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Entheseal structural damage according to OMERACT definitions unveils distinct ultrasound phenotypes in SpA: findings from the DEUS multicentre study

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ABSTRACT

Objectives: To explore the prevalence and distribution of ultrasound-detected lesions indicating structural damage at the enthesis (e.g., bone erosions, enthesophytes, and calcifications) in patients with spondyloarthritis (SpA), comparing those with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), and to investigate the demographic, clinical, and metabolic factors linked to these lesions.

Methods: A cross-sectional analysis was conducted using data from the DEUS study, a multicentre investigation involving 20 rheumatology centres and including 413 patients with SpA (224 with axSpA and 189 with PsA). All participants underwent standardized clinical and ultrasound assessment of the large lower limb entheses (quadriceps tendon, proximal and distal patellar tendons, Achilles tendon, and plantar fascia). Entheseal structural lesions were explored by ultrasound and classified according to OMERACT definitions. Bivariate analyses and multivariate logistic regression were used to assess associations between ultrasound lesions and SpA patients' characteristics.

Results: In SpA patients, enthesophytes were the most common lesion (78.7 %), followed by calcifications (43.6 %) and bone erosions (24.9 %). Enthesophytes were more prevalent in PsA (86.8 %) compared to axSpA (71.9 %) ($p < 0.001$), with no significant differences in erosions and calcifications. However, lesion distribution varied across different entheses.

Multivariate analysis revealed that entheseal erosions were significantly associated with inflammatory markers, HLA-B27 positivity, clinical enthesitis, and longer disease duration. Enthesophytes were significantly linked to PsA, psoriasis, clinical enthesitis, and longer disease duration. Calcifications were positively associated with hypertension, metabolic syndrome, and obesity. All lesions were associated with biologic DMARD use.

Conclusions: This study reveals a high prevalence of ultrasound-detected structural damage at the enthesis and identifies distinct SpA phenotypes based on these findings.

Introduction

Enthesitis represents a critical domain in spondylarthritis (SpA), including axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), characterized by inflammation at the insertion site of tendons, ligaments, and joint capsules into the bone [1]. Enthesitis plays a central role in SpA pathogenesis, diagnosis, management, and treatment [2,3]. The traditional method for assessing enthesitis is physical examination, however, this lacks specificity in distinguishing inflammatory from biomechanically driven forms [4].

In this context, ultrasound has emerged as a valuable tool, enhancing the detection of SpA-related enthesitis, and therefore supporting clinical examination in the distinction between inflammatory and non-inflammatory entheseal pain [5–7].

While most studies identify power Doppler (PD) signal as the most reliable indicator of inflammatory lesion in enthesitis associated with SpA, bearing significant implications for differential diagnosis, disease activity and potentially prognosis, the clinical relevance of structural damage detected at entheses remains much less understood [8].

In inflammatory arthritis, such as rheumatoid arthritis (RA) and PsA, joint structural damage, particularly bone erosions, serves as a well-established marker of disease severity and a primary determinant of long-term disability [9–11]. In RA, joint bone erosions are routinely used as outcome measures in clinical trials and their detection should prompt the need for aggressive treatment escalation according to current international guidelines [12].

In contrast, the relevance of structural damage at entheseal sites, encompassing bone erosions, enthesophytes, and calcifications, has yet to be fully elucidated in SpA. While these lesions have begun to gain attention as exploratory outcomes in clinical trials, their broader application as markers of disease activity, severity, and potentially as guides for treatment decisions remains limited [13].

In a previous study by our group—the DEUS study (Defining Enthesitis on Ultrasound in Spondyloarthritis)—entheseal bone erosions were the only structural lesions that effectively distinguished SpA patients from controls [14]. Furthermore, another analysis from the DEUS study demonstrated a strong association between the presence of a PD signal at the enthesis, indicating active inflammation, and structural damage, even among patients with subclinical enthesitis [5]. In another study, Achilles tendon erosions cluster at the proximal insertion and superior tuberosity, linking their topography to biomechanical stress, fibrocartilage distribution, and inflammation-driven damage [15]. Additional studies showed a high prevalence of entheseal calcifications and enthesophytes in patients without SpA, including healthy subjects, particularly those with metabolic comorbidities and older age [16].

We hypothesize that structural damage on ultrasound, particularly bone erosions, may reflect a more inflammatory disease phenotype in SpA. Additionally, different findings of structural damage might be associated with distinct clinical and demographic features in SpA, providing insights into their clinical relevance in these patients.

Based on these hypotheses, the objectives of this study were to investigate the prevalence and distribution of ultrasound findings indicative of structural damage at the enthesis (bone erosions, enthesophytes and calcifications) in patients with SpA and their association with demographic, clinical, and metabolic factors that might identify different disease phenotypes.

Methods

Study design and population

The current study presents a cross-sectional pre-specified analysis of the DEUS study involving patients diagnosed with SpA, including axSpA and PsA [14]. The design of the DEUS study has been previously described [14]. Briefly, consecutive patients fulfilling the SpA international Society (ASAS) classification criteria for axSpA [17] and ClASsification criteria for Psoriatic ARthritis (CASPAR) for PsA [3] were recruited from 20 rheumatology centres. Patients with axSpA were subclassified into 'radiographic' and 'non-radiographic' subtypes [18].

Exclusion criteria included patients younger than 18 years, those with a history of major knees or ankle joint surgery or trauma, SpA patients with concurrent fibromyalgia, and those having performed intense physical activity in the two weeks preceding clinical evaluation. A control group was included in the original work made by patients with osteoarthritis and fibromyalgia (not included in the current analysis).

Data collection

Demographic and clinical data were collected, including age, sex, body mass index (BMI), HLA-B27 status (when available), physical activity (times per week), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease duration, and presence of skin psoriasis.

The presence of metabolic conditions was registered, namely dyslipidaemia, diabetes, obesity, systemic hypertension, and metabolic syndrome (definitions in Supplementary Table 1).

The Leeds Enthesitis Index (LEI) was calculated in SpA patients [19]. Tender and swollen joint counts were documented on a 0–68 and 0–66 scale, respectively, in SpA patients. Specific measures used for PsA, and their relative components, included the Disease Activity in Psoriatic Arthritis score (DAPSA) [20], while for axSpA, additional assessments included the Ankylosing Spondylitis Disease Activity Score (ASDAS) [21], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [22], Bath Ankylosing Spondylitis Functional Index (BASFI) [23], and Bath Ankylosing Spondylitis Metrology Index (BASMI) [24]. The Health Assessment Questionnaire Disability Index (HAQ-DI) [25] was also used for both axSpA and PsA patients.

The use of current disease-modifying antirheumatic drug (DMARD) therapy, including conventional synthetic (cs) DMARDs and biologic (b) DMARDs, and use of steroidal anti-inflammatory or non-steroidal anti-inflammatory drugs (NSAIDs) were collected.

A rheumatologist performed physical examination to identify clinical enthesitis in all patients, defined as the presence of tenderness upon palpation, movement, or contraction against resistance, with or without swelling at the enthesis [26]. The following entheses were evaluated: the patellar insertion of the quadriceps tendon, the patellar insertion of the patellar tendon, the tibial insertion of the patellar tendon, the calcaneal insertion of the Achilles tendon, and the calcaneal insertion of the plantar fascia. Previous episodes of enthesitis (diagnosed by a physician) were also recorded.

Ultrasound assessment

Ultrasound evaluations were performed by rheumatologists and sonographers participating in the study, blinded to the clinical findings, on the same day of the physical examination. The scans were executed on the same entheses evaluated by physical examination, following the European Alliance of Associations for Rheumatology (EULAR) guidelines on the use of musculoskeletal ultrasound in rheumatology [27].

The current study focused on the elementary lesions of enthesitis indicative of structural damage, which were defined following the Outcome Measures in Rheumatology (OMERACT) ultrasound taskforce [28,29]:

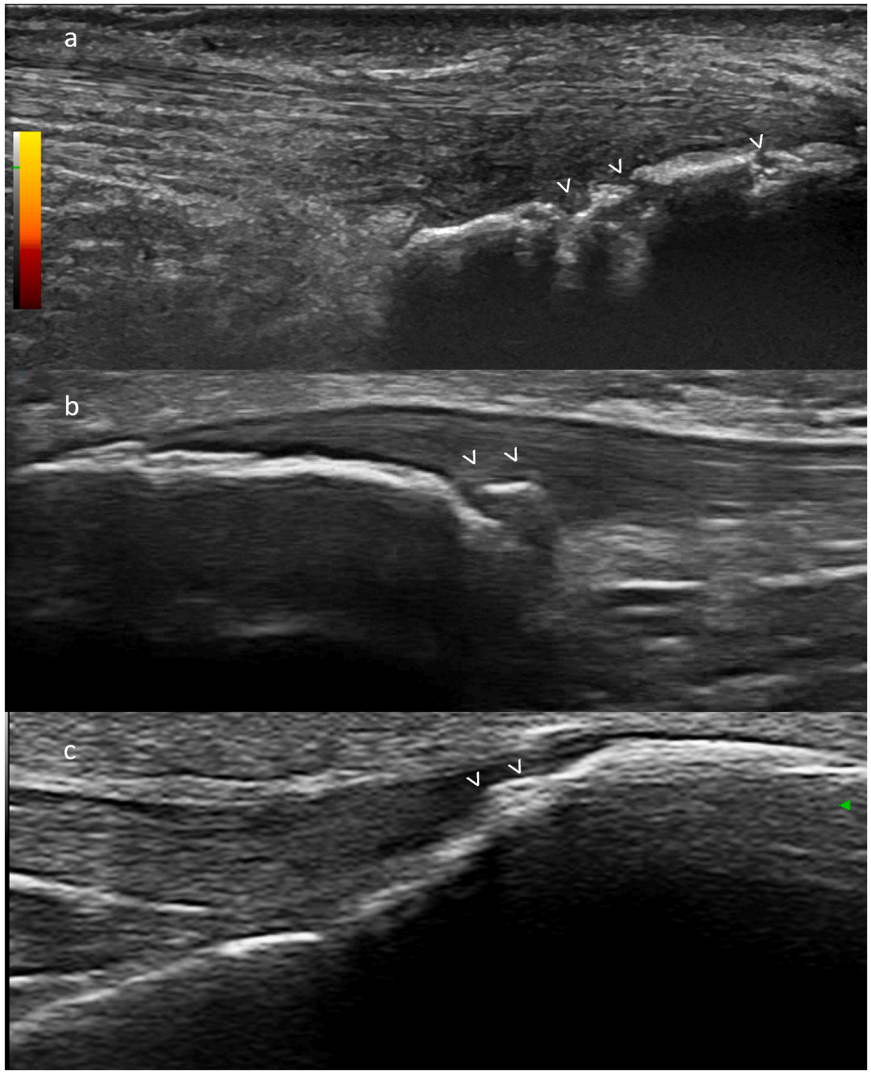

Fig. 1. Representative ultrasound images of bone erosions (a), enthesophytes (b) and calcifications (c) in SpA patients.
Figure a shows multiple bone erosions in the calcaneal bone at the enthesis of the Achilles. Figure b presents a pre-insertional calcification at the proximal insertion of the patellar tendon. into the patellar bone. Figure c displays enthesophytes at the distal patellar insertion into the anterior tibial tuberosity. The respective lesions are indicated by arrowheads. All patients were diagnosed with SpA.

- Ø Enthesophytes: step-up of bony prominence, visible in two perpendicular planes at the end of the bone contour of the enthesis.
- Ø Calcifications: hyperechoic foci, with or without acoustic shadow, detected at the enthesis (<2 mm from the cortical bone).
- Ø Bone erosions: cortical break with a step-down contour defect, visible in two perpendicular planes, at the insertion of the enthesis.

Fig. 1 provides an illustrative example of ultrasound detected bone erosions at the enthesis, enthesophytes and calcifications.

Before this study, the participants of the DEUS study carried out an online exercise to evaluate inter- and intra-rater reliability in assessing OMERACT ultrasound elementary lesions of enthesitis, including those of structural damage [30]. This previous study showed an almost perfect agreement regarding the assessment of bone erosions, and a substantial agreement for calcifications and enthesophytes.

Statistical analysis

Descriptive statistics summarized patients' demographic and clinical characteristics. Lesion prevalence (erosions, enthesophytes, calcifications) and their distribution by entheseal site, were summarized in contingency tables, stratified by SpA subtype. Group comparisons used Pearson's chi-squared test.

To evaluate how the presence of entheseal bone erosions, enthesophytes, and calcifications combines at the patient level, regardless of their anatomical location, we constructed an upset plot using these three elementary damage lesions as features to define intersection groups for all possible combinations. This method allowed us to assess visually and numerically how these elementary lesions co-occur within individual patients, providing an overview of the overlapping structural damage patterns.

To explore associations between clinical variables and each structural lesion were explored using Fisher's exact test on all the binary clinical variables and on binarized continuous variables. Structural lesions were treated as binary outcomes (presence vs. absence) for erosions, enthesophytes, and calcifications. This approach allowed us to detect potential threshold-based associations that may not emerge with continuous modelling. For continuous variables dichotomization was based on clinically meaningful cut-offs. Specifically, impaired spinal mobility was defined as BASMI ≥3.1 [31], impaired physical function as BASFI ≥2.5 [32], and disability as HAQ-DI ≥1.5. High peripheral disease activity corresponded to DAPSA ≥28 [20], while axial disease activity was defined by BASDAI >6 [33] or ASDAS ≥2.1 [34]. Physical inactivity was defined as engaging in structured physical activity ≤1 time per week, in line with thresholds commonly used to identify individuals not meeting international physical activity recommendations [35], older age was defined as ≥65 years, and joint involvement as the presence of any tender and swollen joints. "Early SpA" was defined by axial symptoms duration ≤24 months [36].

Considering that different types of elementary lesions may exhibit overlap, morphological similarities, or frequently co-occur on ultrasound examination, only predictors with a p-value<0.05 in any of the three univariate analyses were included in multivariable models as response variables to assess whether their associations with a specific elementary damage lesion type remained significant after adjusting for the presence of the other two lesion types, as well as for age and sex, given their impact on entheseal structural damage [16]. Categorical features were modelled with logistic regressions, whereas continuous features with linear regressions. The inclusion of the three elementary lesions in the same models was justified after confirming acceptable levels of multicollinearity using the Variance Inflation Factor and Condition Index. This allowed us to assess the independent association of clinical and demographic variables with each lesion type while controlling for the presence of the other lesions. Data analysis was conducted using R (https://www.R-project.org) and RStudio (PBC, Boston, MA).

Results

A total of 413 SpA patients were included, with 4130 entheseal sites assessed via ultrasound. The main demographic, clinical, and treatment characteristics (overall SpA, and by axSpA and PsA subgroups), are reported in Supplementary Tables 2–4.

As shown in Table 1, enthesophytes were the most common lesion (78.7 %), followed by calcifications (43.6 %) and bone erosions (24.9 %). PsA patients had a higher prevalence of enthesophytes than axSpA (86.8 % vs 71.9 %, $p < 0.001$), particularly at the quadriceps tendon, Achilles tendon, and plantar fascia. No difference in overall erosion prevalence was observed, although axSpA patients had more erosions at the Achilles tendon and significantly more at the plantar fascia. Calcifications showed similar distribution, except at the plantar fascia, where PsA patients had a higher prevalence.

An overview of the distribution and overlap of the three structural features in axSpA and PsA patients is presented in Fig. 2. Of 413 patients, 123 (29.8 %) had enthesophytes alone, 109 (26.4 %) both enthesophytes and calcifications, and 64 (15.5 %) had none. A combination of enthesophytes and erosions was found in 38 (9.2 %) patients, while all three features in 55 (13.3 %). Additionally, 14 (3.4 %) had calcifications alone, 8 (1.9 %) had erosions alone, and 2 (0.5 %) had both calcifications and erosions.

Patients with erosions more frequently had raised CRP (37.9 % vs 25.5 %, $p = 0.018$), ESR (25.2 % vs 14.5 %, $p = 0.013$), HLA-B27 positivity (82.8 % vs 65.9 %, $p = 0.048$), clinical enthesitis (43.7 % vs 26.5 %, $p = 0.001$), LEI>0 (47.6 % vs 28.4 %, $p < 0.001$), and enthesitis history (57.3 % vs 25.8 %, $p < 0.001$). They also more frequently used cDMARDs (62.1 % vs 41.9 %, $p = 0.011$) and were less likely to present early SpA (11.7 % vs 21.9 %, $p = 0.021$) (Table 2).

Patients with enthesophytes showed a higher prevalence of skin psoriasis (48.0 % vs 20.5 %, $p < 0.001$), PsA (50.5 % vs 28.4 %, $p < 0.001$), older age (14.8 % vs 0.0 %, $p < 0.001$), metabolic syndrome (22.2 % vs 10.2 %, $p = 0.012$), diabetes (9.9 % vs 2.3 %, $p = 0.022$), and systemic hypertension (30.2 % vs 15.9 %, $p = 0.008$). They also had more frequently a LEI > 0 (37.2 % vs 18.2 %, $p < 0.001$), clinical enthesitis (34.5 % vs 17.0 %, $p = 0.002$), enthesitis history (37.2 % vs 20.5 %, $p = 0.003$), cDMARDs use (46.8 % vs 22.7 %, $p = 0.002$), higher BASMI scores (30.2 % vs 17.4 %, $p = 0.050$), and at least one tender joint (39.4 % vs 25.0 %, $p = 0.014$) (Table 2). In contrast, these patients were less likely to be HLA-B27 positive (66.1 % vs 80.2 %, $p = 0.037$) and to have non-radiographic axSpA (24.1 % vs 38.4 %, $p = 0.032$), and more often physically inactive (57.2 % vs 31.8 %, $p < 0.001$), with concordantly higher levels of physical activity in patients without enthesophytes ($p < 0.001$) (Table 2).

Patients with calcifications had higher prevalence of enthesitis history (38.9 % vs 29.6 %, $p = 0.048$), active DAPSA scores (14.4 % vs 4.6 %, $p = 0.017$), metabolic syndrome (27.8 % vs 13.3 %, $p < 0.001$), obesity (33.9 % vs 21.0 %, $p = 0.031$), systemic hypertension (37.8 % vs 18.9 %, $p < 0.001$), and more bDMARD use (60.0 % vs 48.1 %, $p = 0.016$). They had lower prevalence of elevated ESR (12.8 % vs 20.6 %, $p = 0.044$), early SpA (14.4 % vs 23.2 %, $p = 0.023$), and oral steroid use (10.6 % vs 20.5 %, $p = 0.032$). There was a trend toward higher skin psoriasis prevalence (47.2 % vs 38.2 %, $p = 0.063$) and lower ASDAS active disease (39.5 % vs 51.3 %, $p = 0.058$) (Table 2).

As shown in Table 3, multivariable logistic regression analysis - adjusted for age, sex, and ultrasound lesions of structural damage (e.g., enthesophytes and calcifications when evaluating bone erosions, and vice versa) – confirmed most bivariate associations for bone erosions. Bone erosions were independently associated with increased odds of HLA-B27 positivity (OR 2.48, $p = 0.013$), elevated CRP (OR 1.95, $p = 0.004$), and raised ESR (OR 2.30, $p = 0.002$). Erosions were also significantly associated with enthesitis history (OR 4.66, $p < 0.001$), clinical enthesitis (OR 2.24, $p < 0.001$), LEI (Beta 0.39, $p = 0.006$), and disease duration (Beta 44, $p < 0.001$), while showing a negative association with diabetes (OR 0.39, $p = 0.048$) and age (Beta −4.2, $p =$

Table 1
Prevalence and distribution of the OMERACT ultrasound elementary lesions of damage in patients with SpA grouped by diagnosis (axSpA and PsA).

OMERACT damage lesion	Overall				Quadriceps tendon				Patellar proximal				Patellar distal				Achilles tendon				Plantar fascia			
	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]	SpA N = 413	axSpA N = 224	PsA N = 189	p-value[1]
Bone erosions	103 (24.9 %)	62 (27.7 %)	41 (21.7 %)	0.2	23 (5.6 %)	15 (6.7 %)	8 (4.2 %)	0.3	15 (3.6 %)	7 (3.1 %)	8 (4.2 %)	0.5	14 (3.4 %)	8 (3.6 %)	6 (3.2 %)	0.8	64 (15.5 %)	36 (16.1 %)	28 (14.8 %)	0.7	23 (5.6 %)	20 (8.9 %)	3 (1.6 %)	**0.001**
Enthesophytes	325 (78.7 %)	161 (71.9 %)	164 (86.8 %)	**<0.001**	210 (50.8 %)	99 (44.2 %)	111 (58.7 %)	**0.003**	108 (26.2 %)	53 (23.7 %)	55 (29.1 %)	0.2	73 (17.7 %)	39 (17.4 %)	34 (18.0 %)	0.9	262 (63.4 %)	129 (57.6 %)	133 (70.4 %)	**0.007**	122 (29.5 %)	49 (21.9 %)	73 (38.6 %)	**<0.001**
Calcifications	180 (43.6 %)	93 (41.5 %)	87 (46.0 %)	0.4	82 (19.9 %)	37 (16.5 %)	45 (23.8 %)	0.064	40 (9.7 %)	22 (9.8 %)	18 (9.5 %)	>0.9	70 (16.9 %)	43 (19.2 %)	27 (14.3 %)	0.2	73 (17.7 %)	38 (17.0 %)	35 (18.5 %)	0.7	36 (8.7 %)	10 (4.5 %)	26 (13.8 %)	**<0.001**

[1] Pearson's Chi-squared test. Acronyms. axSpA: Axial Spondylarthritis; OMERACT: Outcome Measures in Rheumatology; PsA: Psoriatic Arthritis; SpA: spondyloarthritis.

0.002).

In multivariable analysis, enthesophytes presence was strongly associated with skin psoriasis (OR 3.52, $p < 0.001$), enthesitis history (OR 2.36, $p = 0.003$), clinical enthesitis (OR 1.98, $p = 0.003$), and PsA diagnosis (OR 1.68, $p = 0.046$). Enthesophytes were negatively associated with physical activity (Beta −0.73, $p = 0.007$). Both enthesophytes and calcifications positively correlated with age (Beta 12, $p < 0.001$, and Beta 3.7, $p < 0.001$, respectively).

Furthermore, calcifications were the only lesion independently associated with hypertension (OR 2.34, $p < 0.001$), metabolic syndrome (OR 2.83, $p < 0.001$), and obesity (OR 1.49, $p = 0.045$). Conversely, calcifications were negatively associated with ASDAS (Beta −0.52, $p = 0.007$).

Erosions were associated with bDMARDs (OR 2.23, $p < 0.001$), cDMARDs (OR 2.46, $p < 0.001$), and steroids (OR 1.93, $p = 0.044$). Enthesophytes were associated with cDMARD (OR 2.49, $p < 0.001$), but not with steroids. Calcifications were positively associated with bDMARD use (OR 1.50, $p = 0.027$) and negatively associated with oral steroid use (OR 0.49, $p = 0.016$).

Discussion

This study assesses the prevalence and distribution of elementary structural lesions at the enthesis in the largest cohort of SpA patients to date, including axSpA and PsA. We examined erosions, enthesophytes, and calcifications - defined according to OMERACT - and explored their associations with key demographic, clinical, and metabolic factors. Our findings underscore the potential of ultrasound-detected lesions as markers of disease severity and phenotypic variation.

We observed a high prevalence of ultrasound-detected structural lesions in SpA patients, with enthesophytes being the most common, followed by calcifications and bone erosions.

Enthesophytes were more prevalent in PsA than axSpA, suggesting a relative predominance in PsA, though their high prevalence in both subtypes limits their utility as a specific disease marker. This difference may be influenced by demographic factors, as PsA patients were significantly older, and enthesophytes strongly associated with age. This aligns with known epidemiological trends, wherein axSpA tends to present earlier than PsA [37]. Notably, the distribution of lesions varied by anatomical site. For instance, erosions were more frequent in axSpA at the plantar fascia, quadriceps tendon, and Achilles tendon, but less common at the proximal patellar tendon. Calcifications were more prevalent at the quadriceps tendon, Achilles tendon, and plantar fascia, but less so at the distal patellar tendon. These patterns suggest that, while overall lesion prevalence is similar (except for enthesophytes), their topographical distribution differs between SpA subtypes.

A key finding of this study is the distinct pattern of associations between specific ultrasound-detected lesions of structural damage and clinical, demographic, and metabolic characteristics. These differences underscore the heterogeneous nature of entheseal involvement in SpA and suggest that each lesion may reflect unique underlying pathogenic mechanisms, as already shown for spinal entheseal involvement [38].

Entheseal erosions were closely linked to systemic inflammatory markers, including CRP, ESR, and HLA-B27 positivity. The association with HLA-B27 supports its known role in osteitis and erosive changes in the sacroiliac joints and peripheral skeleton [39], highlighting the inflammatory basis of these lesions. Erosions were also strongly associated with clinical enthesitis (including LEI and enthesitis history), emphasizing their connection to inflammation and related symptoms. The low frequency of isolated erosions, compared to their occurrence alongside other lesions (Fig. 2), suggests these may reflect an early, inflammation-driven stage of structural damage, potentially preceding compensatory changes like enthesophytes and calcifications. As disease progresses and patients age, erosions may become less detectable due to bone remodelling or masking by new bone formation. Importantly, in multivariate analysis, erosions remained significantly associated with

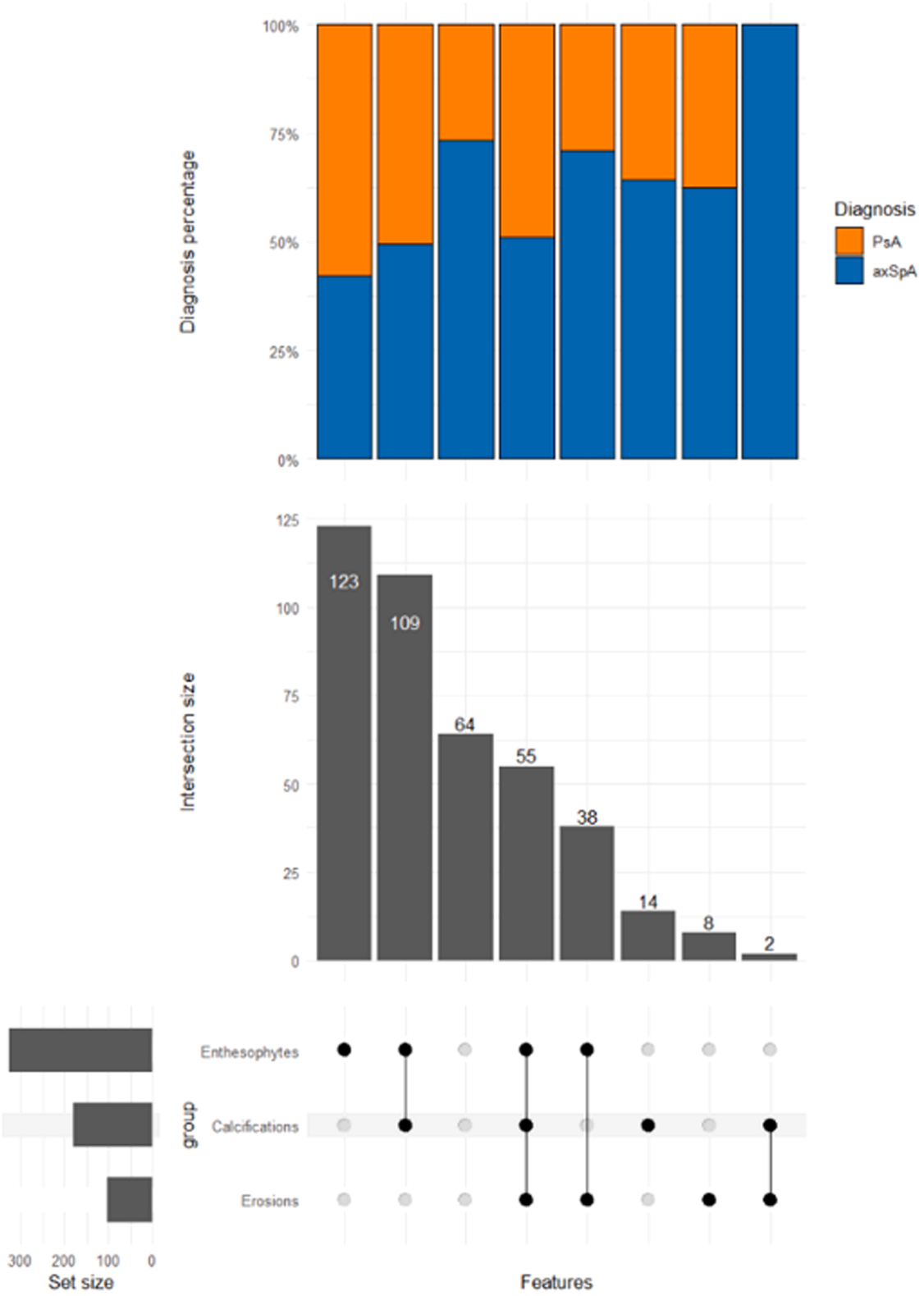

Fig. 2. UpSet plot of the distribution and intersection of erosions, enthesophytes and calcifications across patients with axSpA and PsA.
Top bar chart shows the percentage distribution of diagnoses (PsA in orange and axSpA in blue) across each intersection of structural features. Acronyms. axSpA: axial spondyloarthritis. PsA: psoriatic arthritis.

longer disease duration, indicating how they reflect cumulative inflammatory burden. However, our cross-sectional design limits conclusions about lesion progression over time. Lastly, erosions were the only lesion significantly associated with use of cDMARDs, bDMARDs, and steroids, supporting their role as a marker of disease severity.

In contrast to erosions, enthesophytes were not associated with systemic inflammation (CRP or ESR), but rather with clinical and historical enthesitis. Given that nearly half of SpA patients may not exhibit

Table 2
Bivariate analysis assessing the differences of demographic, clinical, serological, and metabolic features with the three damage OMERACT elementary lesions in SpA patients.

Characteristic	Erosions			Enthesophytes			Calcifications		
	Absent $N = 310$[1]	Present $N = 103$[1]	p-value[2]	Absent $N = 88$[1]	Present $N = 325$[1]	p-value[2]	Absent $N = 233$[1]	Present $N = 180$[1]	p-value[2]
Diagnosis			0.2			**<0.001**			0.4
Axial SpA	162 (52.3 %)	62 (60.2 %)		63 (71.6 %)	161 (49.5 %)		131 (56.2 %)	93 (51.7 %)	
PsA	148 (47.7 %)	41 (39.8 %)		25 (28.4 %)	164 (50.5 %)		102 (43.8 %)	87 (48.3 %)	
Older age	39 (12.6 %)	9 (8.7 %)	0.3	0 (0 %)	48 (14.8 %)	**<0.001**	27 (12.6 %)	21 (11.7 %)	>0.9
Sex			0.069			0.6			0.3
Female	118 (38.1 %)	29 (28.2 %)		29 (33.0 %)	118 (36.3 %)		88 (37.8 %)	59 (32.8 %)	
Male	192 (61.9 %)	74 (71.8 %)		59 (67.0 %)	207 (63.7 %)		145 (62.2 %)	121 (67.2 %)	
Raised CRP	79 (25.5 %)	39 (37.9 %)	**0.018**	31 (35.2 %)	87 (26.8 %)	0.091	72 (30.9 %)	46 (25.6 %)	0.3
Raised ESR	45 (14.5 %)	26 (25.2 %)	**0.013**	13 (14.8 %)	58 (17.8 %)	0.5	48 (20.6 %)	23 (12.8 %)	**0.044**
HLAB27 positive	114 (65.9 %)	53 (82.8 %)	**0.048**	56 (80.2 %)	111 (66.1 %)	**0.037**	96 (72.2 %)	71 (68.4 %)	0.5
LEI > 0	88 (28.4 %)	49 (47.6 %)	**<0.001**	16 (18.2 %)	121 (37.2 %)	**<0.001**	70 (30.0 %)	67 (37.2 %)	0.12
DAPSA active disease activity	14 (9.0 %)	4 (9.3 %)	>0.9	2 (7.7 %)	16 (9.3 %)	>0.9	5 (4.6 %)	13 (14.4 %)	**0.017**
ASDAS active disease activity	74 (44.9 %)	30 (48.1 %)	0.6	28 (42.0 %)	76 (47.4 %)	0.5	67 (51.3 %)	37 (39.5 %)	0.078
BASDAI high disease activity	34 (19.1 %)	15 (23.4 %)	0.5	8 (12.3 %)	41 (22.8 %)	0.053	28 (21.1 %)	21 (18.9 %)	0.8
BASMI impaired mobility	38 (24.9 %)	19 (31,2 %)	0.4	11 (17.4 %)	46 (30.2 %)	**0.050**	29 (24.0 %)	28 (30.8 %)	0.2
BASFI impaired functionality	69 (43.3 %)	29 (47.2 %)	0.6	23 (36.1 %)	75 (47.2 %)	0.13	57 (44.5 %)	41 (44.4 %)	>0.9
Disability	17 (6.3 %)	9 (9.0 %)	0.4	7 (8.9 %)	19 (6.5 %)	0.5	16 (7.7 %)	10 (6.1 %)	0.6
Swollen joint presence	85 (27.4 %)	33 (32.0 %)	0.4	20 (22.7 %)	98 (30.2 %)	0.2	66 (28.3 %)	52 (28.9 %)	>0.9
Tender joint presence	114 (36.8 %)	36 (35.0 %)	0.7	22 (25.0 %)	128 (39.4 %)	**0.014**	89 (38.2 %)	61 (33.9 %)	0.3
"Early" SpA	68 (21.9 %)	12 (11.7 %)	**0.021**	22 (25.0 %)	58 (17.8 %)	0.11	54 (23.2 %)	26 (14.4 %)	**0.023**
Non-radiographic SpA	45 (28.4 %)	19 (29.6 %)	0.8	25 (38.4 %)	39 (24.1 %)	**0.032**	41 (31.5 %)	23 (25.4 %)	0.3
Physical Inactivity	157 (50.6 %)	58 (56.3 %)	0.3	28 (31.8 %)	186 (57.2 %)	**<0.001**	111 (47.6 %)	98 (54.4 %)	0.2
Physical activity			0.6			**<0.001**			0.3
0–1/week	157 (50.6 %)	58 (56.3 %)		27 (30.7 %)	188 (57.8 %)		114 (48.9 %)	101 (56.1 %)	
2–3/week	97 (31.3 %)	30 (29.1 %)		35 (39.8 %)	92 (28.4 %)		78 (33.5 %)	49 (27.2 %)	
4–7/week	56 (18.1 %)	15 (14.6 %)		26 (29.5 %)	45 (13.8 %)		41 (17.6 %)	30 (16.7 %)	
Metabolic syndrome	60 (19.4 %)	21 (20.6 %)	0.8	9 (10.2 %)	72 (22.2 %)	**0.012**	31 (13.3 %)	50 (27.8 %)	**<0.001**
Diabetes	29 (9.4 %)	5 (4.9 %)	0.2	2 (2.3 %)	32 (9.9 %)	**0.022**	16 (6.9 %)	18 (10.0 %)	0.3
Hypercholesterolaemia	83 (28.8 %)	22 (21.5 %)	0.2	18 (20.5 %)	87 (26.8 %)	0.2	51 (21.9 %)	54 (30.0 %)	0.078
Hypertension	86 (27.7 %)	26 (25.2 %)	0.6	14 (15.9 %)	98 (30.2 %)	**0.008**	44 (18.9 %)	68 (37.8 %)	**<0.001**
Obesity	79 (25.5 %)	21 (20.4 %)	0.3	21 (23.9 %)	79 (24.3 %)	>0.9	49 (21.0 %)	61 (33.9 %)	**0.031**
Clinical enthesitis	82 (26.5 %)	45 (43.7 %)	**0.001**	15 (17.0 %)	112 (34.5 %)	**0.002**	71 (30.5 %)	56 (31.1 %)	0.9
History of enthesitis	80 (25.8 %)	59 (57.3 %)	**<0.001**	18 (20.5 %)	121 (37.2 %)	**0.003**	69 (29.6 %)	70 (38.9 %)	**0.048**
Skin psoriasis	134 (43.2 %)	40 (38.8 %)	0.4	18 (20.5 %)	156 (48.0 %)	**<0.001**	89 (38.2 %)	85 (47.2 %)	0.063
Use of bDMARDs	159 (51.3 %)	61 (59.2 %)	0.2	44 (50.0 %)	176 (54.2 %)	0.5	112 (48.1 %)	108 (60.0 %)	**0.016**
Use of cDMARDs	130 (41.9 %)	64 (62.1 %)	**0.011**	20 (22.7 %)	152 (46.8 %)	**0.002**	94 (40.3 %)	87 (48.3 %)	0.4
Use of steroids	40 (12.9 %)	15 (14.6 %)	0.4	13 (14.8 %)	42 (12.9 %)	>0.9	36 (15.5 %)	19 (10.6 %)	**0.032**
Use of NSAIDs	95 (30.6 %)	39 (37.9 %)	0.2	27 (30.7 %)	107 (32.9 %)	0.5	77 (33.0 %)	57 (31.7 %)	0.9
Calcifications	123 (39.7 %)	55.3 (55 %)	**0.005**	16 (18.2 %)	164 (50.5 %)	**<0.001**			
Enthesophytes	232 (74.8 %)	93 (90.3 %)	**<0.001**				161 (69.1 %)	164 (91.1 %)	**<0.001**
Erosions				10 (11.4 %)	93 (28.6 %)	**<0.001**	46 (19.7 %)	57 (31.6 %)	**0.005**

[1] n (%).
[2] Pearson's Chi-squared test; Fisher's exact test.

Legend. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARDs: biological Disease-Modifying Anti-Rheumatic Drugs; CI: Confidence Interval; csDMARDs: conventional synthetic Disease-Modifying Anti-Rheumatic Drugs; CRP: C-Reactive Protein; DAPSA: Disease Activity index for PSoriatic Arthritis; ESR: Erythrocyte Sedimentation Rate; HAQ: Health Assessment Questionnaire; HLA-B27: Human Leukocyte Antigen B27; NSAID: Non-Steroidal Anti-Inflammatory Drug; PsA: Psoriatic Arthritis; SpA: Spondylarthritis.

elevated acute-phase reactants, this lack of association is not unexpected. These findings suggest that enthesophytes may arise through mechanisms distinct from systemic inflammation, such as localized inflammation, mechanical stress, and the presence of skin psoriasis [40]. Moreover, this could be partially in keeping with their onset during the remodelling, post-inflammatory phase or related to metabolic factors. Indeed, their strong association with older age - known to drive new bone formation - supports the notion that local and age-related factors play key roles. The higher burden of obesity and metabolic dysfunction in PsA compared to axSpA may partly explain the increased prevalence of new bone formation in PsA. Indeed, univariable analyses revealed significant associations between both enthesophytes and calcifications and metabolic markers such as metabolic syndrome, obesity, and diabetes. These findings support the hypothesis that metabolic factors may contribute to peripheral new bone formation in PsA and may underlie axial PsA cases that present with a diffuse idiopathic skeletal hyperostosis (DISH)-like phenotype, which can be difficult to distinguish from axial SpA [41]. While Bakirci and colleagues found a significant correlation between the presence of enthesophytes and physical activity, this correlation was not observed in the current study [42]. In fact, higher physical activity was associated with the absence of enthesophytes. However, the cross-sectional design of the study and the variability in types of physical activity – an aspect which was not systematically investigated in the current study – prevent us from drawing firm conclusions, requiring further investigations.

Previous studies have linked peripheral enthesophytes to axial syndesmophytes, suggesting that both may share common mechanisms such as chronic mechanical stress and inflammation [43]. In our cohort, enthesophytes were negatively associated with non-radiographic axSpA, reinforcing the idea that they are more closely tied to age, metabolic dysfunction, and skin psoriasis than to early-stage axial disease, which typically shows limited structural change.

Calcifications demonstrated a different profile, showing associations with age, metabolic syndrome, diabetes, and hypertension. Tendinous

Table 3
Multivariable logistic regression of demographic and clinical features (including treatment) associated with OMERACT damage elementary lesions at univariate analysis.

OMERACT damage lesion	HLA B27 positivity			CRP positive			Raised ESR		
	OR[1]	95 % CI[1]	p-value	OR[1]	95 % CI[1]	p-value	OR	95 % CI[1]	p-value
Erosions	2.48	1.24, 5.19	**0.013**	1.95	1.18, 3.23	**0.004**	2.30	1.34, 3.88	**0.002**
Enthesophytes	0.98	0.50, 1.90	>0.9	1.09	0.67, 1.79	0.7	1.68	0.92, 3.21	0.10
Calcifications	1.18	0.65, 2.12	0.6	0.81	0.53, 1.21	0.3	0.66	0.40, 1.07	0.092
OMERACT damage lesion	**Hypertension**			**Obesity (BMI > 30)**			**Diabetes**		
	OR[1]	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**
Erosions	0.78	0.45, 1.32	0.4	0.71	0.41, 1.20	0.2	0.39	0.13, 0.094	**0.048**
Enthesophytes	0.97	0.56, 1.70	>0.9	1.17	0.71, 1.99	0.5	1.25	0.57, 3.03	0.6
Calcifications	2.34	1.59, 3.48	**<0.001**	1.49	1.01, 2.20	**0.045**	1.54	0.90, 2.69	0.12
OMERACT damage lesion	**Metabolic Syndrome**			**Skin psoriasis**			**Non radiographic Axial SpA**		
	OR[1]	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**
Erosions	0.93	0.52, 2.08	0.8	1.24	0.79, 1.95	0.3	1.40	0.70, 2.76	0.3
Enthesophytes	1.11	0.62, 2.08	0.7	3.52	2.04, 6.36	**<0.001**	0.56	0.28, 1.15	0.11
Calcifications	2.83	1.36, 3.83	**<0.001**	1.08	0.75, 1.57	0.7	0.97	0.51, 1.86	>0.9
OMERACT damage lesion	**Enthesitis history**			**Disease duration**			**Clinical enthesitis**		
	OR[1]	**95 % CI[1]**	**p-value**	**Beta**	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**
Erosions	4.66	2.99, 7.28	**<0.001**	44	20, 68	**<0.001**	2.24	1.45, 3.49	**<0.001**
Enthesophytes	2.36	1.37, 4.22	**0.003**	9.1	−14, 32	0.4	1.98	1.27, 3.15	**0.003**
Calcifications	1.03	0.69, 1.54	0.9	−3.6	−22, 15	0.7	1.03	0.73, 1.47	0.9
OMERACT damage lesion	**Age**			**Psoriatic Arthritis diagnosis**			**ASDAS**		
	Beta	**95 % CI[1]**	**p-value**	**OR**	**95 % CI[1]**	**p-value**	**Beta**	**95 % CI[1]**	**p-value**
Erosions	−4.2	−6.9, −1.5	**0.002**	0.69	0.43, 1.13	0.2	0.30	−0.10, 0.71	0.14
Enthesophytes	12	9.3, 14	**<0.001**	1.68	1.00, 2.97	**0.046**	0.25	−0.16, 0.66	0.2
Calcifications	3.7	1.6, 5.7	**<0.001**	0.97	0.63, 1.48	0.9	−0.52	−0.89, −0.15	**0.007**
OMERACT damage lesion	**LEI**			**BASMI**			**Physical activity – times week**		
	Beta	**95 % CI[1]**	**p-value**	**Beta**	**95 % CI[1]**	**p-value**	**Beta**	**95 % CI[1]**	**p-value**
Erosions	0.39	0.12, 0.67	**0.006**	0.12	−0.43, 0.67	0.7	−0.26	−0.72, 0.19	0.3
Enthesophytes	0.23	−0.07, 0.53	0.14	0.06	−0.52, 0.64	0.8	−0.73	−1.3, −0.20	**0.007**
Calcifications	0.19	−0.05, 0.44	0.13	−0.08	−0.57, 0.41	0.2	0.09	−0.32, 0.49	0.7
OMERACT damage lesion	**Use of bDMARDs**			**Use of csDMARDs**			**Use of steroids**		
	OR[1]	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**	**OR[1]**	**95 % CI[1]**	**p-value**
Erosions	2.23	1.43, 3.46	**<0.001**	2.46	1.50, 4.06	**<0.001**	1.93	1.02, 3.64	**0.044**
Enthesophytes	1.59	1.02, 2.52	**0.043**	2.49	1.48, 4.27	**<0.001**	1.15	0.60, 2.28	0.7
Calcifications	1.50	1.05, 2.15	**0.027**	1.02	0.68, 1.54	>0.9	0.49	0.27, 0.87	**0.016**

All these analyses were adjusted by age and sex and enthesitis damage lesions (i.e., erosions, enthesophytes, and calcifications). Legend. ASDAS: Ankylosing Spondylitis Disease Activity Score; LEI: **Leeds Enthesitis Index;** BASMI: Bath Ankylosing Spondylitis Metrology Index; bDMARDs: biologic disease modifying drugs; BMI: Body Mass Index; CI: Confidence Interval; CRP: C-Reactive Protein; csDMARDs: conventional synthetic disease modifying drugs. ESR: Erythrocyte Sedimentation Rate; HLA-B27: Human Leukocyte Antigen B27; OMERACT: Outcome Measures in Rheumatology; OR: Odds Ratio; SpA: Spondylarthritis.

calcifications have previously been linked to dysmetabolic states, which promote abnormal calcium deposition. These conditions, often age-related, contribute to a systemic milieu favourable for calcification, similar to tendinopathy [44,45]. After adjusting for other lesions, calcifications were not associated with clinical or historical enthesitis, inflammatory markers, or HLA-B27, supporting their development through non-inflammatory pathways. As shown in Fig. 2, calcifications and enthesophytes frequently co-occurred, yet their distinct clinical associations suggest partially divergent pathogenic drivers. Despite imaging similarities, which have prompted OMERACT to propose joint scoring of these two lesions, their unique profiles support evaluating them separately to potentially better understand SpA mechanisms [40].

Biologic therapies as well as targeted therapies, are effective in controlling inflammation and improving symptoms in SpA [56]. Several studies have demonstrated their ability to reduce disease progression [46–48]. However, their effects on structural entheseal damage remain less defined. Further studies are needed to determine whether TNF inhibitors, other biologics, and targeted therapies can prevent or stabilize structural lesions. Additionally, it would be valuable to investigate whether lifestyle or metabolic interventions can influence the development or progression of calcifications.

Ultrasound-detected structural damage often does not correlate with symptoms. This was reflected by the lack of association between structural lesions and HAQ-DI, consistent with previous findings [5,49,50]. Notably, enthesophytes and calcifications are also common in asymptomatic individuals, particularly older adults, suggesting these may reflect age-related changes [42,51]. Future research should investigate whether improvements in ultrasound findings align with better clinical outcomes. Such evidence could support treat-to-target strategies that integrate imaging and patient-reported outcomes, enabling more personalized and effective disease management.

This study has several key strengths that enhance its relevance in SpA and PsA research. Notably, its multi-centre design allows for greater generalizability, and the large cohort represents the most comprehensive dataset of SpA and PsA patients with detailed clinical and ultrasound assessments. By integrating clinical and imaging data, this study provides valuable insights to guide clinical decision-making and future research. Another important strength is the prior validation of ultrasound assessments for OMERACT-defined elementary lesions, including structural damage, with demonstrated inter- and intra-rater reliability, confirming the accuracy of the findings [30].

However, the cross-sectional design limits our ability to establish causal relationships. Consequently, it remains unclear how these findings might change over time or in response to treatment. A longitudinal approach would provide deeper insights into the evolution of entheseal lesions and the impact of therapeutic interventions. Future studies should investigate the potential of ultrasound for monitoring disease activity and predicting long-term disability, particularly in patients at high risk of developing structural damage at the enthesis (i.e., those with 'active' inflammation). The absence of other complementary imaging modalities, such as X-rays or MRI, also limits the depth of the analysis, especially regarding axial involvement of the spine and sacroiliac joints, critical for understanding disease burden and progression. Additionally, this study did not assess the relationship between enthesitis and joint

inflammation or joint structural damage, which would offer a more comprehensive view of the structural burden and the interaction between these two domains in SpA. A previous ultrasonography and histology study showed that entheseal bone erosions occur mainly at the proximal insertion and superior tuberosity of the Achilles tendon, likely reflecting local biomechanical stress and fibrocartilage distribution, and linking mechanical loading, inflammation, and bone damage [15]. However, we did not stratify erosions based on their specific topographical location (e.g., distal, proximal, or bursal aspect), which may limit our understanding of their origin. Future studies with site-specific analyses are warranted to address this limitation. Furthermore, the presence of bursitis adjacent to the Achilles or distal patellar enthesis was not systematically assessed and therefore not included in the analysis, as this lesion is not included among the OMERACT-defined enthesitis lesions [28,29]. Future studies integrating this data could help refine phenotypic differentiation in SpA. Finally, despite rigorous study design and experienced sonographers, variability in ultrasound interpretation remains a limitation, underscoring the need for standardized imaging protocols and further validation in future studies.

Conclusions

This study demonstrates a high prevalence of ultrasound-detected structural damage at the enthesis and highlights distinct SpA phenotypes based on lesion patterns. Ultrasound proved value in differentiating disease subtypes: enthesophytes were more characteristic of PsA, erosions reflected an inflammation-driven course, and calcifications were linked to metabolic and age-related factors. These findings underscore the potential of ultrasound in profiling disease and informing personalized management strategies in SpA.

Authors' statement

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Ethics statements

This study was conducted according to the Helsinki declaration and was approved by the ethic committee of the participating centres (leading centre Polytechnic University of Marche, Comitato Etico Regionale delle Marche (CERM n: 50/2021)). All patients provided informed written consent.

CRediT authorship contribution statement

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Declaration of competing interest

EC has received speaking fees from Novartis and IBSA outside the submitted work. He also consulting fees from Horizon Therapeutics and research grants from FOREUM. . JM has received speaking fees from UCB, Galapagos and Novartis, and support for attending meetings or congresses from Novartis and Lilly, outside the submitted work. PE has received speaking fees from Abbvie, Activa, Anatptysbio, Astra-Zeneca, BMS, Boehringer Ingelheim, Galapagos, Gilead, Immunovant, Janssen, Lilly, and Novartis outside the submitted work. He has also received research grant support from Abbvie, BMS, Lilly, Novartis, Pfizer, Samsung outside the submitted work. EF has received speaking fees from AbbVie, Bristol-Myers Squibb, Celgene, Novartis, Pfizer, Roche and Union Chimique Belge Pharma outside the submitted work. ADM has received speaking fees from Janssen and Astrazeneca, and research grant support from Alfasigma, outside the submitted work. All other

authors have declared no conflict of interest.

Data availability statement

Data are available upon reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152823.

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