ORIGINAL ARTICLE

Prevalence and Clinical Characteristic of Inflammatory Arthritis in Thai Patients with Systemic Sclerosis: A Cross-Sectional Study

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Background: Systemic sclerosis is a type of autoimmune connective tissue disease. It is more prevalent in the Northern and Northeastern regions of Thailand compared to other regions, with diffuse cutaneous systemic sclerosis (dcSSc) being the most common subtype. Musculoskeletal involvement, including arthritis, is a major cause of disability and reduced quality of life in patients with systemic sclerosis.

Objective: To investigate the prevalence of arthritis in patients with systemic sclerosis and define the clinical association with arthritis.

Materials and Methods: The present research was an observational analytical study conducted at Sunpasitthiprasong Hospital, Ubon Ratchathani Province, Thailand, between January 2022 and January 2023. One hundred ninety-seven patients with systemic sclerosis were included in the study, and logistic regression analysis was used for investigating the clinical association with arthritis.

Results: One hundred ninety-seven patients were included and comprised of 138 (70.1%) with arthritis. The majority of patients with arthritis were female, at 71.1%, and dcSSc, at 91.4%, with the mean age of 51.6±11.8 years. Multivariable logistic regression analysis after controlling for other variables revealed that periarticular osteopenia was significantly associated with arthritis in patients with systemic sclerosis (95% confidence interval: 8.34 to 67.36).

Conclusion: Arthritis was a common clinical feature in systemic sclerosis for 70.1%. The presence of periarticular osteopenia was independently associated with arthritis. This clinical factor could be utilized to aid in the diagnosis of arthritis in systemic sclerosis patients and improve treatment outcomes.

Keywords: Systemic sclerosis; Scleroderma; Inflammatory arthritis; Musculoskeletal; Joint contractures; Hand involvement

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Systemic sclerosis is a rare connective tissue disease, which is classified as an autoimmune disease. In Thailand, it is more prevalent in the northeastern region compared to other parts of the country. Systemic sclerosis can be categorized into two main types, limited systemic sclerosis (lcSSc) and diffuse systemic sclerosis (dcSSc). Diffuse systemic sclerosis, which is more common in Thailand, has worse prognosis as it often involves internal organ complications, particularly the lungs and heart[1].

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Musculoskeletal symptoms are found in 24% to 97% of systemic sclerosis patients[2-6]. Inflammatory arthritis is one of the commonly observed clinical features in the musculoskeletal system. It contributes to disability and poor quality of life[3,6-8], and is a risk factor for depression, affecting 36% to 65% of systemic sclerosis patients[3]. Additionally, small joint contractures and tendon friction rubs are associated with disease severity and progression[9-11]. These manifestations are more frequently seen in patients with diffuse systemic sclerosis[7]. Small joint contractures, in particular, indicate joint damage and have been reported in up to 30% of systemic sclerosis patients within the first four years of symptom onset. Furthermore, their presence is associated with increased mortality rates in systemic sclerosis patients[12]. Although pulmonary and cardiac complications are the major causes of mortality in systemic sclerosis, patients with small joint contractures were often delayed diagnosis and treatment[2].

The diagnosis of arthritis in systemic sclerosis patients lacks clear criteria compared to rheumatoid arthritis (RA). Currently, there is limited data on arthritis in systemic sclerosis patients in Thailand and other countries, resulting in unclear diagnostic and treatment guidelines. This may lead to delayed diagnosis and treatment for the patients. Therefore, the present study aimed to determine the prevalence of arthritis in systemic sclerosis patients and examine the clinical differences between patients with and without arthritis. The findings from the present study may provide valuable insights in accurately and promptly assessing joint-related issues in systemic sclerosis patients, guiding appropriate treatment, preventing small joint contractures, reducing disability, and improving the quality of life for individuals with systemic sclerosis. The results of the present study may contribute to the development of future guidelines for the diagnosis and management of systemic sclerosis patients.

Materials and Methods

The present research study employed an analytical observational design using a cross-sectional study approach. The study focused on patients with systemic sclerosis, a condition characterized by inflammatory arthritis, who were 18 years or older and receiving treatment at the Sunpasitthiprasong Hospital, Ubon Ratchathani Province, Thailand. The study was conducted between January 31, 2022 and January 31, 2023.

The inclusion criteria were patients with systemic sclerosis, both new and existing patients, who did or did not have arthritis, and volunteered to participate.

The exclusion criteria included patients diagnosed with arthritis due to other causes, such as overlap syndromes particularly RA, arthritis from crystal deposition, infectious arthritis, and osteoarthritis. One hundred ninety-seven individuals met the specified criteria and were included in the study.

Ethical approval was obtained from the Institutional Research Ethics Committee (approval No. CA code 007/2565).

Data collection

The researchers collected data from patients diagnosed with systemic sclerosis by utilizing a research questionnaire. In addition, they gathered information on the prevalence and clinical characteristics of the patients, with prior consent obtained from each participant. Patients with systemic sclerosis both with and without arthritis were subjected to medical history interviewed, physical examination, and various laboratory tests, including rheumatoid factor (RF), anti-cyclic citrullinated peptide (CCP), anti-nuclear antibody (ANA), anti-scl70, anti-centromere, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) tests. Radiographic images of the hands and fingers were also taken, and the results were interpreted by a rheumatologist.

Operational definitions

The diagnosis of systemic sclerosis arthritis in the present study detected by rheumatologist referred to patients exhibiting joint pain, swelling, redness, warmth, difficulty in movement, or morning stiffness, with any of these symptoms, and confirmed by inflammatory markers (such as ESR, CRP). The disease classification was based on the 2013 international American College of Rheumatology/ European League Against Rheumatism (ACR/ EULAR) classification criteria for systemic sclerosis, updated and validated in 2013. The present study considered early-onset systemic sclerosis as a disease duration of less than three years, starting from the onset of symptoms or Raynaud's phenomenon until the study's commencement. Late-onset systemic sclerosis referred to a disease duration of three years or more, starting from the onset of symptoms or Raynaud's phenomenon until the study's commencement. Extra-articular manifestation included internal organ involvements such as pulmonary, gastrointestinal, cardiac, renal, and musculoskeletal. Overlap syndrome diagnosis encompassed patients with coexisting systemic sclerosis and other rheumatic conditions such as RA, systemic lupus erythematosus (SLE), dermatomyositis, vasculitis, and Sjogren's syndrome.

Statistical analysis

The research was analyzed the data by IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The data were analyzed using descriptive statistics for categorical variables, such as percentages and frequencies, and for continuous variables, such as mean, standard deviation (SD), median, and interquartile range (IQR). The measures of association were assessed by presenting percentages and 95% confidence intervals (CIs). The statistical significance of differences between patients with systemic sclerosis arthritis and those without arthritis were tested using Student's t-test for continuous data and chi-square test for

categorical data. Factors found to be associated with the occurrence of systemic sclerosis arthritis were further analyzed using logistic regression. Univariate logistic regression analysis was conducted with a significance level of p-value less than 0.05, and variables with a p-value less than 0.05 were included in the multivariate logistic regression analysis. Adjusted odds ratios with 95% CIs and p-values from the tests with a significance level of less than 0.05 were reported as statistically significant.

Results

One hundred ninety-seven patients with systemic sclerosis, including 138 with arthritis, accounting for a prevalence of 70.1% (95% CI 61.76 to 78.44), were included in the present study. The study flow is presented in Figure 1.

The analysis of the study

Inflammatory arthritis in systemic sclerosis was 70.1% and 8.1% had calcinosis related arthropathy and tendinopathy. Regarding the type of arthritis, small joint involvement with 4 to 10 affected joints was the most common, accounting for 46.7%. This was followed by involvement of 1 to 3 small joints in 19.8%, and 2 to 10 large joints in 0.5%, as shown in Table 1.

When considering the clinical characteristics of arthritis in patients with systemic sclerosis, it was found that the average age of the patients at the time of the study was 57.3±11.0 years. The average age at the onset of systemic sclerosis symptoms was 51.6±11.8 years. The median duration of the disease from the onset of symptoms was four years, with an IQR of two to eight years. The majority of patients were female, accounting for 72.6%.

The most common type of systemic sclerosis observed was diffuse cutaneous systemic sclerosis, accounting for 91.4%. Extra-articular manifestations were present in 55.3% of the patients, with calcinosis cutis being the most prevalent at 46.7%. The next most common manifestations were hand joint deformity and carpal tunnel syndrome, at 32.5% and 4.1%, respectively. The average score for skin tightness, assessed using the modified Rodnan skin score (mRSS), was 11.9±6.2. Organs' involvement was present in 98.5% of the patients, with interstitial lung disease (ILD) being the most prevalent at 69.5%. Esophageal involvement and digital ulcer/gangrene were the next most common, at 56.9% and 40.1%, respectively.

Laboratory findings revealed that the average

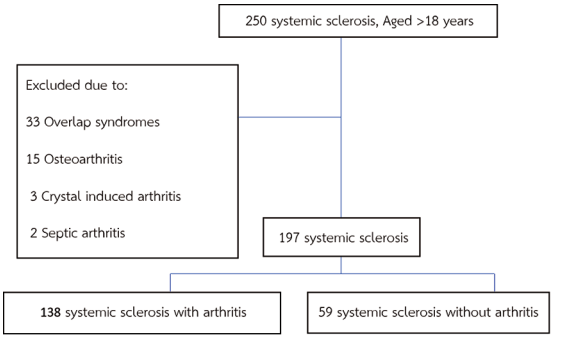

Figure 1. Study flow diagram.

Table 1. Prevalence, types, and number of arthritis in patients with systemic sclerosis

Clinical findings	n (%)
Arthritis	138 (70.1)
1 large joint	0 (0.0)
2 to 10 large joints	1 (0.5)
1 to 3 small joints (with or without large joint)	39 (19.8)
4 to 10 small joints (with or without large joint)	92 (46.7)
More than 10 joints (at least 1 small joint)	1 (0.5)

ESR was 57.9±30.3, and the median CRP level was 3 (IQR 0.8 to 8.0). Serological tests showed that anti-CCP was positive in 1.0% of cases, RF was positive in 3.6% of cases, and ANA was positive in 98.0% of cases. The most common immunofluorescence pattern observed in ANA testing was speckled nucleolus homogenous, accounting for 42.6%. The next most common patterns were nucleolus homogenous and speckled, accounting for 12.2% and 9.1%, respectively. The highest titer detected was 1 to 1,280, found in 81.7% of cases. Lower titers of 1 to 160, 1 to 640, and 1to 320 were found in 5.1%, 4.1%, and 4.1% of cases, respectively. Anti-Scl70 was positive in 77.7% of cases, with the highest titer being 3+ in 61.9% of cases. Anti-centromere was positive in 11.7% of cases, with the highest titer being 3+ in 9.1% of cases.

The hand radiographs revealed that 86.8% of patients had abnormalities, with digital tuft resorption being the most prevalent at 73.1%. This was followed by periarticular osteopenia at 60.9% and calcinosis cutis at 47.2%. Erosion of the joints was found in 1.5% of cases, with Metacarpophalangeal and Wrist in 0.5%. The highest number of joints with erosion was 2, accounting for 1.0% of cases.

Comparing the clinical features between systemic sclerosis patients with arthritis and without arthritis, the patients with arthritis had a shorter

disease duration compared to those without arthritis. In terms of radiographic abnormalities, including periarticular osteopenia and joint space narrowing, they were more prevalent in patients with arthritis compared to those without arthritis. The clinical comparison between patients with arthritis and without arthritis is presented in Table 2.

Based on the univariate analysis, factors associated with the occurrence of arthritis in systemic sclerosis were duration, periarticular osteopenia, and joint space narrowing (Table 3).

When these clinical factors were analyzed together using multivariable logistic regression, presence of periarticular osteopenia was the only independent factor associated with arthritis in systemic sclerosis (Table 3). Patients with systemic sclerosis who had periarticular osteopenia had significantly associated with systemic sclerosis arthritis (95% CI 8.34 to 67.36, p<0.001).

Discussion

The present study found that 70.1% of all patients with systemic sclerosis had inflammatory arthritis. The clinical factor significantly associated with the systemic sclerosis arthritis was the presence of periarticular osteopenia, which is related to bone loss in the small joints of hand. This early characteristic indicates joint damage and is associated with joint destruction in patients with systemic sclerosis[13].

The arthritis of systemic sclerosis studied in the present research may differ from the previous studies. In the present study, systemic sclerosis arthritis was found in the early stage of the disease, different from the studies of Sandler et al.[11] and Avouac et al[13]. However, Foocharoen et al.[1] found arthritis in the early stage of the disease similar to the present study.

The presence of anti-CCP was found to be positive in only 1% in the present study, which is different from Wielosz et al.[14], who reported in 10% of the cases. Regarding positive RF, as Wielosz et al.[14] reported result in 17.1% and Young et al.'s study 30%[15] whereas the present study was only 3.6% positive RF.

The present study excluded overlap syndrome, which differed from Horimoto and Costa[16] that reported a prevalence of 6.6%, and Foocharoen et al.[17] that found a prevalence of overlap syndrome with systemic sclerosis at 13.2%. The present study found the clinical factor significantly associated with the development of systemic sclerosis arthritis was periarticular osteopenia. On the other hand, Wielosz et al.[14] found anti-CCP was a predictive factor for the development of inflammatory arthritis in patients with systemic sclerosis[3,18-21].

Finally, the author found that hand radiographs showed abnormalities in 86.8% of the cases, with the highest prevalence of phalanges resorption in 73.1%, followed by periarticular osteopenia at 60.9%, and calcinosis cutis at 47.2%. These findings differed from the results of Horimoto and Costa[16], as they reported abnormalities in 42.6% of cases, with phalanges resorption in 65.4% and calcinosis in 34.6%. Erosion of the bones, found in 1.5% of cases in the present study, differs with the findings of Jacques et al.[10] who reported a prevalence of bone erosion of 10.6%. Sakata et al.[22] also found bone erosion in 19% of cases.

The present study is the first comparative study conducted in Thailand that examines patients with systemic sclerosis with and without arthritis using statistical analysis to control for a range of factors. It includes the evaluation of serological tests and radiographic assessments of the hands by rheumatologists. However, the present study had limitations. It was conducted in a referral hospital, which may not fully represent the population of systemic sclerosis patients from community hospitals or other provinces. Further studies are necessary to include a more diverse population and provide a comprehensive approach to the management of arthritis in systemic sclerosis patients in the future.

Conclusion

Inflammatory arthritis is a common clinical feature in systemic sclerosis. The presence of periarticular osteopenia is independently clinically associated with inflammatory arthritis. This clinical factor could be utilized to aid in the diagnosis of inflammatory arthritis in systemic sclerosis patients and improve treatment outcomes.

What is already known on this topic?

Frequent occurrence of inflammatory arthritis is commonly found in patients with systemic sclerosis and is a significant factor that contributes to a poor quality of life.

However, diagnosis and treatment of inflammatory arthritis in systemic sclerosis can still be challenging due to the lack of clear guidelines.

What does this study add?

This study adds that screening for diagnosis of inflammatory arthritis in systemic sclerosis patients

Table 2. Comparison of clinical features, laboratory findings, and radiographic features between systemic sclerosis patients with and without arthritis

Variable	Total (n=197)	Arthritis (n=138)	No arthritis (n=59)	p-value
Age (years); mean±SD	57.3±11.0	56.6±10.0	58.9±13.0	0.195
Age of onset; mean±SD	51.6±11.8	51.3±11.4	52.4±12.6	0.575
Sex				0.683
Male	54 (27.4)	39 (28.3)	15 (25.4)	
Female	143 (72.6)	99 (71.7)	44 (74.6)	
Duration; median (IQR)	4 (2 to 8)	4 (1 to 8)	6 (3 to 8)	0.011*
Type; n (%)				
Diffuse cutaneous systemic sclerosis	180 (91.4)	124 (89.9)	56 (94.9)	0.247
Limited cutaneous systemic sclerosis	17 (8.6)	14 (10.1)	3 (5.1)	
Extra articular musculoskeletal; n (%)				
Calcinosis cutis	92 (46.7)	63 (45.7)	29 (49.2)	0.652
Joint contraction/ deformity	64 (32.5)	44 (31.9)	20 (33.9)	0.782
Carpal tunnel syndrome	8 (4.1)	8 (5.8)	0 (0)	0.108
Trigeminal neuralgia	2 (1.0)	2 (1.4)	0 (0)	1.00
Tendon friction rub	1 (0.5)	1 (0.7)	0 (0)	1.00
mRSS (score); mean±SD	11.9±6.2	11.5±6.0	13.1± 6.6	0.107
Raynaud's phenomenon; n (%)	174 (88.3)	119 (86.2)	55 (93.2)	0.162
Organ involvement; n (%)				
ILD	137 (69.5)	96 (69.6)	41 (69.5)	0.992
Esophageal involve	112 (56.9)	83 (60.1)	29 (49.2)	0.154
Digital ulcer/gangrene	79 (40.1)	52 (37.7)	27 (45.8)	0.289
Myositis	26 (13.2)	18 (13.0)	8 (13.6)	0.922
PAH	21 (10.7)	15 (10.9)	6 (10.2)	0.884
SRC	3 (1.5)	2 (1.4)	1 (1.7)	1.00
Pericardial effusion	1 (0.5)	1 (0.7)	0 (0)	1.00
Inflammatory marker; n (%)				
ESR, mean±SD	57.9±30.3	56.9±29.2	60.3±32.9	0.471
• Normal (0 to 15 mm/hour)	7 (3.6)	6 (4.3)	1 (1.7)	0.677
• Abnormal (>15 mm/hour)	190 (96.4)	132 (95.7)	58 (98.3)	
CRP; median (IQR)	3 (0.8 to 8.0)	2.28 (0.8 to 6.4)	4.07 (0.8 to 10)	0.075
• Normal (0 to 3 mg/L)	100 (50.8)	74 (53.6)	26 (44.1)	0.219
• Abnormal (>3 mg/L)	97 (49.2)	64 (46.4)	33 (55.9)	
Serology; n (%)				
Anti-CCP, positive	2 (1.0)	1 (0.7)	1 (1.7)	0.510
RF, positive	7 (3.6)	7 (5.1)	0 (0)	0.105
ANA, positive	193 (98.0)	135 (97.8)	58 (98.3)	1.00
• Speckled	125 (63.5)	89 (64.5)	36 (61.0)	0.643
• Nucleolus	129 (65.5)	86 (62.3)	43 (72.9)	0.153
• Homogenous	140 (71.1)	95 (68.8)	45 (76.3)	0.292
• Cytoplasmic	12 (6.1)	8 (5.8)	4 (6.8)	0.754
• Fine speckled	5 (2.5)	2 (1.4)	3 (5.1)	0.160
• Centromere	13 (6.6)	11 (8.0)	2 (3.4)	0.351
Anti-Scl70, positive	153 (77.7)	106 (76.8)	47 (79.7)	0.660
Anti-centromere, positive	23 (11.7)	17 (12.3)	6 (10.2)	0.667
Characteristics of abnormal hand radiographs; n (%)	171 (86.8)	125 (90.6)	46 (78.0)	0.017*
Digital tuft resorption	144 (73.1)	100 (72.5)	44 (74.6)	0.759
Periarticular osteopenia	120 (60.9)	109 (79.0)	11 (18.6)	<0.001*
Calcinosis cutis	93 (47.2)	64 (46.4)	29 (49.2)	0.721
Joint contracture	61 (31.0)	41 (29.7)	20 (33.9)	0.560
Joint space narrowing	36 (18.3)	33 (23.9)	3 (5.1)	0.002*
Marginal erosion	4 (2.0)	4 (2.9)	0 (0)	0.319

SD=standard deviation; IQR=interquartile range; mRSS=modified Rodnan skin score; ILD=interstitial lung disease; PAH=pulmonary arterial hypertension; SRC=scleroderma renal crisis; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; CCP=citrullinated protein antibody; RF=rheumatoid factor; ANA=antinuclear antibody

* Statistically significant

Table 2. (continued)

Variable	Total (n=197)	Arthritis (n=138)	No arthritis (n=59)	p-value
Joints with erosion, positive; n (%)	3 (1.5)	3 (2.2)	0 (0)	0.556
Number of joints with erosion; n (%)				
1	1 (0.5)	1 (0.7)	0 (0)	0.521
2	2 (1.0)	2 (1.4)	0 (0)	

SD=standard deviation; IQR=interquartile range; mRSS=modified Rodnan skin score; ILD=interstitial lung disease; PAH=pulmonary arterial hypertension; SRC=scleroderma renal crisis; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; CCP=citrullinated protein antibody; RF=rheumatoid factor; ANA=antinuclear antibody

* Statistically significant

Table 3. Univariate and multivariate logistic regression analyses of clinical factors associated with or without arthritis

Clinical factors	Univariate		Multivariate	
	OR (95% CI)	p-value	OR 95% CI	p-value
Age (every 1 year increasing)	0.98 (0.95 to 1.01)	0.195	0.98 (0.95 to 1.02)	0.306
Age of onset (every 1 year increasing)	0.99 (0.97 to 1.02)	0.573		
Sex (Male[a])				
Female	0.87 (0.43 to 1.73)	0.683		
Duration (year)	0.95 (0.9 to 0.99)	0.042*	0.95 (0.89 to 1.02)	0.128
Type (Limited[a])				
Diffuse cutaneous systemic sclerosis	0.47 (0.13 to 1.72)	0.256		
Extra articular musculoskeletal (No[a])				
Joint contraction/deformity	0.91 (0.48 to 1.74)	0.782		
Calcinosis cutis	0.87 (0.47 to 1.6)	0.652		
Skin mRSS	0.96 (0.91 to 1.01)	0.108	0.95 (0.88 to 1.02)	0.132
Organ involvement				
Raynaud's phenomenon (No[a])	0.46 (0.15 to 1.4)	0.171	0.99 (0.25 to 3.99)	0.998
Digital ulcer/gangrene (No[a])	0.72 (0.39 to 1.33)	0.290		
Myositis (No[a])	0.96 (0.39 to 2.34)	0.922		
Esophageal involve (No[a])	1.56 (0.85 to 2.88)	0.155	0.91 (0.4 to 2.07)	0.827
ILD (No[a])	1.00 (0.52 to 1.95)	0.992		
PAH (No[a])	1.08 (0.4 to 2.93)	0.884		
Inflammatory marker				
ESR (Normal[a])	0.38 (0.05 to 3.22)	0.374		
CRP (Normal[a])	0.98 (0.94 to 1.01)	0.137	0.51 (0.22 to 1.19)	0.118
Serology				
Anti-CCP (Negative[a])	0.42 (0.03 to 6.88)	0.546		
ANA (Negative[a])		0.828		
• ANA positive type	0.78 (0.08 to 7.62)			
• Speckled nucleolus homogenous (No[a])	0.66 (0.36 to 1.23)	0.191	0.82 (0.36 to 1.9)	0.648
• Nucleolus homogenous (No[a])	1.69 (0.6 to 4.77)	0.320		
• Speckled (No[a])	2.24 (0.62 to 8.04)	0.218		
• Homogenous (No[a])	0.94 (0.28 to 3.19)	0.923		
• Centromere (No[a])	3.98 (0.49 to 32.13)	0.195	5.21 (0.48 to 56.7)	0.176
Anti-Scl70 (Negative[a])	0.85 (0.4 to 1.79)	0.660		
Anti-centromere (Negative[a])	1.24 (0.46 to 3.32)	0.667		
Characteristics of abnormal hand radiographs (No[a])	2.72 (1.17 to 6.29)	0.02*	0.4 (0.13 to 1.23)	0.109
Periarticular osteopenia (No[a])	16.4 (7.57 to 35.52)	<0.001*	23.7 (8.34 to 67.36)	<0.001*
Joint space narrowing (No[a])	5.87 (1.72 to 19.98)	0.005*	1.38 (0.33 to 5.71)	0.656
Joint contracture (No[a])	0.82 (0.43 to 1.58)	0.561		
Calcinosis cutis (No[a])	0.9 (0.49 to 1.65)	0.721		
Phalanges resorption (No[a])	0.9 (0.45 to 1.8)	0.759		

mRSS=modified rodnan skin score; ILD=interstitial lung disease; PAH=pulmonary arterial hypertension; SRC=scleroderma renal crisis; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; CCP=citrullinated protein antibody; RF=rheumatoid factor; ANA=antinuclear antibody

[a] Comparative reference group, * Statistically significant

can be done with hand radiograph, which shows periarticular osteopenia.

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Conflicts of interest

The author declares no conflict of interest.

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