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EXTENDED REPORT

Disparity between ultrasound and clinical findings in psoriatic arthritis

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ABSTRACT

Objective To investigate the association between psoriatic arthritis (PsA)-specific clinical composite scores and ultrasound-verified pathology as well as comparison of clinical and ultrasound definitions of remission.

Methods We performed a prospective study on 70 consecutive PsA patients. Clinical assessments included components of Disease Activity Index for Psoriatic Arthritis (DAPSA) and the Composite Psoriatic Disease Activity Index (CPDAI). Minimal disease activity (MDA) and the following remission criteria were applied: CPDAI joint, entheses and dactylitis domains (CPDAI-JED)=0, DAPSA≤3.3, Boolean's remission definition and physician-judged remission (rem-phys). B-mode and power Doppler (PD-) ultrasound findings were semiquantitatively scored at 68 joints (evaluating synovia, peritendinous tissue, tendons and bony changes) and 14 entheses. Ultrasound remission and minimal ultrasound disease activity (MUDA) were defined as PD-score=0 and PD-score ≤1, respectively, at joints, peritendinous tissue, tendons and entheses.

Results DAPSA but not CPDAI correlated with B-mode and PD-synovitis. Ultrasound signs of enthesitis, dactylitis, tenosynovitis and perisynovitis were not linked with clinical composites. Clinical remission or MDA was observed in 15.7% to 47.1% of PsA patients. Ultrasound remission and MUDA were present in 4.3% and 20.0% of patients, respectively. Joint and tendon-related PD-scores were higher in patients with active versus inactive disease according to CPDAI-JED, DAPSA, Boolean's and rem-phys, whereas no difference was observed regarding enthesitis and perisynovitis. DAPSA≤3.3 (OR 3.9, p=0.049) and Boolean's definition (OR 4.6, p=0.03) were more useful to predict MUDA than other remission criteria.

Conclusions PsA-specific composite scores partially reflect ultrasound findings. DAPSA and Boolean's remission definitions better identify MUDA patients than other clinical criteria.

INTRODUCTION

Current data indicate limited correlations between ultrasound and clinical findings of inflammation in rheumatic diseases.[1 2] In rheumatoid arthritis (RA), for example, sonographic signs of active disease were observed in patients with clinical remission and conversely, active inflammation was excluded in 20% of RA patients despite painful swelling.[1 3–5] Similarly, in psoriatic arthritis (PsA) sonography and MRI revealed a higher sensitivity for the detection of joint inflammation than clinical examination.[6–10] MRI bone oedema scores correlated with MRI erosion scores and x-ray-verified structural damage, but were unrelated to the disease activity score-28 (DAS-28).[11] Other ultrasound studies revealed a high prevalence of subclinical enthesitis in patients with PsA and psoriasis without arthropathy.[12–14] These studies, however, are limited by the incomplete assessment of PsA features by sonography and/or the comparison of imaging findings with disease activity measures routinely used in RA.

The value of ultrasound to detect residual inflammation in PsA patients without clinical activity is elusive so far. A definition of clinical remission has not been established; only criteria for minimal disease activity (MDA) were recently validated in two prospective PsA cohorts.[15–17] Two PsA-specific composite scores, namely the Disease Activity Index for Psoriatic Arthritis (DAPSA) and the Composite Psoriatic Disease Activity Index (CPDAI) were recently proposed.[18 19] DAPSA mainly focuses on peripheral arthritis combining tender joint (TJ) and swollen joint (SJ) counts, patient's pain and global assessment as well as C reactive protein (CRP),[18] whereas CPDAI corroborates several PsA-specific domains, including joint disease, enthesitis, dactylitis, skin and axial manifestations as well as quality of life.[19] DAPSA and CPDAI were sensitive to changes in treatment studies; however, a comparison of these scores with ultrasound findings as well as an evaluation regarding their value for remission assessment have not been performed so far.

In the present study, we investigated the association between DAPSA, CPDAI and its components with ultrasound signs of inflammation and structural damage in a cohort of consecutive PsA patients. In addition, we compared ultrasound and clinical definitions of remission and MDA.

METHODS

Patients

We performed a prospective study on 70 consecutive PsA patients between July 2011 and May 2012. All patients fulfilled the ClASsification for Psoriatic ARthritis criteria and had peripheral articular manifestations.[20] The study was approved by the institutional review board of the Medical University Graz and written informed consent was obtained from each patient.

Patients underwent complete history and clinical assessments by one of two rheumatologists (JG and JH) unaware of ultrasound results (see online supplementary file for detailed description of methods). The following parameters were

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recorded: number of TJ and SJ (66/68 articular index), number of fingers and toes affected by dactylitis, the presence of enthesitis at the following sites: lateral epicondyle, triceps insertion, quadriceps insertion, proximal and distal patellar tendon insertion, distal insertion of the adductor magnus tendon, insertion of the achilles tendon as well as the proximal insertion of plantar aponeurosis. The Leeds Enthesitis Index (LEI) and a clinical counterpart to the Madrid Sonographic Enthesis Index (MASEI) termed clinical MASEI as well as clinical MASEI +lateral epicondyle (clinical MASEI+E) were calculated.[21 22] The Psoriasis Area Severity Index (PASI),[23] Dermatology Life Quality Index,[24] Health Assessment Questionnaire (HAQ),[25] patient's global assessment of disease activity (PGA), patients' pain assessment (Ptpain) as well as evaluator's global assessment of disease activity (EGA) determined on Visual Analogue Scales (range 0–100 mm) were also recorded. Axial involvement (according to Assessment of SpondyloArthritis international Society classification criteria) was retrospectively determined by chart review.[26] Bath Ankylosing Spondylitis Disease Activity Index,[27] and Ankylosing Spondylitis Quality of Life,[28] were assessed in patients with axial disease. Blood samples were routinely tested for erythrocyte sedimentation rate (ESR, range 0–10 mm/first hour) and CRP (range 0–5 mg/L) levels. DAPSA and CPDAI scores were calculated as previously described (see online supplementary table S1).[18 19]

We applied the following criteria for clinical remission: (1) MDA defined as five out of seven of the following criteria: TJ≤1, SJ≤1, PASI≤1, Ptpain≤15 mm, PGA≤20 mm and HAQ≤0.5; enthesitis score (out of clinical MASEI+E)≤1[17 21]; (2) CPDAI=0 or CPDAI joint, entheses and dactylitis domains (CPDAI-JED)=0 as stated; (3) DAPSA≤3.3 (similar to remission definition using the Simplified Disease Activity Index)[29]; (4) a Boolean's definition of remission (similar to ACR/European League Against Rheumatism (EULAR) remission criteria) for RA with all of the following: TJ≤1, SJ≤1, MASEI+E≤1, dactylitis score≤1, EGA≤1, PGA≤1 and CRP≤1 mg/dl[29]; and (5) remission as judged by the evaluating physician without application of formal criteria (rem-phys). These definitions (except for MDA) are not evidence based and should therefore be used neither in clinical trials nor in daily routine until they are validated by future studies.

Ultrasound protocol

For the complete ultrasound protocol, see online supplementary file and table S2. Examples of characteristic ultrasound findings are depicted in online supplementary figure S1.

In brief, sonographic evaluations were performed by one of two rheumatologists (CDe and RH) on the same day of clinical investigation. B-mode and power Doppler (PD) sonography were performed at 68 joints and 14 entheses. The duration of each examination was 90 min. We used a MyLab Twice Ultrasound Device (Esaote, Genova, Italy) with two multifrequency linear transducers (6–18 MHz and 4–13 MHz). Grey-scale synovitis (GSS) as well as PD-signals at joints (PD-j-score) were subjectively graded from 0 to 3 in accordance with recent publications.[4 30–32] Perisynovitis was investigated by dorsal scans of metacarpophalangeal joints (MCP) 2–5 and was graded in B-mode (B-perisyn) and PD (PD-perisyn) with 0=normal or 1=abnormal.[33] Tenosynovitis was identified in B-mode (B-teno) and graded from 0 to 3 (wrists and ankles) or with 0=absent or 1=present at small joints. PD-signals related to tenosynovitis (PD-teno) were graded from 0 to 3.

Ultrasound dactylitis was defined by the combination of flexor tenosynovitis affecting the entire finger or toe with MCP/metatarso-phalangeal, proximal interphalangeal (PIP) and distal interphalangeal (DIP) synovitis.[34 35]

Erosions or osteophytes were semiquantitatively graded from 0 to 3 (adapted from Finzel *et al*[36]).

Enthesitis was graded according to MASEI.[21 37] A reduced enthesitis score (Sono-LEI) was additionally calculated.

Sum scores were calculated for GSS-score (range 0–204), PD-j-score (0–204), osteophytes (0–168), erosions (0–168), B-perisyn (0–8), PD-perisyn (0–8), B-teno (0–80) and PD-teno (0–192). Enthesitis sum scores ranged from 0 to 136 (MASEI) and from 0 to 70 (Sono-LEI). A modified MASEI also included the enthesis of the lateral epicondyle (MASEI+E, range 0–158). We also assessed scores focusing on the number of entheses with PD-signals: PD-MASEI (range 0–12), PD-MASEI+E (0–14) and PD-LEI (0–6). In addition, a global ultrasound sum score (GLUS) combining GSS-score, PD-j-score, B-perisyn, PD-perisyn, B-teno, PD-teno and MASEI was calculated (range 0–832).

Ultrasound remission and minimal ultrasound disease activity (MUDA) were defined as a PD-score=0 and a PD-score≤1, respectively, at joints, peritendinous tissue, tendons and entheses. In addition, we used a PD-score=0 at joints, entheses or tendons to make comparisons with the corresponding clinical findings.

Statistical analysis

Statistical analysis was performed using SPSS (V.19.0). Descriptive statistics were used to summarise the data. Proportions were analysed by the χ^2 test (or Fisher's exact test as appropriate) and quantitative results were compared using the Mann–Whitney U test. Correlations were analysed by the Spearman's rank correlation test.

Multivariate logistic regression models were developed to investigate the possible association between clinical factors and MUDA. See online supplementary file for details. Interobserver variability of ultrasound was investigated in 15 (21.4%) patients using intraclass correlation coefficient (ICC) or Cohen's κ as indicated.

RESULTS

Clinical findings

Patients' characteristics are summarised in online supplementary table S3.

Fifty-one (72.9%) patients had ≥1 TJ, 40 (57.1%) had ≥1 SJ, 26 (37.1%) had ≥1 painful enthesal site and 8 (11.4%) presented with dactylitis. Forty-eight (68.6%) and 24 (34.3%) patients suffered from current skin and/or nail involvement, respectively.

MDA was found in 21 (30.0%) PsA patients; however, 5 (23.8%) of them had >1TJ, 3 (14.3%) >1SJ, 7 (33.3%) a PASI>1, 2 (9.5%) Ptpain>15 mm, 2 (9.5%) PGA>20 mm and 2 (9.5%) a HAQ>0.5. None of these patients had a clinical MASEI+E>1.

According to CPDAI categories (see online supplementary table S1 for definitions) 53 (75.7%), 21 (30.0%), 8 (11.4%) and 48 (68.6%) had active joint, enthesal, dactylitis and/or skin disease, respectively. Seven patients (10.0%) had axial involvement; all of them were active according to CPDAI. A CDPAI=0 was found in five (7.1%) patients. No activity in the CPDAI joint, entheses and dactylitis domains (ie, CPDAI-JED=0) was observed in 15 patients (21.4%). Nine (60.0%) and zero of them had activity in the skin and axial domains, respectively. We used CPDAI-JED=0 for further analyses due to the low number of cases with CPDAI=0. DAPSA remission was achieved by 12 (17.1%) patients and 11 (15.7%) patients fulfilled the Boolean's definition of remission. Thirty-three (47.1%) patients

were in clinical remission according to physician's opinion (rem-phys). Online supplementary table S4 indicates the number of patients fulfilling more than one clinical definition of remission or MDA.

Correlations between clinical and ultrasound findings

The prevalence and scorings of ultrasound-verified pathologies are depicted in online supplementary table S5.

Clinical composites versus ultrasound scores

DAPSA showed weak-to-moderate correlations with total GLUS, GSS- and PD-j-scores as depicted in figure 1A, but was not associated with ultrasound scores of enthesitis, dactylitis, tenosynovitis or perisynovitis.

CPDAI correlated with GLUS ($corr_{coeff}$ 0.29, p=0.02) but not with individual ultrasound scores of arthritis, enthesitis, dactylitis, tenosynovitis or perisynovitis. Analysing the CPDAI joint domain, we found higher GSS- and PD-j-scores among patients with moderate or high joint activity compared with patients with no activity (figure 1B). No difference was found comparing the prevalence of perisynovitis between groups. Combining GSS-scores with B-perisyn and PD-j-scores with PD-perisyn and correlating these scores with DAPSA and CPDAI joint domains revealed results similar to the findings presented in figure 1 (using GSS- and PD-j-scores instead).

Ultrasound-verified dactylitis was more common (37.5% vs 3.2%, p=0.009) among patients with active CPDAI dactylitis domain (n=8) compared with those without (n=62). We found no association of MASEI, Sono-LEI, PD-MASEI, PD-MASEI+E or PD-LEI with disease activity according to the CPDAI enthesitis domain.

Association between clinical findings, inflammatory markers and ultrasound scores

As depicted in table 1, weak-to-moderate correlations were observed between SJ or TJ and GSS or PD-joint counts. Combined GSS+B-perisyn and PD-j-scores+PD-perisyn scores also revealed weak-to-moderate correlations with SJ, TJ, EGA and ESR ($corr_{coeffs}$ ranging from 0.26 to 0.53, p<0.05 for all analyses). The clinical LEI was associated with sonographic MASEI and Sono-LEI, whereas clinical examination of MASEI entheses was unrelated to the corresponding ultrasound score. PD-MASEI, PD-MASEI+E and PD-LEI were not associated with clinical items. Clinical and ultrasound dactylitis scores were moderately correlated, whereas ultrasound-verified tenosynovitis (B-teno, PD-teno as well as tenosynovitis of the entire flexor digitorum tendon) did not reflect clinical dactylitis scores. ESR correlated with GSS- and PD-j-scores/joint counts, whereas CRP was not associated with ultrasound inflammation. EGA was related to GSS- and PD-j-scores/joint counts and HAQ weakly correlated with MASEI.

Findings in patients with clinical or ultrasound-defined remission/MDA

Ultrasound results in patients with clinical remission/MDA

As detailed in online supplementary table S6, we found higher GSS- and PD-j-scores in patients with active versus inactive disease according to CPDAI-JED, DAPSA and rem-phys. Patients failing Boolean's remission definition had higher PD-values compared with those fulfilling the criteria. GSS- and PD-j-scores were similar in patients with MDA and individuals not fulfilling the MDA criteria. Excluding those six MDA patients with a TJ count and/or SJ count >1 yielded a lower PD-j-score among the remaining MDA patients compared with those not fulfilling the MDA criteria (median 1.0 (range 0–13.0) vs 4.0 (0–31.9), p=0.041).

PD-teno scores were significantly different in patients with active versus inactive disease according to all clinical definitions; however, median PD-teno scores were zero in all groups.

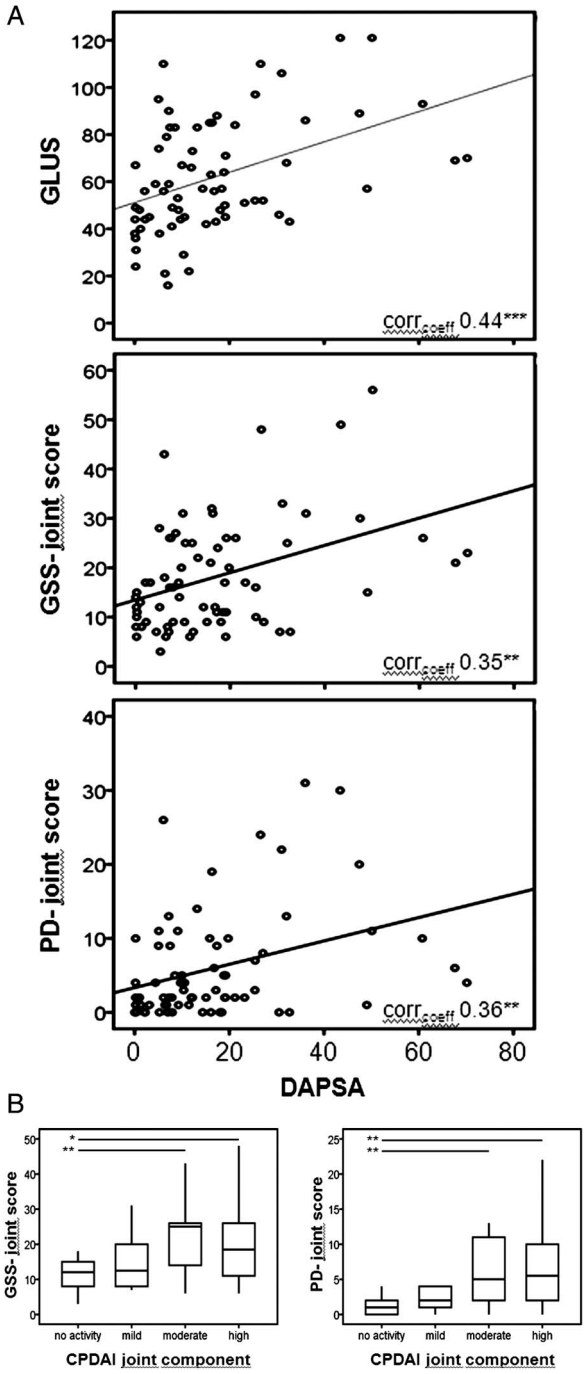

Figure 1 Association between clinical composites and ultrasound inflammation. (A) Scatter plots indicate the correlation between Disease Activity Index for Psoriatic Arthritis and global ultrasound sum score, grey-scale synovitis (GSS-joint score) or power Doppler (PD-joint score) scores; ***p<0.001 and **p<0.01 according to Spearman's rank correlation test; (B) Box plots indicate GSS-joint scores and PD-joint scores at different levels of disease activity according to Composite Psoriatic Disease Activity Index joint domain (no activity, n=17; mild activity, n=10; moderate activity, n=17; high activity n=26). *p<0.05, **p<0.01 according to Mann–Whitney U test.

Table 1 Association between clinical findings, inflammatory markers and ultrasound scores

	SJ	TJ	LEI	Ptpain	EGA	PGA	HAQ	dactylitis	ESR	CRP
GSS-score	NS	NS	–	NS	0.33**	NS	NS	–	0.41***	NS
GSS-count	0.42***	NS	–	NS	0.26**	NS	NS	–	0.35**	NS
PD-j-score	NS	NS	–	NS	0.37**	NS	NS	–	0.48***	NS
PD-j-count	0.48***	0.30*	–	NS	0.34**	NS	NS	–	0.47***	NS
perisyn	NS	NS	–	NS	NS	NS	NS	–	NS	NS
MASEI	–	–	0.30*	NS	NS	NS	0.24*	–	NS	NS
PD-MASEI	–	–	NS	NS	NS	NS	NS	–	NS	NS
PD-MASEI+E	–	–	NS	NS	NS	NS	NS	–	NS	NS
Sono-LEI	–	–	0.24*	NS	NS	NS	NS	–	NS	NS
PD-LEI	–	–	NS	NS	NS	NS	NS	–	NS	NS
ultrasound-dactylitis	–	–	–	NS	NS	NS	NS	0.41***	NS	NS

Correlation coefficients according to Spearman's rank correlation test are shown.
Significance levels were not corrected for multiple testing.
Ptpain, EGA and PGA were measured on a Visual Analogue Scale (range 0–100 mm) and are expressed in millimetres.
*p<0.05.
**p<0.01.
***p<0.001.
–, not tested; CRP, C reactive protein (normal range 0–5 mg/L); dactylitis, clinical dactylitis score; ultrasound- dactylitis, ultrasound-defined dactylitis; EGA, evaluator's global assessment of disease activity; ESR, erythrocyte sedimentation rate (normal range 0–10 mm/first hour); GSS-count, number of joints with GSS-score ≥1; GSS-score, grey-scale synovitis score of joints; HAQ, Health Assessment Questionnaire; LEI, number of painful entheses according to Leeds Enthesitis Index; MASEI, Madrid Sonographic Enthesis Index; NS, not significant; PD-j-count, number of joints with PD-j-score ≥1; PD-j-score, power Doppler (PD) score of joints; PD-LEI, number of entheses (according to Sono-LEI) with PD-signals; PD-MASEI+E; number of entheses (according to MASEI plus lateral epicondyle) with PD-signals; PD-MASEI; number of entheses (according to MASEI) with PD-signals; perisyn, B-mode and/or PD-perisynovitis; PGA, patient's global assessment of disease activity; Ptpain, patients' pain assessment; Sono-LEI, reduced enthesitis score focusing on lateral epicondyle, dist. Patella and Achilles tendons (ratings according to MASEI); SJ, swollen joint count; TJ, tender joint count.

B-teno, B-perisyn, PD-perisyn and MASEI as well as PD-MASEI, PD-MASEI+E and PD-LEI were comparable between patients with and without active disease.

The prevalence of patients with a PD-score>0 at joints, perisynovial tissue, entheses and tendons according to clinical definitions of remission/MDA is shown in table 2 (see online supplementary table S7 shows the corresponding values for a PD-score>1).

Ultrasound-defined dactylitis was present only in patients with active disease according to MDA, CPDAI-JED, DAPSA and Boolean's criteria, whereas one-fifth of patients with dactylitis were considered to be in remission by the evaluating physician.

Association of clinical composite scores with MUDA

Three (4.3%) patients were in ultrasound remission (ie, PD-score=0 at all investigated sites) and 14 (20.0%) patients

Table 2 Prevalence of patients with a PD-score>0 at joints, perisynovial tissue, entheses or tendons according to clinical remission/MDA criteria

	PD-j-score >0 n (%)	PD-perisyn>0 n (%)	PD-MASEI+E>0 n (%)	PD-teno>0 n (%)
MDA				
r (21)	16 (76.2)	3 (14.3)	15 (71.4)	4 (19.0)
a (49)	40 (81.6)	7 (14.3)	28 (57.1)	19 (39.6)*
CPDAI-JED				
r (15)	10 (66.7)	3 (20.0)	11 (73.3)	2 (13.3)
a (55)	46 (83.6)	7 (12.7)	32 (58.2)	21 (38.9)*
DAPSA				
r (12)	7 (58.3)	2 (16.7)	8 (66.7)	1 (8.3)
a (58)	49 (84.5)**	8 (13.8)	35 (60.3)	22 (38.6)**
Boolean's				
r (11)	5 (54.5)	1 (9.1)	8 (72.7)	1 (9.1)
a (59)	50 (84.7)**	9 (15.3)	35 (59.3)	22 (37.9)*
rem-phys				
r (33)	25 (75.8)	3 (9.1)	21 (63.6)	7 (21.9)
a (37)	31 (83.3)	7 (18.9)	22 (59.5)	16 (43.2)*

*p<0.1; **p<0.05 according to Fisher's exact test.
a, active disease—the number of patients in remission or with active disease is shown in parenthesis; Boolean's, Boolean's definition of remission; rem-phys, remission as judged by the treating physician; CPDAI-JED, joint, entheses and dactylitis domains of the Composite Psoriatic Disease Activity Index; DAPSA, Disease Activity Index for Psoriatic Arthritis; MDA, minimal disease activity; n, number (percentage in parenthesis); MASEI, Madrid Sonographic Enthesis Index; PD-j-score, power Doppler (PD) score of joints; PD-MASEI-E, sum of entheses with PD-signals; enthesal sites were scanned according to Madrid Sonographic Enthesis Index plus lateral epicondyle; PD-perisyn, PD within peritendinous tissue; PD-teno, sum score of PD-signals related to tenosynovitis; r, remission/MDA.

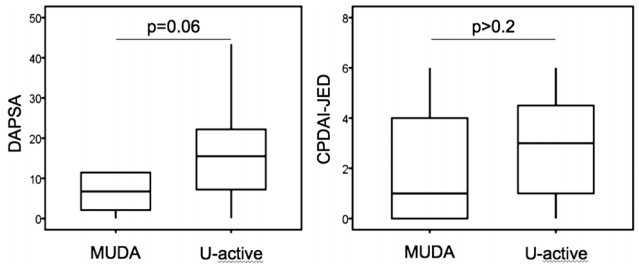

Figure 2 Disease Activity Index for Psoriatic Arthritis (DAPSA) and joint, entheses and dactylitis domains of the Composite Psoriatic Disease Activity Index (CPDAI-JED) scores in patients with and without minimal ultrasound disease activity (MUDA). DAPSA as well as CPDAI-JED are shown for patients with MUDA defined as a power Doppler-score≤1 at joints, peritendinous tissue, tendons and entheses and ultrasound-verified active disease (U-active). Whisker–box plots show the median and 50% of cases within the boxes and all data excluding mavericks between the end points of the whiskers. Differences were tested by the Mann–Whitney U test.

were found with MUDA (ie, PD-score≤1). Due to the low number of cases with ultrasound remission, we used MUDA for further analyses.

DAPSA values were lower in patients with MUDA compared with patients with ultrasound-verified active disease, whereas CPDAI (complete score as well as CPDAI-JED) was similar in both groups (figure 2).

Out of the evaluated clinical indices, only the DAPSA and Boolean's remission definitions were useful for the discrimination between patients with and without MUDA (table 3).

Association of individual clinical factors with MUDA

To identify individual clinical factors associated with MUDA, we performed pairwise comparisons and multipredictor logistic regression analysis.

The number of SJ and TJ tended to be lower in patients with MUDA compared with those with active disease in pairwise comparisons (median 0 (range 0–6) vs 1 (0–15), p=0.062 and 5.5 (0–59.0) vs 1.0 (0–33.0), p=0.088, respectively), whereas enthesitis (according to Leeds, clinical MASEI or clinical MAEI +E scores), Ptpain, PGA, EGA, HAQ, dactylitis score, ESR and CRP were similar in both groups.

According to multivariate logistic regression analysis, only TJ count>1 was associated with MUDA (OR 6.8, 95% CI 1.8 to 25.6, p=0.005). Correction of the model for demographic factors as listed in the online supplementary file did not change the primary result (p=0.005).

Clinical findings at joints, entheses and tendons with or without hypervascularisation

Next, we compared clinical factors with individual ultrasound definitions of remission (ie, PD-score=0) and active disease regarding joints, perisynovial tissue, entheses, tendons and dactylitis. The results are shown in table 4 (see online supplementary table S8 shows data for PD-score≤1 vs >1).

The proportion of patients with activity in the CPDAI joint domain was higher in patients with ultrasound-defined active synovitis (82.1% vs 50.0%, p=0.012) and active tenosynovitis (91.3% vs 67.4%, p=0.039) than in patients without hypervascularisation at these sites. All patients with ultrasound-verified dactylitis had at least one PD-signal at tendons and/or joints. Active disease according to CPDAI dactylitis domain was more common in patients with ultrasound-defined dactylitis compared with those without (60.0% vs 7.7%, p=0.009). No differences were found concerning activity in the CPDAI entheses and CPDAI joint domains comparing patients with/without ultrasound-verified active enthesitis or perisynovitis, respectively.

Association between ultrasound-verified structural damage and clinical or sonographic inflammatory findings

The median number of joints with erosion(s) was 4.5 (range 0–25) and the median number of joints with osteophytes was 42 (4–56). The PD-joint count ($corr_{coeff}$ 0.37, p=0.002), the PD-j-score ($corr_{coeff}$ 0.41, p<0.001) and TJs ($corr_{coeff}$ 0.25, p=0.035) were the only parameters associated with the number of erosive joints. Comparing patients with and without erosive disease, we found no difference regarding the clinical and ultrasound parameters tested. Sonography detected osteophytes were neither associated with sonographic nor associated with clinical/laboratory signs of inflammation.

Enthesal erosions were found in 47 (67.1%) patients (median number of entheses with erosions 1.0 (range 0–7.0)) and all patients had at least one enthesophyte (median number of enthesophytes 8.0 (1.0–12.0)). Enthesal erosions and enthesophytes were weakly correlated ($corr_{coeff}$ 0.29, p=0.014), whereas other sonographic findings and clinical markers were unrelated to structural enthesal lesions. Also, no difference was found comparing patients with and without enthesal erosions regarding clinical and ultrasound scores of inflammation.

Interobserver variability

Reproducibility of ultrasound findings ranged from fair to good. ICC for GSS-score was 0.40 (95% CI 0 to 0.75), for PD-j-score 0.71 (0.32 to 0.89), for tenosynovitis 0.74 (0.38 to 0.91), for osteophyte score 0.93 (0.80 to 0.97) and for enthesitis score (grading according to MASEI) 0.75 (0.28 to 0.93). Reliability of

Table 3 Sensitivity and specificity of clinical criteria to identify patients with MUDA (n=14)

	Sensitivity (%)	Specificity (%)	OR (95% CI)	p Value*
MDA (n=21)	35.7	71.4	1.4 (0.4 to 5.8)	0.60
CPDAI-JED (n=15)	28.6	80.4	1.6 (0.4 to 6.2)	0.47
DAPSA (n=12)	35.7	87.5	3.9 (1.0 to 15.0)	0.049
Boolean's (n=11)	35.7	89.3	4.6 (1.2 to 18.5)	0.030
rem-phys (n=33)	64.3	57.1	2.4 (0.7 to 8.1)	0.15

MUDA was defined as a PD-score ≤1 at joints, peritendonal tissue, tendons and entheses.
*According to χ^2 test.
Boolean's, Boolean's definition of remission; CPDAI-JED, joint, entheses and dactylitis domains of the Composite Psoriatic Disease Activity Index; DAPSA, Disease Activity Index for Psoriatic Arthritis; MDA, minimal disease activity; MUDA, minimal ultrasound disease activity; rem-phys, remission as judged by the treating physician.

Table 4 Comparison of clinical scores according to ultrasound-defined remission and active disease at joints, entheses and tendons

	n	SJ	TJ	enthes.	Ptpain	EGA	PGA	HAQ	dactylitis	ESR	CRP
PD-j-score											
0	14	0 (0–4)	NS	–	NS	NS	NS	NS	–	6.5 (1–17)	NS
≥1	56	1 (0–15)**								10 (1–74)*	
PD-perisyn											
0	60	NS	NS	–	NS	NS	NS	NS	–	NS	NS
≥1	10										
PD-MASEI+E											
0	27	–	–	NS	NS	NS	NS	NS	–	NS	NS
≥1	43										
PD-teno											
0	47	0 (0–10)	2 (0–59)	–	NS	NS	30 (0–80)	NS	NS	6 (1–47)	2 (0–20.3)
≥1	23	3 (0–15.)**	7 (0–33)**				40 (0–80)*			18 (5–74)***	4.8 (0.6–49.5)*
PD-dactylitis											
0	65	1 (0–15)	3 (0–59	–	NS	20 (0–80)	NS	NS	0 (0–10)	NS	NS
≥1	5	5 (3–13)**	13 (6–26)*			30 (30–60)*			2 (0–4)***		

Data are shown as median and range in parenthesis.
Ptpain, EGA and PGA were measured on a Visual Analogue Ccale (range 0–100 mm) and are expressed in millimetres.
*p<0.05.
**p<0.01.
***p<0.001.
–, not tested; CRP, C reactive protein (normal range 0–5 mg/L); EGA, evaluator's global assessment of disease activity; enthes., number of painful entheses according to Leeds, clinical MASEI or clinical MAEI+E scores; ESR, erythrocyte sedimentation rate (normal range 0–10 mm/first hour); HAQ, Health Assessment Questionnaire; dactylitis, dactylitis score; MASEI, Madrid Sonographic Enthesis Index; n, number of cases; NS, not significant; PD-dactylitis, ultrasound-defined dactylitis with PD-signals at involved joints and/or tendons; PD-j-score, power Doppler (PD)-score of joints; PD-MASEI-E, sum of entheses with PD-signals; enthesal sites were scanned according to Madrid Sonographic Enthesis Index plus lateral epicondyle; PD-perisyn, PD within peritendinous tissue; PD-teno, sum score of PD-signals related to tenosynovitis; PGA, patient's global assessment of disease activity; Ptpain, patient's pain assessment; SJ, swollen joint count; TJ, tender joint count.

perisynovitis was determined by Cohen's κ because all but one patient had a perisynovitis score of zero or one. The reliability to identify a patient with perisynovitis was 0.82 (p=0.001).

DISCUSSION

Our data demonstrate a disparity between ultrasound and clinical findings in PsA. DAPSA and CPDAI moderately correlated with GLUS; DAPSA and CPDAI joint domains were linked with GSS- and PD-j-scores, but none of the composites adequately reflected the extent of enthesitis, tenosynovitis or perisynovitis. A considerable proportion of PsA patients in clinical remission or MDA had ultrasound-verified active inflammation at joints, tendons, peritendinous tissue and/or entheses. DAPSA and the Boolean's remission definition performed better than the other criteria to identify patients with MUDA. Joint erosions but not osteophytes or structural enthesal lesions were associated with ultrasound or clinical signs of inflammation similar to a previous MRI study in PsA and earlier ultrasound reports in RA.[11 38 39]

A high prevalence of subclinical synovitis and enthesitis was previously observed in psoriasis patients and we know from earlier RA studies that ultrasound-verified active inflammation is present in up to half of patients in clinical remission.[4 12 14 40 41] In RA, subclinical arthritis was of high prognostic value concerning future clinical relapses and progression of erosions.[42–44] The relevance of inflammatory ultrasound findings at joints, tendons, peritendinous tissue and/or entheses regarding the outcome of PsA patients in clinical remission is elusive so far. Clinically proven enthesitis contributed to worse function and decreased quality of life and we observed a weak correlation between MASEI and HAQ.[22 45 46] A small study in psoriasis patients (without arthritis) suggested that ultrasound-verified enthesitis might predict onset of PsA.[47] Given the high prognostic relevance of PD in RA, the value of intraenthesal PD-signals will be of particular interest for future outcome trials in PsA. Ultrasound enthesitis composite scores such as MASEI measuring signs of chronic inflammation (erosions and enthesophytes), signs that can be acute, chronic or both (structural alterations, enthesal thickening) and acute signs (PD-signals) are probably less relevant for such studies.[48]

Dactylitis was clinically observed more frequently than by sonography contrasting the high sensitivity of ultrasound to detect synovitis and enthesitis. This result is explained by the conservative definition of dactylitis applied (arthritis of MCP, PIP and DIP plus flexor tenosynovitis). The combination of arthritis and tenosynovitis was deemed as the underlying pathology of dactylitis in earlier publications, whereas recent ultrasound studies indicate that isolated tenosynovitis is the most common ultrasound abnormality and arthritis occurs in 50% of cases only.[34 35 49] Notably, flexor tenosynovitis was not related to clinical dactylitis scores, whereas the present ultrasound definition of dactylitis was linked with the CPDAI dactylitis domain and the number of dactylitic fingers/toes.

Perisynovitis, that is, extensor peritendon inflammation at MCPs, is a specific pathology in patients with early PsA.[33] The relevance of this sonographic pattern, once the diagnosis is established, however, is unknown. Perisynovitis neither did correlate with SJ/TJ at MCPs, nor was it linked with any other clinical measure. Combining perisynovitis and synovitis scores into a single item revealed similar correlations with clinical factors compared with synovitis scores alone. Whether perisynovitis should be scored separately or considered as part of the synovial complex and whether perisynovitis might contribute to structural damage are issues that have to be clarified by future research.

ESR but not CRP moderately correlated with ultrasound signs of joint inflammation contrasting previous data in RA.[4] One earlier study found higher ESR values in PsA patients with polyarticular disease compared with patients with other manifestations, whereas CRP levels were comparable in both groups.[50]

Further studies are now required to address the hypothesis that in PsA ESR better reflects polyarticular inflammation than CRP.

A clinical definition of remission has not been established for PsA. MDA resulted from a recent Group for Research and Assessment of Psoriasis and Psoriatic Arthritis project aimed at the development of an instrument to assess 'treatment to target' in PsA.[51] MDA indicates low disease activity and is useful to distinguish between patients with high and low risk of radiographic progression.[15 16] Arthritis (as well as other PsA manifestations) is nevertheless present in a considerable proportion of patients possibly explaining ongoing structural joint damage in a part of PsA patients despite fulfilling MDA criteria.[15 16] DAPSA and CPDAI were recently proposed as PsA-specific composites.[18 19] As cut-offs defining disease activity states are not yet available, we considered a DAPSA≤3.3 and a CPDAI-JED score=0 as markers of clinical remission. The components and calculations of DAPSA are similar to Simplified Disease Activity Index (SDAI) and a SDAI≤3.3 is accepted for remission in RA.[29] This cut-off is certainly not evidence based for PsA and is therefore recommended neither for use in clinical trials nor for daily routine. We cannot exclude that another cut-off might be more suitable; however, the high prevalence of patients showing PD-signals despite DAPSA≤3.3 argues against a higher cut-off.[29] A CPDAI=0 suggests complete absence of clinical activity; however, only 7% of our patients fulfilled this definition. Residual skin activity was found in the majority of patients despite absence of musculoskeletal symptoms and a reduced score, CPDAI-JED performed better for our study. Lastly, a Boolean's remission definition was used in accordance with the 2011 ACR/EULAR remission proposal for RA. This definition and DAPSA were the only useful clinical criteria to distinguish between patients with and without MUDA.[29]

We used MUDA for most of our comparisons because only three patients had no PD-signals at joints, tendons, peritendinous tissue and entheses despite the relatively low median clinical disease activity in our cohort. The absence of PD-signals as a marker of remission was previously proposed for RA[4 52]; however, the practical relevance of such a definition for PsA (given the low prevalence of patients fulfilling these criteria) is questionable. Besides, the ongoing improvement of PD technique increases the probability to detect PD-signals in patients in clinical remission and a minimum of hypervascularisation may therefore still be acceptable.[40] Whether MUDA distinguishes between patients with high and low risk of unfavourable outcomes has to be clarified by future research.

Reproducibility of ultrasound findings was comparable with that of earlier reports in PsA and RA.[1] We focused on hands and elbows because a second extensive ultrasound examination of all joints and enthesal sites was not feasible. Most ultrasound abnormalities could be adequately scored; unfortunately, the prevalence of dactylitis was too low to calculate interobserver variability in this sample.

Our study has several strengths: (1) we compared the new PsA-specific clinical composite scores DAPSA and CPDAI as well as MDA with sonographic findings, whereas previous reports usually 'borrowed' clinical measures from RA.[10 11] The most important difference between these composites is the inclusion of different PsA manifestations in CPDAI and MDA (thus representing composite disease scores), whereas DAPSA is a composite arthritis score reflecting not-joint-related PsA manifestations indirectly by PGA and Ptpain.[18] As these scores measure different aspects of the disease, a better correlation of DAPSA with ultrasound-verified joint inflammation than CPDAI and MDA could be expected. However, excluding those MDA patients with a TJ count and/or SJ count >1 resulted in a better association between clinical and ultrasound results of disease activity. (2) We included all inflammatory and structural ultrasound abnormalities previously described in PsA, whereas earlier studies usually focused on a limited number of sonographic pathologies.[10–12 14 33] Ultrasound findings, however, were not compared with other imaging techniques such as x-ray or MRI because we aimed at the comparison between sonographic and clinical items.

The most important limitations of our study were the low number of patients fulfilling clinical and ultrasound remission criteria; the low reliability of GSS (possibly explaining the lack of statistical correlation of GSS with other variables) as well as the extensiveness of sonographic assessments (90 min for each patients). Reduced PsA-specific ultrasound scores are currently developed with the aims of (1) a correlation with clinical composites, (2) sensitivity to change after interventions and (3) specificity for remission assessment. Our study may constitute the basis for such a score and a study investigating the variance of ultrasound findings during follow-up as well as the minimal number of joints (and related structures) and entheses to be investigated is currently underway.

In summary, we show a disparity between ultrasound and clinical findings in PsA. Current clinical PsA composite scores (and its joint components) correlate with ultrasound-verified synovitis, whereas enthesitis, tenosynovitis and perisynovitis are not adequately represented by these indices. DAPSA and Boolean's remission definitions were the most useful indices discriminating between patients with and without MUDA. Joint erosions are associated with PD-signals, whereas enthesal structural damage is not linked with ultrasound inflammation.

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Disparity between ultrasound and clinical findings in psoriatic arthritis

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Notes