The Journal of Rheumatology 2023;50:197–203
doi:10.3899/jrheum.220547
First Release December 1 2022

The Journal of Rheumatology

Sex-Based Differences in Sonographic and Clinical Findings Among Patients With Psoriatic Arthritis

Victoria Furer[1], Jonathan Wollman[1], David Levartovsky[1], Valerie Aloush[1], Ofir Elalouf[1], Hagit Sarbagil-Maman[1], Liran Mendel[1], Sara Borok[1], Daphna Paran[1], Ori Elkayam[1], and Ari Polachek[1]

ABSTRACT. ***Objective.*** To investigate sex-based sonographic differences in patients with psoriatic arthritis (PsA).

Methods. The study population included consecutive prospectively recruited patients with PsA, as determined by the CASPAR (Classification for Psoriatic Arthritis) criteria, who underwent clinical and physical examinations, followed by a detailed ultrasound (US) evaluation (greyscale and Doppler). US evaluation included 52 joints, 40 tendons, and 14 points of entheses (Modified Madrid Sonographic Enthesis Index [MASEI] plus lateral epicondyles) performed by an experienced sonographer blinded to the clinical data. The US score was based on the summation of a semiquantitative score for synovitis, tenosynovitis, and enthesitis. The US enthesitis score was categorized into inflammatory lesions (ie, hypoechogenicity, thickening, bursitis, and Doppler) and structural lesions (ie, enthesophytes/calcifications and erosions).

Results. The study population of 158 patients included 70 males and 88 females. The males had higher rates of employment ($P = 0.01$), Psoriasis Area and Severity Index scores ($P = 0.04$), and mean swollen joint counts ($P = 0.04$). The total US score and its subcategory scores—the synovitis and tenosynovitis scores—were similar for both sexes, whereas the total enthesitis score and its subcategory score—the inflammatory enthesitis score—were significantly higher for the males compared to the females ($P = 0.01$ and $P = 0.005$, respectively). Hypoechogenicity, thickening, and enthesophytes were more prevalent in males compared to females ($P < 0.05$). Multivariate ordinal logistic regression models showed that male sex was associated with a higher US inflammatory enthesitis score compared to female sex (odds ratio 1.96, $P = 0.02$).

Conclusion. Sonographic enthesitis was more prevalent in males compared to females with PsA. These differences were not reflected by enthesitis disease activity scores derived from clinical assessment.

Key Indexing Terms: enthesitis, gender, inflammation, psoriatic arthritis, spondyloarthritis, ultrasound

Psoriatic arthritis (PsA) is a multidomain disease affecting the musculoskeletal (MSK) system. It develops in up to 30% of patients with psoriasis, with an equal male-female ratio.[1] The disease domains include psoriasis, peripheral joint disease, axial disease, dactylitis, and enthesitis expressed as inflammation at tendon, ligament, and joint-capsule insertions into bones. The disease is heterogeneous and can manifest with the involvement of single or multiple MSK sites and can range from mildly to severely debilitating arthritis.

Enthesitis is considered a key manifestation of PsA.[2,3] McGonagle et al[4] proposed the synovio-entheseal complex model, suggesting enthesis as the primary site of inflammation spreading to adjacent periarticular and articular sites. Enthesitis can be among the first, but often unrecognized, symptoms of PsA.[5] The presence of enthesitis has been consistently associated with a high disease burden and radiographic damage in both peripheral and axial joints.[6,7] Based on its pathogenetic and clinical importance in PsA, enthesitis has been recognized as one of the main MSK outcome domains and treatment targets by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis.[8]

In clinical practice, disease evaluation in PsA is usually based on physical examination. However, relying solely on this method may be misleading since findings from the physical examination might not accurately reflect the inflammatory burden.[9,10] Several studies showed that ultrasound (US) was superior to physical examinations by providing a useful and reliable tool in the assessment of inflammation and structural damage.[11] As such, US is emerging as a preferred modality for assessing and monitoring disease activity in PsA, especially enthesitis.[12]

The accumulating body of evidence suggests that sex might have a different impact on the clinical and radiographic manifestations of PsA. Several reports have shown that males had more axial disease,[13-15] more radiographic progression,[13,14,16] and worse psoriasis,[15,17] whereas females had higher disease activity,[15,16,18] more physical activity limitations, more extensive work disability,[14,15,17,19] more severely impaired quality of

[1]*V. Furer, MD, J. Wollman, MD, D. Levartovsky, MD, V. Aloush, MD, O. Elalouf, MD, H. Sarbagil-Maman, MD, L. Mendel, MSc, S. Borok, MD, D. Paran, MD, O. Elkayam, MD, and A. Polachek, MD, Department of Rheumatology, Tel Aviv Sourasky Medical Center affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. A. Polachek, MD, Department of Rheumatology, Tel Aviv Sourasky Medical Center, 6 Weizmann Street, Tel Aviv 6423906, Israel. Email: arikpolachek@yahoo.com.

Accepted for publication September 27, 2022.

life,[14-17,19] and a higher rate of fibromyalgia.[20] In addition, other studies demonstrated better response to biologic treatments, such as tumor necrosis factor inhibitors, interleukin 17 inhibitors, and interleukin 12/23 inhibitors, among male patients with PsA compared to female patients.[21-25]

The data on differences in US findings between males and females with PsA are limited. To the best of our knowledge, no previous studies have compared differences in sonographic features, such as synovitis and tenosynovitis, in patients with PsA based on sex. The current reports refer mainly to enthesitis, and the results are contradictory, with a few studies reporting more sonographic enthesitis among males,[26,27] whereas others demonstrate a greater involvement among females or show no difference whatsoever.[28,29] Further, none of these earlier studies focused entirely and comprehensively on differences in diverse US features between males and females. The aim of this study was to investigate sex-based differences among patients with PsA who concomitantly underwent comprehensive clinical examinations and US studies.

METHODS

Patients and settings. The study included patients with PsA who were recruited consecutively and prospectively between July 2018 and September 2020. All of the participants fulfilled the CASPAR (ClASsification for Psoriatic Arthritis) criteria.[30] The study was conducted at the Department of Rheumatology, Tel Aviv Sourasky Medical Center, which serves as a primary, secondary, and tertiary referral center for patients with PsA. The study was approved by the local ethics committee (TLV-0196-18), and all the patients signed an informed consent form upon enrollment into the study.

Clinical assessment. Two experienced rheumatologists (VF and O. Elkayam) completed a comprehensive clinical assessment according to a standardized protocol, including demographics and disease characteristics. The physical examination included BMI, tender joint count (n = 68), swollen joint count (SJC; n = 66), the Leeds Enthesitis Index (LEI), the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index, dactylitis count, tender points assessment, body surface area, and the Psoriasis Area and Severity Index (PASI) for psoriasis evaluation. Pain assessment, patient global assessment, and physician global assessment were evaluated by a visual analog scale ranging from 0 to 10. Several patient-reported outcomes were examined, including the Health Assessment Questionnaire (HAQ), the 36-item Short Form Health Survey, the Ankylosing Spondylitis Quality of Life score, the Dermatology Life Quality Index, the Functional Assessment of Chronic Illness Therapy Fatigue scale for evaluation of fatigue, and the Beck Depression questionnaire for the assessment of depression. The presence of fibromyalgia was evaluated by the 2016 fibromyalgia classification criteria.[31] Patients were specifically asked about the extent of physical activity in association with 2 variables: physical occupation, defined as an occupation that involves physical activity, and sports exercise, defined as a regular sports activity on a weekly basis.

PsA disease activity was measured by the Disease Activity Index for Psoriatic Arthritis (DAPSA),[32] the Composite Psoriatic Disease Activity Index (CPDAI)[33] based on 5 domains (ie, joints, skin, entheses, dactylitis, and axial disease), and the Psoriatic Arthritis Disease Activity Score.[34] In addition, minimal disease activity (MDA)[35] was assessed as an outcome measure. Finally, blood samples were taken to measure C-reactive protein.

US assessment. The US assessment was carried out by a rheumatologist (AP) with 5 years of experience in MSK US. The scanning was performed using the Affinity 50 US system (Philips Healthcare) on the same day of the clinical evaluation. A high-frequency (5-18 MHz) linear transducer was used for superficial structures, and an additional linear transducer with a frequency of 5 to 12 MHz was used for deeper structures. For superficial structures, a Doppler frequency of 6.7 MHz and a pulse repetition frequency (PRF) of 700 Hz were used. For deeper structures, power Doppler (PD) settings were standardized with a Doppler frequency of 8 MHz, where the gain was adjusted until the background signal was removed; a PRF of 700 Hz; and a low wall filter. The US assessment was performed in a darkened room, and the sonographer was blinded to the clinical data. All of the patients were asked to stop nonsteroidal antiinflammatory drug use 3 days before the scheduled evaluation.

All of the patients completed a standardized US assessment, including 52 joints, 40 tendons, and 14 entheses points. The scanned joints included the following: metacarpophalangeal, proximal phalangeal, distal phalangeal, wrist, radioulnar, elbow, knee (ie, suprapatellar recess), ankle, talonavicular, anterior subtalar, and metatarsophalangeal joints. The scanned tendons included the following: 5 extensor tendons of the fingers, 5 flexor tendons of the fingers, 6 wrist extensor compartments, peroneal tendons, and the tibialis posterior, flexor digitorum longus, and flexor halluces longus in the medial aspect of the ankle. The scanned entheses included 12 sites according to the modified Madrid Sonographic Enthesis Index (MASEI)[36]: the triceps insertion to the olecranon; the quadriceps insertion to the proximal patella; the patellar tendon insertion to the distal patella; tibial tuberosity, Achilles, and plantar fascia insertions to the calcaneus; and the addition of the common extensor tendon to the lateral epicondyle. All of the above-mentioned MSK structures were scanned bilaterally. The total mean US examination time was 135 minutes.

Synovitis was defined as a hypoechoic intracapsular area regardless of the presence or absence of effusion and with or without PD, based on the European Alliance of Associations for Rheumatology (EULAR)–Outcome Measures in Rheumatology (OMERACT) definition.[37] Tenosynovitis was defined as an anechoic or hypoechoic tendon sheath widening around the flexor tendon with or without PD, based on the OMERACT US working group definition.[38] Extensor paratenonitis of the finger joints was defined as hypoechoic or anechoic thickened tissue surrounding the extensor tendon with or without PD.[39] Enthesitis was defined according to the MASEI system, with distribution to its subcategories: inflammatory lesions (ie, thickening, hypoechogenicity, bursitis, and Doppler) and structural lesions (ie, erosions and enthesophytes/calcifications).[36]

Each MSK pathology was scored by a specific scoring scale within 1 week of completion of the US scanning; the grading of each MSK pathology is described in detail in Supplementary Tables S1 and S2, available with the online version of this article. The synovitis scale ranged from 0 to 312, the tenosynovitis scale ranged from 0 to 200, and the enthesitis scale ranged from 0 to 147. The total US score was the sum of these subcategories, and it could range from 0 to 659. An intrareader agreement assessment demonstrated a prevalence-adjusted bias-adjusted kappa (PABAK) of 0.9 for greyscale MSK lesions, and a PABAK of 0.99 for the Doppler. The detailed intrareader agreement results were presented in a previous publication.[40]

Statistical analysis. Descriptive statistics included mean (SD) and median (range) for continuous variables and counts and relative frequencies for categorical variables. Comparison between males and females was determined by a *t* test for 2 independent samples. Categorical variables, except for ordinal outcome variables, were compared with a chi-square test of independence. The continuous enthesitis scores were divided into quartiles to form ordinal variables that were used as outcome measures. The ordinal outcome variables were compared with the nonparametric Jonckheere-Terpstra trend test. The ordinal enthesitis scores were used as outcomes in order to examine the association of male sex with US enthesitis and its subdomains. Univariate and multivariate ordinal logistic regression models were constructed for each ordinal outcome variable to explore association with sex. In addition to the variable of sex, the multivariate models included adjustments for the following known potential confounders: age, BMI, psoriasis duration, physical occupation, sports exercise, C-reactive

protein level, current use of biologics, and current use of conventional synthetic disease-modifying antirheumatic drugs. A 2-sided *P* value less than 0.05 was considered statistically significant. All analyses were conducted with RStudio (version 1.4.1106; RStudio, PBC).

RESULTS

Sex differences regarding demographics and clinical characteristics. The study included 158 patients (females: n = 88, 56%; males: n = 70, 44%; Table 1). The rate of employment was higher among males as compared to females ($P = 0.01$). Males had a significantly higher mean SJC ($P = 0.04$) and a higher PASI ($P = 0.04$) than females, whereas females had significantly more tender points and numerically higher mean SPARCC and LEI enthesitis scores. Both groups were similar in disease activity scores, MDA, and different patient-reported outcomes.

Table 1. Demographics and clinical characteristics according to sex (N = 158).

Characteristics	Female, n = 88, mean (SD)	Male, n = 70, mean (SD)	*P*	Female, n = 88, median (IQR)	Male, n = 70, median (IQR)	*P*
Age, yrs	53.32 (13.40)	50.99 (12.45)	0.26	54.5 (46-65)	48.5 (42.25-61)	0.09
BMI[a]	27.43 (5.16)	27.90 (5.10)	0.57	27.35 (23.84-30.8)	27.48 (24.33-31.52)	0.47
Smoking history, n (%)	36 (41.90)	26 (37.10)	0.83	–	–	–
Employed, n (%)	52 (59.80)	57 (81.40)	0.01	–	–	–
Education, academic, n (%)	70 (78.70)	55 (78.60)	0.27	–	–	–
PsO duration, yrs	19.74 (13.21)	18.06 (15.25)	0.47	14 (6.5-25)	19 (8.75-29)	0.16
PsA duration, yrs	10.63 (11.11)	11.86 (11.89)	0.50	7 (3-14.2)	6.5 (2-18)	0.74
Physical occupation, n (%)	7 (8)	11 (15.9)	0.19	–	–	–
Sports exercise, n (%)	25 (28.4)	25 (36.2)	0.38	–	–	–
TJC	8.19 (9.97)	8.89 (10.10)	0.66	5 (1-11)	6 (1.25-12)	0.80
SJC	0.83 (1.76)	1.73 (3.66)	0.04	0 (0-1)	0 (0-1)	0.35
LEI	1.31 (1.70)	0.87 (1.38)	0.08	1 (0-2)	0 (0-1)	0.11
SPARCC enthesitis	3.17 (3.71)	2.11 (3.20)	0.06	2 (0-5)	1 (0-3)	0.04
Dactylitis (≥ 1), n (%)	5 (5.7)	10 (14.3)	0.12	–	–	–
PASI	1.03 (1.84)	2.49 (6.34)	0.04	0 (0-1)	0.35 (0-2.1)	0.04
PGA	1.86 (1.83)	2.25 (2.33)	0.24	1.45 (0.3-3)	1.5 (0.225-3.88)	0.67
PtGA	5.33 (2.98)	5.34 (3.21)	0.98	5.5 (3-8)	5.55 (2.7-8)	0.97
Pain	5.06 (3.05)	4.98 (3.24)	0.86	5.05 (2.5-7.7)	5.2 (2.025-8)	0.83
CRP, mg/L	7.79 (9.94)	8.77 (8.16)	0.66	4.02 (0.935-12)	4.21 (0.955-9.84)	0.86
HAQ	0.92 (0.82)	0.82 (0.81)	0.39	0.73 (0.25-1.5)	0.56 (0-1.62)	0.24
SF-36 (PCS)	53.55 (27.71)	57.44 (33.44)	0.43	55 (30-76.2)	65 (30-90)	0.27
SF-36 (MCS)	61.36 (22.38)	64.15 (22.88)	0.45	64 (48-80)	68 (52-80)	0.33
FACIT-F	29.39 (13.36)	30.67 (12.89)	0.55	30 (20-39)	33 (20-41)	0.45
Depression	13.60 (12.10)	12.22 (11.23)	0.48	10 (0-47)	8 (0-51)	0.59
MDA, n (%)	28 (32.5)	27 (39.6)	0.44	–	–	–
CPDAI	8.38 (3.54)	7.52 (4.09)	0.17	10 (5-11)	8 (4-11)	0.24
DAPSA	20.29 (14.52)	21.75 (16.83)	0.56	17.79 (9.925-26.8)	20.8 (8.551-29.54)	0.73
PASDAS	3.54 (1.91)	3.54 (2.55)	0.99	3.66 (2.066-4.9)	3.69 (1.333-5.3)	0.73
Fibromyalgia, n (%)	28 (31.50)	14 (20.0)	0.15	–	–	–
Tender points	4.53 (5.62)	2.27 (4.18)	0.006	2 (0-8)	0 (0-3)	0.003
Treatment, n (%)						
csDMARDs	39 (43.80)	29 (41.40)	0.88	–	–	–
Apremilast	1 (1.1)	3 (4.3)	0.45	–	–	–
Biologics	48 (53.90)	38 (54.30)	> 0.99	–	–	–

Data are reported as mean (SD) or median (IQR), as stated in the column headings, unless otherwise indicated. [a] BMI is calculated as weight in kilograms divided by height in meters squared. CPDAI: Composite Psoriatic Disease Activity Index: CRP: C-reactive protein; csDMARD: conventional synthetic disease-modifying antirheumatic drug; DAPSA: Disease Activity Index for Psoriatic Arthritis; FACIT-F: Functional Assessment of Chronic Illness Therapy Fatigue scale; HAQ: Health Assessment Questionnaire; LEI: Leeds Enthesitis Index; MCS: mental component summary; MDA: minimal disease activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PCS: physical component summary; PGA: physician global assessment; PtGA: patient global assessment; PsA: psoriatic arthritis; PsO: psoriasis; SF-36: 36-item Short Form Health Survey; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada; TJC: tender joint count.

Sex differences regarding sonographic scores. Males had significantly higher total US enthesitis (P = 0.01) and greyscale enthesitis scores (P = 0.01) compared to females (Table 2). The total US, synovitis, and tenosynovitis scores were similar for both sexes.

Sonographic enthesitis features. Males had a significantly higher sonographic active inflammatory score compared to females (P = 0.005; Table 3). This difference was derived from significantly higher hypoechogenicity and thickening compared to females (P < 0.001). Enthesophytes/calcifications were significantly more prevalent among males (P = 0.048).

Sonographic enthesitis involvement by site. Males had either a significant or a nonsignificant trend toward a higher sonographic enthesitis score at most enthesitis sites (Table 4). In the Achilles and quadriceps, the difference was derived from higher inflammatory scores, whereas triceps, distal patella, and tibial tuberosity levels were derived from a higher structural score. There were no group differences for the lateral epicondyles and plantar fascia.

Table 2. Comparison of sonographic scores between males and females.

	Female, n = 88	Male, n = 70	*P*
Total US score[a]	34.55 (20.71)	39.21 (24.97)	0.20
Total GS score	30.95 (18.61)	35.11 (21.00)	0.19
Total PD score	5.00 (5.78)	5.40 (7.19)	0.69
Synovitis[a]			
Total US score	12.72 (10.43)	11.49 (9.04)	0.32
GS score	12.69 (11.97)	11.36 (10.96)	0.47
PD score	1.42 (2.14)	1.34 (2.71)	0.84
Tenosynovitis			
Total US score	3.62 (5.00)	4.01 (4.64)	0.62
GS score	2.51 (3.80)	2.91 (3.65)	0.50
PD score	1.11 (1.96)	1.10 (1.75)	0.96
Enthesitis			
Total US score	18.22 (10.73)	23.80 (17.37)	0.01
GS score	15.75 (9.88)	20.84 (14.42)	0.01
PD score	2.47 (3.14)	2.96 (4.38)	0.40

Data are reported as mean (SD). [a]Synovitis was based on the EULAR-OMERACT score. EULAR: European Alliance of Associations for Rheumatology; GS: greyscale; OMERACT: Outcome Measures in Rheumatology; PD: power Doppler; US: ultrasound.

Table 3. Prevalence of sonographic enthesitis features according to sex.

	Female	Male	*P*
Active inflammatory lesions, mean (SD)	8.80 (6.02)	12.33 (9.36)	0.005
Hypoechogenicity	262 (21.3)	278 (28.4)	< 0.001
Thickening	271 (22)	350 (35.7)	< 0.001
Doppler	72 (5.8)	69 (7)	0.29
Bursitis	26 (7.4)	28 (10)	0.31
Chronic structural lesions, mean (SD)	9.42 (7.05)	11.47 (9.69)	0.13
Erosion	45 (3.7)	48 (4.9)	0.18
Enthesophytes/calcifications	433 (35.1)	385 (39.3)	0.048

Data are in n (%) unless otherwise indicated.

Table 4. Sonographic site enthesitis scores according to sex.

	Female	Male	*P*
Lateral epicondyle			
Total score	3.66 (3.48)	3.29 (3.56)	0.51
Inflammatory score	2.12 (2.50)	2.24 (2.33)	0.76
Structural score	1.53 (1.88)	1.04 (1.84)	0.10
Triceps			
Total score	1.81 (2.45)	3.29 (4.02)	0.005
Inflammatory score	0.91 (1.47)	1.46 (2.31)	0.09
Structural score	0.82 (1.39)	1.83 (2.67)	0.007
Quadriceps			
Total score	3.36 (3.07)	4.14 (3.55)	0.14
Inflammatory score	0.97 (1.55)	1.66 (2.20)	0.02
Structural score	2.40 (2.19)	2.49 (2.08)	0.80
Distal patella			
Total score	1.25 (2.13)	2.44 (3.74)	0.01
Inflammatory score	0.70 (1.55)	1.29 (2.43)	0.07
Structural score	0.55 (1.19)	1.16 (1.81)	0.01
Tibial tuberosity			
Total score	2.70 (2.85)	3.89 (3.33)	0.02
Inflammatory score	2.24 (2.44)	3.01 (2.47)	0.05
Structural score	0.47 (1.07)	0.87 (1.53)	0.02
Achilles tendon			
Total score	3.60 (3.71)	4.67 (3.90)	0.04
Inflammatory score	0.90 (1.83)	1.66 (2.13)	0.02
Structural score	2.70 (2.66)	3.01 (2.36)	0.44
Plantar fascia			
Total score	1.86 (2.33)	2.09 (2.51)	0.56
Inflammatory score	0.97 (1.42)	1.01 (1.45)	0.83
Structural score	0.90 (1.33)	1.07 (1.39)	0.42

Data are reported as mean (SD).

Association between sex and sonographic enthesitis. The different US enthesitis scores were divided into 4 categories in order to examine the association between male sex and US-demonstrated enthesitis (Supplementary Table S3, available with the online version of this article). A multivariate ordinal logistic regression model showed that males were more likely to have a higher US inflammatory enthesitis score than females (P = 0.02; Table 5). In addition, there was a trend toward an association between male sex and structural score (P = 0.10).

DISCUSSION

PsA has been characterized by several sex-related differences in its clinical manifestation, distribution of joint and axial involvement, radiographically demonstrated damage, as well as function, quality of life, and response to treatment.[13-25] The current study compared the sonographic and clinical characteristics of a well-defined PsA cohort, and the results revealed a significant difference in the prevalence of sonographic enthesitis among male patients compared to female patients, whereas no significant difference was demonstrated in clinical enthesitis indices between the 2 groups. The present study showed that males were more frequently employed and had higher mean SJC and PASI values, whereas females had significantly more tender points and displayed a nonsignificant trend toward higher mean SPARCC and LEI scores.

Table 5. Comparison of male and female sex-related US enthesitis scores[a].

	OR (95% CI)	*P*
Total US enthesitis score		
Male sex: univariate analysis	1.22 (0.69-2.18)	0.48
Male sex: multivariate analysis	1.68 (0.90-3.17)	0.10
Total US inflammatory enthesitis score		
Male sex: univariate analysis	1.77 (1.01-3.14)	0.049
Male sex: multivariate analysis	1.96 (1.09-3.59)	0.02
Total US structural enthesitis score		
Male sex: univariate analysis	1.23 (0.70-2.18)	0.46
Male sex: multivariate analysis	1.68 (0.90-3.16)	0.10

[a] Ordinal logistic regression analysis was performed and was adjusted for age, BMI, psoriasis duration, physical occupation, sports exercise, C-reactive protein, current use of biologics, and current use of conventional synthetic disease-modifying antirheumatic drugs. OR: odds ratio; US: ultrasound.

Similar to the current study, a few studies showed that males had more extensive skin involvement compared to females.[15,17] Previous studies that compared the extent and pattern of peripheral joint involvement did not show a clear distinction between the sexes.[14,15,17,18] Many clinical variables were comparable for both sexes in the current study, including those pertaining to disease activity indices, MDA, and quality of life. Similarly, Kenar et al[41] did not find any difference in CPDAI values between males and females with PsA. In contrast, the large studies by Orbai et al[18] and Duruöz et al[15] (458 and 1038 patients with PsA, respectively) reported that females had a significantly higher disease activity than males, as measured by the DAPSA and MDA. In addition, those 2 studies, as well as others, showed that females had higher pain, fatigue, and depression scores and higher scores on the Psoriatic Arthritis Impact of Disease questionnaire and the HAQ compared to males.[14-18] Possible explanations for these discrepancies could be attributed to the relatively small number of patients and cultural differences in the present study compared to the other studies.

The tendency toward more clinical enthesitis among our female patients was also demonstrated in studies that included patients with spondyloarthropathy, showing that clinical enthesitis is more common and more severe among female patients with spondyloarthropathy.[20,42] Our group had reported that patients with PsA with concomitant fibromyalgia had significantly higher scores of clinical enthesitis.[40] The female patients in the current study also had more fibromyalgia tender points. The proximity of the enthesitis sites to the fibromyalgia tender points suggests that the higher scores of clinical enthesitis could be influenced by fibromyalgia and not necessarily by an inflammatory process. Previous studies that compared PsA alone to PsA with fibromyalgia or to patients with fibromyalgia alone showed that clinical enthesitis scores were more prevalent among those with fibromyalgia—either alone or with PsA—compared to those with only PsA; even so, findings of sonographic enthesitis were comparable between those with PsA alone and those with PsA with fibromyalgia and more prevalent compared to those with only fibromyalgia.[29,40,43] Hence, US may serve as a better tool for enthesitis assessment.[40]

The present study demonstrated more sonographic enthesitis among male patients with PsA, whereas the prevalence of synovitis and tenosynovitis was comparable between the sexes. The differences in sonographic enthesitis were derived from both inflammatory features, such as hypoechogenicity and thickening, and structural findings, such as enthesophytes and calcifications. Further, these sonographic discrepancies were observed in the majority of the enthesitis sites. Alhussain et al[26] found higher scores of inflammatory enthesitis in both male patients with PsA and male patients with ankylosing spondylitis, but they did not provide scores for the PsA group in isolation. Eder et al[27] demonstrated an association between male sex and sonographic enthesitis in a cohort of patients with PsA, patients with psoriasis, and healthy controls; however, again, details on sex differences specific to the PsA group were not provided. In contrast, Wervers et al[28] did not find any association between sex and sonographic enthesitis in a cohort of 84 patients with PsA. In addition, Macchioni et al[29] reported that female patients with PsA and psoriasis had more sonographic enthesitis changes compared to males.

It should be noted that differences in sonographic enthesitis had also been observed in healthy subjects.[44,45] Bakirci et al's[44] study that included 80 healthy subjects showed that male sex was associated with the presence of sonographic enthesitis. In addition, Guldberg-Møller et al's[45] sample of 64 healthy adults demonstrated a trend toward more thickening and calcifications in the dominant lower leg among males compared to females. The enthesitis scores and the prevalence of the different features of enthesitis, however, were substantially higher in the current study compared to the 2 last-cited studies[44,45]; this may suggest that male predominance in sonographic enthesitis may represent a predisposition among healthy subjects that is further intensified among patients with PsA.

Enthesitis is considered a hallmark of PsA, leading to pain, structural damage, and disability; hence, this serves as a target for treatment.[2-8] Accordingly, the assessment of enthesitis is very important. However, since enthesis is located under the skin, identifying it by physical examination alone could be misleading. US is an imaging modality that can visualize both inflammatory and structural damage. Several studies documented the disparity between physical assessment and US and emphasized the added value of US.[9,10] Specifically, Aydin et al[46] showed mutual clinical and sonographic detection of enthesitis in only 2 out of 6 sites—Achilles and the origin of the patellar tendon—in a cohort of 377 patients with PsA. Kristensen et al[47] demonstrated a moderate correlation between clinical enthesitis indices (ie, LEI and SPARCC) and US enthesitis scores in a sample of 20 patients with PsA. Yamada et al[48] showed that US detected enthesitis more frequently than clinical assessment, with poor agreement between clinical and sonographic enthesitis in 47 patients with PsA. Likewise, the present study demonstrated a significant difference in sonographic evidence of enthesitis between males and females, whereas the comparison by physical examination (ie, LEI and mean SPARCC) did not reach a level of statistical significance.

This study has some limitations that bear mention. It had a cross-sectional design and focused on a single point in time, whereas a longitudinal design could have examined the differences over time, including the differences in response to treatment. The cohort had long-standing disease (mean 10.6 years) and was being well treated, which may have had an effect on the results, limiting the ability to generalize them to patients with early and untreated PsA. In addition, there was no consensus on a single US enthesitis index at study initiation, since the US enthesitis definition from the EULAR had not yet been published.[49] The current study did not demonstrate significant difference in PD activity, which according to the EULAR definition is considered an important pathology of inflammatory enthesitis. However, all patients who were positive for PD also had hypoechogenicity, considered the correspondent inflammatory lesion in greyscale, which could point to low PD sensitivity in US machines and could be a problem in different US machines. In addition, the overall lower prevalence of PD could influence the ability to demonstrate significant differences; it is possible that with higher numbers of patients, this difference could have reached statistical significance. Finally, the EULAR definition does not score each component nor does it discriminate between inflammatory and noninflammatory conditions.

This study has numerous strengths. To the best of our knowledge, this is the first study that directly and comprehensively examined the differences in US features between male and female patients with PsA. The close temporal relation between physical and sonographic examinations contributed to the accuracy of the study results. Finally, this was a well-defined and well-characterized cohort, and it included a large number of diverse clinical features, patient-reported outcomes, disease activity indices, and US parameters.

In summary, the results of this study showed that males had more clinically detected joint and skin involvement compared to females. Enthesitis demonstrated by sonography was more prevalent among male patients compared to female patients with PsA, and these differences were not reflected by enthesitis disease activity scores during clinical evaluations. This finding emphasizes the importance of US in this setting and may shed light on different disease patterns and possible pathophysiology differences between sexes. Further studies that examine the differences over time and in relation to treatment between males and females with PsA are warranted.

ACKNOWLEDGMENT

We acknowledge Esther Eshkol for her editorial assistance.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med 2017;376:957-70.
2. Schett G, Lories RJ, D'Agostino M-A, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731-41.
3. Kaeley GS, Eder L, Aydin SZ, Gutierrez M, Bakewell C. Enthesitis: a hallmark of psoriatic arthritis. Semin Arthritis Rheum 2018;48:35-43.
4. McGonagle D, Lories RJU, Tan AL, Benjamin M. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum 2007;56:2482-91.
5. Scarpa R, Cuocolo A, Peluso R, et al. Early psoriatic arthritis: the clinical spectrum. J Rheumatol 2008;35:137-41.
6. Polachek A, Li S, Chandran V, Gladman DD. Clinical enthesitis in a prospective longitudinal psoriatic arthritis cohort: incidence, prevalence, characteristics, and outcome. Arthritis Care Res 2017;69:1685-91.
7. Polachek A, Cook R, Chandran V, Gladman DD, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis. Arthritis Res Ther 2017;19:189.
8. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022;18:465-79.
9. Husic R, Gretler J, Felber A, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis 2014;73:1529-36.
10. Michelsen B, Diamantopoulos AP, Hammer HB, Soldal DM, Kavanaugh A, Haugeberg G. Ultrasonographic evaluation in psoriatic arthritis is of major importance in evaluating disease activity. Ann Rheum Dis 2016;75:2108-13.
11. Kaeley GS. Visualization of enthesitis by ultrasound: a key diagnostic tool in spondyloarthropathy diagnosis and management. Curr Rheumatol Rep 2020;22:48.
12. Mandl P, Navarro- Compán V, Terslev L, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 2015;74:1327-39.
13. Gladman DD, Brubacher B, Buskila D, Langevitz P, Farewell VT. Psoriatic spondyloarthropathy in men and women: a clinical, radiographic, and HLA study. Clin Invest Med 1992;15:371-5.
14. Eder L, Thavaneswaran A, Chandran V, Gladman DD. Gender difference in disease expression, radiographic damage and disability among patients with psoriatic arthritis. Ann Rheum Dis 2013;72:578-82.
15. Duruöz MT, Gezer HH, Nas K, et al. Gender-related differences in disease activity and clinical features in patients with peripheral psoriatic arthritis: a multi-center study. Joint Bone Spine 2021;88:105177.
16. Geijer M, Lindqvist U, Husmark T, et al. The Swedish early psoriatic arthritis registry 5-year followup: substantial radiographic progression mainly in men with high disease activity and development of dactylitis. J Rheumatol 2015;42:2110-7.
17. Nas K, Capkin E, Dagli AZ, et al. Gender specific differences in patients with psoriatic arthritis. Mod Rheumatol 2017;27:345-9.
18. Orbai A-M, Perin J, Gorlier C, et al. Determinants of patient-reported psoriatic arthritis impact of disease: an analysis of the association with sex in 458 patients from fourteen countries. Arthritis Care Res 2020;72:1772-9.
19. Wallenius M, Skomsvoll JF, Koldingsnes W, et al. Work disability and health-related quality of life in males and females with psoriatic arthritis. Ann Rheum Dis 2009;68:685-9.
20. Brikman S, Furer V, Wollman J, et al. The effect of the presence of fibromyalgia on common clinical disease activity indices in patients with psoriatic arthritis: a cross-sectional study. J Rheumatol 2016;43:1749-54.
21. Højgaard P, Ballegaard C, Cordtz R, et al. Gender differences in biologic treatment outcomes-a study of 1750 patients with psoriatic arthritis using Danish Health Care Registers. Rheumatology 2018;57:1651-60.

22. Vieira-Sousa E, Eusébio M, Ávila-Ribeiro P, et al. Real-world longterm effectiveness of tumor necrosis factor inhibitors in psoriatic arthritis patients from the Rheumatic Diseases Portuguese Register. J Rheumatol 2020;47:609-700.
23. Stober C, Ye W, Guruparan T, Htut E, Clunie G, Jadon D. Prevalence and predictors of tumour necrosis factor inhibitor persistence in psoriatic arthritis. Rheumatology 2018;57:158-63.
24. Ramonda R, Lorenzin M, Carriero A, et al. Effectiveness and safety of secukinumab in 608 patients with psoriatic arthritis in real life: a 24-month prospective, multicentre study. RMD Open 2021;7:e001519.
25. Geale K, Lindberg I, Paulsson EC, et al. Persistence of biologic treatments in psoriatic arthritis: a population-based study in Sweden. Rheumatol Adv Pract 2020;4:rkaa070.
26. Alhussain FA, Gunal EK, Kurum E, et al. Greater magnitude of entheseal microdamage and repair in psoriatic arthritis compared with ankylosing spondylitis on ultrasound. Rheumatology 2019;58:299-303.
27. Eder L, Jayakar J, Thavaneswaran A, et al. Is the MAdrid Sonographic Enthesitis Index useful for differentiating psoriatic arthritis from psoriasis alone and healthy controls? J Rheumatol 2014;41:466-72.
28. Wervers K, Herrings I, Luime JJ, et al. Association of physical activity and medication with enthesitis on ultrasound in psoriatic arthritis. J Rheumatol 2019;46:1290-4.
29. Macchioni P, Salvarani C, Possemato N, et al. Ultrasonographic and clinical assessment of peripheral enthesitis in patients with psoriatic arthritis, psoriasis, and fibromyalgia syndrome: the ULISSE study. J Rheumatol 2019;46:904-11.
30. Taylor W, Gladman D, Helliwell P, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665-73.
31. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum 2016;46:319-29.
32. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. Ann Rheum Dis 2016;75:811-8.
33. Mumtaz A, Gallagher P, Kirby B, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis 2011;70:272-7.
34. Helliwell PS, FitzGerald O, Fransen J, et al. The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis 2013; 72:986-91.
35. Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis 2010;69:48-53.
36. de Miguel E, Cobo T, Muñoz-Fernández S, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. Ann Rheum Dis 2009;68:169-74.
37. D'Agostino M-A, Terslev L, Aegerter P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. RMD Open 2017;3:e000428.
38. Naredo E, D'Agostino MA, Wakefield RJ, et al. Reliability of a consensus-based ultrasound score for tenosynovitis in rheumatoid arthritis. Ann Rheum Dis 2013;72:1328-34.
39. Macía-Villa C, Falcao S, Gutierrez M, Medina J, Hammer HB, De Miguel E. Peritenon extensor tendon inflammation in psoriatic arthritis is an enthesitis-related lesion. J Rheumatol 2019;46:1295-8.
40. Polachek A, Furer V, Zureik M, et al. Role of ultrasound for assessment of psoriatic arthritis patients with fibromyalgia. Ann Rheum Dis 2021;80:1553-8.
41. Kenar G, Yarkan H, Zengin B, Can G, Birlik M, Önen F. Gender does not make a difference in "composite psoriatic disease activity index (CPDAI)" in patients with psoriatic arthritis. Rheumatol Int 2018;38:2069-76.
42. Rusman T, van Vollenhoven RF, van der Horst-Bruinsma IE. Gender differences in axial spondyloarthritis: women are not so lucky. Curr Rheumatol Rep 2018;20:35.
43. Fiorenza A, Bonitta G, Gerratana E, et al. Assessment of enthesis in patients with psoriatic arthritis and fibromyalgia using clinical examination and ultrasound. Clin Exp Rheumatol 2020;38 Suppl 123:31-9.
44. Bakirci S, Solmaz D, Stephenson W, Eder L, Roth J, Aydin SZ. Entheseal changes in response to age, body mass index, and physical activity: an ultrasound study in healthy people. J Rheumatol 2020;47:968-72.
45. Guldberg-Møller J, Terslev L, Nielsen SM, et al. Ultrasound pathology of the entheses in an age and gender stratified sample of healthy adult subjects: a prospective cross-sectional frequency study. Clin Exp Rheumatol 2019;37:408-13.
46. Aydin SZ, Bakirci S, Kasapoglu E, et al. The relationship between physical examination and ultrasonography of large entheses of the Achilles tendon and patellar tendon origin. J Rheumatol 2020;47:1026-30.
47. Kristensen S, Christensen JH, Schmidt EB, et al. Assessment of enthesitis in patients with psoriatic arthritis using clinical examination and ultrasound. Muscles Ligaments Tendons J 2016;6:241-7.
48. Yamada Y, Inui K, Okano T, et al. Ultrasound assessment, unlike clinical assessment, reflects enthesitis in patients with psoriatic arthritis. Clin Exp Rheumatol 2021;39:139-45.
49. Balint PV, Terslev L, Aegerter P, et al. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. Ann Rheum Dis 2018;77:1730-5.