies and ISSc [38]. Sicca symptoms are frequent in SSC; ISSc (50%) and dSSc (49%) [39] and are a frequent cause of morbidity especially in ISSc [39]. Sicca syndrome was prevalent in 68% of SSc patients and primarily related to glandular fibrosis, the hallmark of SSC. The prevalence of secondary Sjögren was 14% and markedly associated with ISSc thus considering it a specific autoimmune subtype of SSC [40]. According to the present results, awareness for its presence is important in both subsets.

Physical health relating to quality of life is adversely affected in patients with SSc. Disability is associated with the presence of a high skin score and with joint involvement which is more disabling than in psA and SSc patients experience more severe pain than those with RA [41].

The pattern of changes of serum COMP, a selective marker for cartilage turnover, is potentially useful for evaluating effects of new drugs in RA. TNF blockade modifies the release of COMP from the tissue and retards the development of joint destruction. Importantly, levels of COMP decreased both in responders and nonresponders which is consistent with the hypothesis that inflammation and tissue destruction are not directly linked. This shows promise of COMP as a noninflammation-related marker in RA, which should be useful for evaluating novel treatment modalities in the disease [42]. The findings in the present study support the argument to consider using new biologic agents in SSC patients with high risk of RA overlap even if the anti-CCP is negative.

The COMP level may become a nonspecific but useful marker for joint involvement in SSc patients to identify those prone to develop joint damage and are at risk of developing SSc–RA overlap syndrome, which is a distinct clinical entity, even with mild arthritis. The present study may throw light on the importance of the hand radiological changes which are absent in the newly proposed criteria ACR/EULAR criteria especially in the SSC patients at risk.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


