https://doi.org/10.52645/MJHS.2022.4.02
UDC: 616.72–002:616.517+616.75/.76

RESEARCH ARTICLE

Impact of comorbidities on the clinical and ultrasound features of psoriatic arthritis

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Manuscript received on: 23.07.2022
Accepted for publication: 25.11.2022
Published: 15.12.2022

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What is not yet known on the issue addressed in the submitted manuscript

It is not known the relationship between comorbidities and clinical evolution and ultrasound characteristics of psoriatic arthritis, which can help to optimize the tactics of patient management and to appreciate the connection between main syndromes and specific clinical expression.

The research hypothesis

When comparing comorbidities in groups of young and middle-aged patients, it was shown that it was higher in the group of middle-aged patients, but the chronological appearance of comorbidities did not differ, which indicates an increase with age in the number of comorbid diseases pathogenetically associated with the evolution of psoriatic arthritis.

The novelty added by manuscript to the already published scientific literature

During clinical and ultrasound examination of the joints and entheses, it was found that, synovitis was detected significantly more often when using ultrasound, which indicates subclinical synovitis. The frequency of enthesitis in the large joints of the upper and lower extremities according to ultrasound data was 13.3%, which is significantly higher than in the case of a clinical examination (7.7%, p<0.001), and this indicates asymptomatic enthesitis.

Summary

Objectives. The objective was to evaluate the relationship of comorbid pathology with the clinical and ultrasound characteristics of the evolution of psoriatic arthritis in order to optimize the management.

Material and methods. In order to achieve the purpose and objectives of the study, a group of 92 patients with psoriatic arthritis was selected, established in accordance with the CASPAR diagnostic criteria (2006). The patients were treated in the rheumatology and arthrology departments of the *Timofei Moșneaga* Republican Clinical Hospital and of the *Saint Trinity* Municipal Clinical Hospital in Chisinau during 2017-2020. A type 1 cohort study is planned (prospective study with retrospective components).

Results. Expression at the time of examination of the history data was observed in 54 (58,7%), clinical enthesitis was observed in 47 (51.1%) patients. During the clinical examination of patients, it was found that the frequency of TJC/14 was 11.3% (145/1288), SJC/14 – 4.5% (58/1288), which was 40% (58/145) among all painful joints. During clinical examination, it was found that the TJC of the upper limbs (74/736, 10.1%) and lower (71/552, 12.9%) do not differ significantly ($\chi^2 = 2.489$, $p = 0.115$). At the same time, the SJC of the lower limbs (43/552, 7.8%) was significantly higher than the upper one (15/736, 2.04%) ($\chi^2 = 24.267$, $p < 0.001$). According to ultrasound data, the number of joints examined was 228/1288 (17.7%), number of inflamed entheses – 90/1288 (6.9%), which was 39.5% among the detected synovitis (90/228). The number of enthesitis were 661/4968 (13.3%), of which 19.4% (128/661) of the entheses were vascularized.

Conclusions. According to ultrasound data, the frequency of detection of enthesitis and synovitis was significantly higher than during the clinical examination ($p < 0.01$). For its part, the psoriatic arthritis activity index (DAPSA) did not correlate with inflammatory changes detected during extensive ultrasound of large joints and entheses according to the "gray scale" and the use of Power-Doppler ($p > 0.05$). On the other hand, vascularization in the entheses is an index of activity independent of age and activity of psoriatic arthritis and psoriasis ($p > 0.05$), and it is a sign of active inflammation which correlates with laboratory markers of inflammation (hs-CRP, $p < 0.05$; ESR, $p < 0.01$).

Keywords: psoriatic arthritis, comorbidities, joint ultrasonography.

Introduction

Psoriatic arthritis (PsA) is a chronic musculoskeletal and cutaneous inflammatory disease that affects about 20-30%

of patients with psoriasis [1, 2]. In addition to musculoskeletal and cutaneous manifestations, patients with PsA have a higher prevalence of comorbidities compared to the general population. More than half of patients with PsA have at least one comorbidity, with up to 40% of patients having more than three comorbidities [2-4]. PsA has a particularly strong association with metabolic diseases and, as a result, with cardiovascular diseases (CVD) [5-6]. There is a higher prevalence of metabolic diseases such as high blood pressure, dyslipidemia, diabetes and obesity compared to patients with psoriasis and without PsA [2, 6-8] or with the general population [2, 5, 9]. PsA is associated with a 55% increased risk of developing CVD, such as ischemic heart disease, cerebrovascular disease, and congestive heart failure [3, 4, 7]. Both, the higher inflammatory burden and the increased incidence and prevalence of traditional CVD risk factors, such as high blood pressure, glucose intolerance, dyslipidemia and obesity in psoriatic disease, seem to play an important role in the development of CVD in PsA [1, 2, 6]. CVD is a major source of morbidity and a leading cause of mortality in PsA [5, 8, 9]. Therefore, addressing these comorbidities can improve quality of life and functional status and reduce healthcare costs as well as mortality in PsA. In this research, we will explore the complex relationship of PsA with metabolic diseases and CVD.

Metabolic syndrome (MetS) is defined by the presence of central obesity, hypertension, insulin resistance, and dyslipidemia [3, 6, 9, 10]. Approximately 24-58% of patients with PsA have MetS, which is higher than that of the general population [4, 7, 9, 11]. In some cohorts that use MetS' NHLBI/AHA validated definition, MetS's prevalence in PsA is up to 59% [6, 9, 11-12]. The chances of having MetS in PsA compared to the general population were 2.68 (CI 95% 1.60 - 4.50) in an outpatient clinic-based study in China [3, 4, 7, 13]. The prevalence of MetS and its components is also usually higher in PsA compared to psoriasis alone: hypertension (37% vs. 20%), hyperlipidemia (21% vs. 15%), diabetes (12% vs. 7%) and obesity (30 vs. 27%) [5, 9, 12]. In addition, there is a higher proportion of patients with MetS PsA compared to rheumatoid arthritis (RA) and other spondyloarthritis (SpA) [3, 7, 8]. MetS prevalence was higher in PsA compared to RA or ankylosing spondylitis (AS) (OR 2.44, CI 95% 1.48–4.01) in an outpatient study of the clinic arthritis. The chances were higher for all components of MetS, including central obesity, decreased blood glucose levels during fasting, hypertriglyceridemia and decreased HDL-C levels [6, 9, 14].

Patients with PsA who are also obese and/or have MetS have been observed to have higher disease activity and weaker treatment results. There may be several reasons for this difference. First, one study found that obese patients tend to have a longer time for diagnosis compared to patients with normal BMI (5.7 vs. 2.8 years). This may be due to the difficulty to examine joints in these patients. Then, obese patients may have worse disease activity reported by patients due to obesity-related functional deficits, and obesity is associated with increased CRP [1-4]. Data from Danish and Icelandic biological registries with 1943 PsA patients also showed higher initial activity of the disease (DAS28, CRP, and visual analog-pain scale) in obese compared to non-obese patients [3, 8, 9].

The purpose of the study was to evaluate the relationship of comorbid pathology with the clinical and ultrasound characteristics of the evolution of psoriatic arthritis in order to optimize the management.

Material and methods

In order to achieve the purpose and objectives of the study, a group of 92 patients with psoriatic arthritis was selected. The diagnosis of PsA was established in accordance with the CASPAR classification criteria (2006). Patients were treated in the rheumatology and arthrology departments of the *Timofei Moșneaga* Republican Clinical Hospital and in the *Saint Trinity* Municipal Clinical Hospital in Chisinau during 2017-2020. A type 1 cohort study is planned (prospective study with retrospective components).

The average age of patients with PsA was 42.9 ± 9.6 years, the average duration of psoriasis was 11 (7; 25.8) years, the average duration of PsA was 7 (2; 11.8) years. Among patients included in the study were 42 men (45.7%) and 50 women (54.3%). Patients' characteristics are given in table 1.

Table 1. Characteristics of patients with PsA.

Index	Values
Men, n (%)	42 (45.7%)
Women, n (%)	50 (54.3%)
Age, years, M ± SD, min-max	42.9 ± 9.6, 22-60
Duration of PsA, years, Me (25; 75)	7 (2; 11.8)
DAPSA, Me (25; 75)	15.2 (10.2; 21.4)
Skin psoriasis (Ps), n (%)	91 (98.9%)
Ps duration, years, Me (25; 75)	11 (7; 25.8)
PASI, Me (25; 75)	3.8 (1.2; 9.6)
TJC/14, Me (25; 75)	1 (0; 3)
SJC/14, Me (25; 75)	0 (0; 2)
hs-CRP, mg/l, Me (25; 75)	5.1 (2.2; 16.1)
ESR, mm/h, Me (25; 75)	20 (11; 30)

Note: *Ps – psoriasis; PASI - Psoriasis Area Severity Index, TJC - tender joints count; SJC – swollen joints count; M – median; SD – standard deviation; DAPSA - Disease Activity in PSoriatic Arthritis.*

A positive family history of psoriasis was detected in 31 (33.7%) patients. At the time of inclusion in the study, 19 (20.6%) patients had disabilities, of which 15 (16.3%) had disabilities due to PsA, and 4 (4.3%) of the patients had a general disease.

Treatment of patients with PsA was carried out in accordance with the recommendations of the National Clinical Protocol „Psoriatic Arthritis in adults" at the time of the study.

Distribution of patients by PsA activity in calculating the DAPSA (Disease Activity in PSoriatic Arthritis) index: most had moderate activity (14-28) of 33 (42%), high (> 28) in

13 (16%) patients, decreased (4 - 14) – 30 (38%), remission (< 4) was observed in 3 (4%) patients.

The distribution of patients according to the activity of cutaneous psoriasis in the calculation of the PASI index was as follows: remission - 7 (8%), mild - 57 (68%), average - 9 (11%) severe - to 11 (13%) patients.

According to the clinical and instrumental methods of the study, the distribution of patients by the involvement of peripheral joints and spine was as follows: polyarthritis was in 63 (68.5%) patients, oligoarthritis – in 19 (20.7%), monoarthritis – 10 (10.9%), included axial manifestations sacroiliitis – in 30 (32.6%) patients and spondylitis – in 23 patients (25%), a combination of sacroiliitis and spondylitis – in 13 patients (14.1%). Patients with isolated axial lesions were absent.

The areas evaluated in the clinical examination (visual evaluation and determination of pain on palpation) and ultrasonographic areas included similar areas:

- Joints (14 in each patient) – acromioclavicular, shoulder, elbow, radiocarpal, hip, knee, talocrural;
- Entheses (54 per patient):
- The lower pole of the calcaneus: plantar aponeurosis entheses (thickness of the planting aponeurosis ≥4.4 mm; erosion of the lower pole of the calcaneus; enthesophyte of the lower pole of the calcaneus);
- Upper pole of the calcaneus: entheses of the Achilles tendon (thickness of the Achilles tendon ≥5.29 mm; retrocalcaneal bursitis; erosion of the posterior pole of the calcaneus; enthesophyte of the posterior pole of the calcaneus);
- Tibial tuberosity: distal patellar ligament entheses (thickness of the patellar ligament ≥4 mm; infrapatellar bursitis; erosion of tibial tuberosity; enthesophyte of tibial tuberosity);
- Lower pole of the patella: entheses of the proximal patellar ligament; the thickness of the patellar ligament ≥4 mm; erosion of the lower pole of the patella; enthesophyte of the lower pole of the patella);
- Upper pole of the patella: entheses of the quadriceps tendon (thickness of the quadriceps tendon ≥6.1 mm; suprapatellar bursitis; erosion of the upper pole of the patella; enthesophyte of the upper pole of the patella);
- Tuberosity of the olecranon: triceps tendon entheses (thickness of the triceps tendon ≥4 mm; olecranon bursitis; olecranon erosion; olecranon enthesophyte; olecranon enthesophyte)

Ultrasound modifications of enthesitis were evaluated according to the ultrasound definition of entheses proposed by OMERACT, using a „gray scale" and Power-Doppler to evaluate vascularization (table 2) [5-8].

Table 2. Definition of ultrasound signs of inflammatory and structural changes in entheses (Consensus of experts).

Inflammatory signs (agreement 100%)	**Structural features (agreement) 100%)**
Localization of the Doppler signal in the entheses	Calcification/enthesophyte in the entheses
Hypoechoic entheses	Erosion at the place of attachment
Thickening of the entheses	

Note: *Final definition of enthesitis - Hypoechoic and/or thickened tendon at the site of insertion on the bone (on the bone at 2 mm), with Doppler signal for active entheses and the presence of erosions and enthesophytes/calcified as a sign of structural damage.*

Ultrasound included counting the following signs:

- in the „gray scale" mode: the number of joints with ultrasound signs of synovitis (the number of synovitis), the number of joints with osteophytes;
- in Power-Doppler mode: the number of joints with ultrasound signs of active synovitis (number of vascularized synovitis);
- number of affected entheses: decrease in echogenicity and thickening of the entheses, number of entheses with the presence of vascularization, number of entheses with structural changes: the presence of erosions, enthesophytes, calcifications.

Taking into account the identified changes, the following ultrasound indices were calculated: GUESS (Glasgow Ultrasound Enthesitis Scoring System), BUSES (Belgrade Ultrasound Enthesitis Score), MASSI (Madrid Sonography Enthesitis Index) and SEI (Sonographic Enthesitis Index).

Results

The patients included in the study were clinically examined and an ultrasound of large joints and entheses were performed (the total number of joints examined was 1288, entheses – 4968).

Expression at the time of examination of the history data was observed in 54 (58,7%), clinical enthesitis was observed in 47 (51.1%) patients. During the clinical examination of patients, it was found that the frequency of TJC/14 was 11.3% (145/1288), SJC/14 – 4.5% (58/1288), which was 40% (58/145) among all painful joints.

During clinical examination, it was found that the TJC of the upper limbs (74/736, 10.1%) and lower (71/552, 12.9%) do not differ significantly ($\chi 2 = 2.489$, $p = 0.115$). At the same time, the SJC of the lower limbs (43/552, 7.8%) was significantly higher than the upper one (15/736, 2.04%) ($\chi 2 = 24.267$, $p < 0.001$).

It should be noted that pain and swelling of the hip joints could not be determined by physical examination; therefore, they were not taken into account in this analysis. TJC/14 and SJC/14 in terms of localization were as follows: acromioclavicular joints - 5 and 0, shoulder - 29 and 2, elbow - 13 and 1, hand joints - 29 and 15, knees - 38 and 25, talocrural - 33 and 18 respectively.

When assessing the involvement of entheses in the projection of large joints, it was found that the number of painful entheses of the upper extremities (71/1472, 4.8%) was significantly lower than the lower ones (310/3496, 8.9%)

($\chi2 = 23,923$, $p < 0.001$). The localization of painful entheses on palpation was as follows: at the place of attachment of the supraspinous muscle - 7, the subosteal muscle - 1, the subscapular muscle - 1, the triceps muscle - 2, at the lateral epicondyle - 35, at the medial epicondyle - 25, at the anterior spines of the iliac bones (upper and lower) - 37, at the posterior spines of the iliac bones - 11, at the sciatic tubercle - 1, in the large trochanter - 5, the medial collateral ligament: proximal section - 16, distal - 25, the lateral collateral ligament: proximal section - 26, distal section - 23, quadriceps muscle - 7, semimembranosus muscle - 8, anterior muscle - 5, posterior muscle - 6, Achilles tendon - 38, plantar fascia - 9.

According to ultrasound data, the number of joints examined was 228/1288 (17.7%), the number of inflamed entheses – 90/1288 (6.9%), which was 39.5% among the detected synovitis (90/228). The number of entheses was 661/4968 (13.3%), of which 19.4% (128/661) of the entheses were vascularized. The number of confirmed was 876/4968 (17.6%). The frequency of enthesitis and synovitis detected in the gray scale mode according to ultrasonographic data is shown in table 3.

Table 3. Frequency of enthesitis and synovitis detected in the "grayscale" mode according to ultrasonographic data.

Upper limbs	Frequency	Lower limbs	Frequency
Joints:			
Acromio-clavicular	46/736 (6.3%)	Coxofemural	28/552 (5.1%)
Humeral	7/736 (0.95%)	Knee	42/552 (7.6%)
Ulnar	18/736 (2.4%)	Talocrural	32/552 (5.8%)
Radiocarpal	47/736 (6.4%)		
Total	118/736 (16%)	**Total**	112/552 (20.3%)*
		Enthesitis:	
Short head of the biceps muscle of the shoulder	10/1472 (0.7%)	Great trochanter: - gluteus minor - gluteus medium	28/3496 (0.8%) 45/3496 (1.3%)
Subscapular muscle	20/1472 (1.4%)	Sciatic tubercle	28/3496 (0.8%)
Nastular muscle	13/1472 (0.9%)	Collateral ligament medial - proximal - distal	53/3496 (1.5%) 20/3496 (0.6%)
Subosteal muscles	2/1472 (0.1%)	Lateral collateral ligament: - proximal - distal	33/3496 (0.9%) 19/3496 (0.5%)
Triceps muscle of the shoulder	11/1472 (0.7%)	Own patellar ligament - proximal - distal	6/3496 (0.2%) 21/3496 (0.6%)
Medial epicondyle	30/1472 (2%)	*"Pes anserinus mirror"*	70/3496 (2%)
Lateral epicondyle	54/1472 (3.7%)	Femoral biceps	9/3496 (0.3%)
		Semi-membranous muscles	36/3496 (1%)
		Quadriceps femoral	23/3496 (0.7%)
		Anterior tibial muscle	19/3496 (0.5%)
		Posterior tibial muscle	18/3496 (0.5%)
		Achilles	27/3496 (0.8%)
		Plantar fascia	43/3496 (1.2%)
Total	144/1472 (9.8%)	**Total**	517/3496 (14.8%)**

Note: **p < 0.05, **p < 0.01.*

When evaluating the differences in the frequency of synovitis of the lower (112/552, 20.3%) and superior (118/736, 16%) limbs, it was found that the synovitis of the lower extremities was significantly more frequent ($\chi2 = 3.897$, $p < 0.05$).

When evaluating the differences in the frequency of enthesitis, it was found that enthesitis of the lower extremities (517/3496, 14.8%) occurred significantly more often than the upper one (144/1472, 9.8%, $\chi2 = 22.502$, $p < 0.001$).

The changes detected in the „gray scale" mode can be a sign not only of an active process, but also of chronic inflammation, therefore the presence of vascularization of synovitis and enthesitis, detected with the help of Power-Doppler, is more likely to indicate the activity of the process. Comparing the frequency of vascularization of large joints of the upper and lower extremities is not possible, since piloting the Doppler signal during inflammation of the hip and talocrural joints is difficult due to the anatomical features of these joints.

In the study it was found that the frequency of enthesitis detected during the clinical examination was 7.7% (the number of painful entheses, 381/4968) compared to 13.3% according to the ultrasound data (the number of entheses, 661/4968), which was significantly lower ($p < 0.001$).

When comparing ultrasound data in the groups of patients with isolated peripheral arthritis (n = 52) and in

combination with axial lesions (n = 40), no differences were found in groups (number of synovitis (by ultrasound examination), number of enthesitis, number of entheses with structural disorders, number of vascular Doppler-positive entheses, GUESS, BUSES, SEI, MASSI, p > 0.05). DAPSA scores were significantly higher in the group of patients with a combination of peripheral arthritis with spinal injuries (p < 0.01). The groups were different in terms of duration of PsA (p = 0.013), severity of psoriatic onychodystrophy (NAPSI, p < 0.01), TJC/14 (p = 0.037) and CRP-hs (p = 0.031) and were higher in the group of patients with peripheral arthritis and axial involvement.

Discussions

It is known that spondyloarthritis mainly affects the joints and entheses of the lower extremities, therefore, in most cases; the entheses of the lower extremities were included in various clinical indices of enthesitis. In this study, during an extensive clinical examination and ultrasound of the joints and entheses of the upper and lower extremities, depending on the „gray scale", it was shown that the frequency of synovitis of the lower limbs (20.3%) was significantly higher than the upper one (16%) (p < 0.05), and the entheses of the lower extremities (14.8%) were observed significantly more often than the upper part (9.8%), (p < 0.001), which corresponds to the literature data [6, 10, 13]. The identified differences can be explained by the higher frequency of trauma of the enthesis of the lower extremities, which, according to the theory of biomechanical stress, is one of the triggers for the development of enthesitis [2, 8, 11, 14]. However, this has not been demonstrated for vascularized entheses, the frequency of which does not differ according to location (p > 0.05).

Despite the low incidence of obesity (25%), it should be noted a higher frequency of overweight patients (33.3%), as well as an increase in the ratio of chest circumference to body circumference (57.1%), which should also be taken into account. With the increase in thoracic circumference, body circumference and BMI of the patient, the number of comorbid conditions increased significantly (p < 0.01). Several directions of research are needed to examine the link between PsA and obesity to further determine whether obesity is a consequence of PsA. Other potential mechanisms linking obesity in PsA and cardiovascular risk (dyslipidemia, high blood pressure, insulin resistance, and smoking) have not yet been identified. The effect of obesity on the activity of PsA and the response to DMARD therapy and TNFα inhibitors [6, 11-13] has been demonstrated, in addition, weight loss has contributed to a decrease in the severity of joint and entheses inflammation, as well as in the activity of skin psoriasis [4, 6, 9].

When comparing comorbidities in groups of young and middle-aged patients, it was shown that comorbidity was higher in the group of middle-aged patients (p < 0.05), and chronological comorbidities (p > 0.05) in groups does not differ, which indicates an increase with age mainly in the number of comorbid diseases pathogenetically associated with the course of PsA. The presence of axial lesions in patients with peripheral arthritis did not increase the number of comorbid diseases in patients with PsA (p > 0.05).

In this case, patients with peripheral arthritis and spinal cord injury had a longer duration of PsA (p = 0.013), severity of psoriatic onychodystrophy (NAPSI, p < 0.01), PsA activity (DAPSA), TJC/14 (p < 0.05) and higher levels of hs-CRP (p < 0.05) compared to patients with isolated peripheral arthritis. Interestingly, ultrasonographic parameters of joint and entheses lesions do not differ.

During the clinical examination carried out and the ultrasound of the joints and entheses, it was found that synovitis (17.7%) was detected significantly more often than with the help of a clinical examination (TJC/14 and SJC/14, 4.7% and 11.3%, p < 0.01), which indicates subclinical synovitis. The frequency of entheses in the large joints of the upper and lower extremities according to ultrasound data was 13.3%, which is significantly higher than in the case of a clinical examination (7.7%, p < 0.001), and this also indicates asymptomatic entheses, a finding consistent with the literature [4-7, 9-12].

The higher frequency of detection of pathological changes according to ultrasound data compared to a clinical examination is a serious reason for an extensive evaluation of the ultrasound signs of inflammation and joint entheses - its nature and localization - and the determination of their role in patient management.

Conclusions

According to ultrasound data, the frequency of detection of enthesitis and synovitis were significantly higher than during the clinical examination (p < 0.01). In turn, the activity index PsA (DAPSA) did not correlate with the inflammatory changes detected during the extensive ultrasound of large joints and entheses according to the „gray scale" and with the use of Power-Doppler (p > 0.05).

Vascularization in the entheses is an index of activity independent of age and activity of PsA and psoriasis (p > 0.05) a sign of active inflammation with correlation with laboratory markers of inflammation (hs-CRP p < 0.05, ESR p < 0.01). At the same time, the SMI technique demonstrated comparable results with Power-Doppler in identifying the frequency of vascularized synovitis of large joints (52.6% vs 44.4%, p > 0.05); when assessing entheses vascularization, the frequency of SMI+ vascularized entheses were significantly higher than Power-Doppler+ (33.3% vs. 17.1%, p < 0.001).

Abbreviations

AS – Ankylosing Spondylitis; BMI – body mass index; BUSES – Belgrade Ultrasound Enthesitis Score; CASPAR – The ClASsification for Psoriatic Arthritis; CI – Confidence Interval; CVD – cardiovascular diseases; DAPSA – Disease Activity in PSoriaticArthritis; DAS-28 – Disease Activity Score; DMARD – Disease-modifying antirheumatic drugs; ESR – erythrocyte sedimentation rate; GUESS – Glasgow Ultrasound Enthesitis Scoring System; hs-CRP – high sensitivity C-reactive protein; M – median; MASSI – Madrid Sonography Enthesitis Index; MetS – metabolic syndrome; NAPSI –

Nail Psoriasis Severity Index; NHLBI/AHA – National Heart; Lung; and Blood Institute / American Heart Association; OR – Odds Ratio; PASI – Psoriasis Area Severity Index; Ps – psoriasis; PsA – psoriatic arthritis; RA – rheumatoid arthritis; SD – standard deviation; SEI – Sonographic Enthesitis Index; SJC – swollen joints count; SpA – Spondyloarthritis; TJC – tender joints count; TNFα – Tumor Necrosis Factor-α.

Declaration of conflict of interest

Nothing to declare

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