Ultrasound description of cortical-entheseal bone remodeling in peripheral entheses of patients with psoriasis and nonspecific musculoskeletal symptoms

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Submitted: 25/07/2024

Accepted: 10/10/2024

Abstract

Aims: ultrasound (US) diagnosis of enthesitis is burdened of low specificity, especially when it is performed in patients with psoriasis (PsO) but without clinical psoriatic arthritis (PsA), because of mechanical, dysmetabolic and age-related concurrent enthesopatic changes. We propose a novel US score to quantify the cortical-entheseal bone remodeling burden of several peripheral entheses, aiming to improve the specificity of US for PsA-related enthesitis, and to evaluate its diagnostic value in PsO patients with subsequent diagnosis of psoriatic arthritis (PsO/PsA).

Methods: clinical and US data of 119 consecutive patients with moderate/severe PsO and nonspecific musculoskeletal symptoms, were included in this retrospective study. PsO patients underwent a multi-joint US examination and a subsequent rheumatologic visit to evaluate concurrent PsA clinical diagnosis, in a scenario of real clinical practice. The cortical-entheseal bone remodeling has been evaluated with a morphologic gray-scale US score named "CERTUS" (Cortical-Entheseal Remodeling Tuscany Ultrasonographic Score, range 0-36), grading the combination of both enthesophytes and erosions in a semiquantitative scale. A variant of CERTUS, with Power Doppler (PD), was calculated too (CERTUS-PD, range 0-48), scoring PD signals into erosions. The sum of the scores obtained for 12 peripheral entheses was used as global score for statistic aims. The new bone formation at extensor tendon entheses at distal inter-phalangeal (DIP) joints were also recorded.

Results: a clinical diagnosis of PsO/PsA was made in 48/119 PsO patients (40.3%), showing older age ($p<0.001$), higher BMI ($p=0.015$), prevalence of metabolic syndrome ($p=0.014$) and smoking habit ($p<0.001$). CERTUS (AUROC 0.814) showed a highest specificity cut-off=11 (sensitivity 41.4%, specificity 100%), whereas CERTUS-PD (AUROC 0.828) showed a highest specificity cut-off=13 (sensitivity 37.9%, specificity 100%). CERTUS and CERTUS-PD correlated with both other validated US scores as Belgrade Ultrasound Enthesitis Score (BUSES) ($p<0.001$), DACTylitis glObal Sonographic (DACTOS) score ($p=0.05$ and $p=0.031$ respectively), amount of synovitis ($p=0.036$ and $p=0.04$ respectively), enthesitis ($p<0.001$) and entheseal new bone formation on DIP joints ($p=0.029$ and $p=0.031$ respectively).

Conclusions: the scoring system named CERTUS (and its variant with PD) is a quick tool to quantify cortico-entheseal bone remodeling burden in PsO patients, improving the specificity of US to diagnose patients with subclinical PsA-related enthesitis.

Keywords: Psoriatic arthritis; Psoriasis; Early detection; Ultrasonography; Ultrasound; Enthesitis.

Key messages

. The novel scoring system CERTUS can improve specificity of US in the diagnosis of subclinical PsA-related enthesitis.

. The scoring system CERTUS is a quick tool to quantify cortico-entheseal bone remodeling burden in psoriatic patients

Introduction

Up to 30% of psoriasis patients can develop psoriatic arthritis (PsA), with a median time between the diagnosis of skin and joint disease of 7-8 years. PsA can rarely anticipate the skin disease in about 7-15 % of patients[1].

Three clinically quiet phases after PsO onset and before clinically detected PsA has been proposed: a preclinical (activation of immune system in presence of risk factors for progression), a subclinical (imaging findings without symptoms), and a prodromal phase (imaging findings with nonspecific arthralgia and fatigue[2, 3]. More recently, a multidisciplinary EULAR taskforce re-defined the prodromal phase as the subclinical phase of PsA, where the co-existence of imaging findings and nonspecific arthralgia indicate a PsO subset group at particularly high risk for PsA development in a short term[4].

Enthesitis, the inflammation involving the insertion of tendons, ligaments and joint capsule, is considered the hallmark primary lesion in spondyloarthritis (SpA), including PsA[5, 6] and recent works suggest that enthesitis is the main imaging feature of subclinical phase linked to the future evolution in clinical PsA (with synovio-entheseal inflammation)[7-9]. Therefore, a potential window of opportunity for early diagnosis and timely intervention is based on identifying patients with PsO, nonspecific arthralgia and subclinical enthesitis features that may subsequently develop clinical PsA[10].

The clinical diagnosis of enthesitis is often burdened of low accuracy and often relies on imaging confirmation with ultrasound (US) or magnetic resonance (MRI)[11, 12]. Nevertheless, both US and MRI could have a low specificity for the diagnosis of SpA-related enthesitis, when used without clinical correlation[13,14]. In particular, the US differentiation of SpA-related enthesitis from degenerative, dysmetabolic, ageing or overuse enthesopathy is debated and controversial[15-19].

In 2018, the Outcome Measures in Rheumatology (OMERACT) ultrasound Group provided consensus-based definitions for the lesions of enthesitis in SpA[20] whereas in 2019 The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) produced an enthesitis US tool to be used for diagnostic purpose[21]. Accordingly, entheseal thickening, hypoechogenicity, and PD signal should be regarded as US findings indicative of "active entheseal inflammation", whereas calcifications, enthesophytes, and bone erosions signify "structural entheseal damage". On the other hand, US features of SpA-related enthesitis are frequent also in health[22, 23], in dysmetabolic patient[18, 24, 25], in ageing and overloading entheses[26-28]. Moreover, the mandatory criteria of entheseal thickening and hypoechogenicity show low discriminative values between healthy and SpA-related enthesiti[29, 30] and enthesitic vascularity is rarely observed in subclinic and early PsA[31, 32]. Therefore, the US diagnosis of enthesitis in a context of preclinical PsA, could be burdened by low specificity and subsequent risk of overdiagnosis and overtreatment of PsO patients with nonspecific musculoskeletal symptoms.

The more specific features of Spa-related enthesitis are probably those describing the sub-entheseal osteitis process: inflammatory immune infiltrate (described only in SpA-related enthesitis, but evaluable only on biopsy) [33, 34], sub-entheseal bone marrow edema (more intense and wide in SpA-related enthesitis, but visible only with MRI) [35, 36], subsequent erosions and new bone formation driven by neo-vascularization from sub-entheseal marrow (evaluable also by US)[34, 36-38]. Entheseal erosions are the most specific sign of SpA-related enthesistis, as they are the rarest features in non-SpA enthesopathy[14, 37, 39-41].

The entheseal new bone formation can be topographically and temporally distinct from bone erosion, at least for simple traction spurs, originating from intramembranous ossification[42]. On the other hand, gross spurs, originating from endochondral ossification and mainly described in dysmetabolic and in SpA-related conditions, can be coupled with entheseal erosions[19, 41,43, 44]. Because of these reasons such entheseal abnormalities deserve an accurate description, as suggested in a recent scoring method for PsA-related enthesitis[21, 45]. Moreover, the few studies that have explored the association between sonographic enthesitis and radiographic joint damage in PsA showed that entheseal bone damage subscores have a stronger correlation with joint and axial progression, with respect to soft tissues entheseal inflammation subscores[46-50].

In this context, we have proposed a novel gray-scale US score to detect cortico-entheseal bone remodeling of several peripheral entheses in a large cohort of PsO patients with definite onset of nonspecific musculoskeletal symptoms. The score aimed to improve the specificity of US in the diagnosis of PsA-related enthesitis, grading only the entheseal remodeling process without considering tendon abnormalities, and to correlate this scoring system with clinical data.

Moreover, a modified version of the score, with adding cortical-entheseal Power Doppler US (PDUS) appearance, has been tested too.

Patients and Methods

Patient recruitment

Consecutive patients with moderate/severe skin and/or nail psoriasis (PsO) with definite onset of nonspecific musculoskeletal symptoms, but without clinical synovitis, enthesitis, dactylitis or back pain, from outpatient Dermatology Unit, were included in this retrospective study.

The "definite onset of nonspecific musculoskeletal symptoms" was intended as persistent, or at least recurrent, musculoskeletal pain or discomfort, not referred to a specific joint site or tendon, nor associated to focal swelling, and possibly associated with morning stiffness <1 hour and/or fatigue, with a definite onset (with respect a previous period of complete absence of such musculoskeletal symptoms), and not imputable to clinical synovitis, enthesitis, dactylitis or inflammatory spinal disease.

All patients with PsO had a diagnosis of skin and/or nail psoriasis confirmed by a dermatologist and were unclassifiable as PsA with the Classification of Psoriatic Arthritis (CASPAR) CASPAR criteria[51]. Patients were included if aged over 18 years, with no gender restriction.

Exclusion criteria were a previous diagnosis of any other autoimmune rheumatic disease, malignancy, pregnancy, lactation and concomitant treatment with bDMARDs for PsO.

All patients underwent:

-1) a standardized multi-joint US examination in Rheumatology Unit carried out by a single rheumatologist 20-years-experienced in ultrasonography and

-2) a subsequent rheumatologic visit within the following three months. Rheumatologic final diagnosis of PsA was clinical, based on anamnestic, physical examination, laboratory, radiologic and ultrasonographic data (the ultrasonographic data was comprehensive of both written descriptive report and significant printed images, but without any reference to CERTUS or other scoring system). All patients diagnosed with PsA were tested for fitting in CASPAR classification criteria, also using US data as entry criteria (i.e. presence of subclinical US-depicted synovitis, tenosynovitis, enthesitis)[52].

For this preliminary retrospective study, we used the data of first 119 patients, examined from February 2021 to January 2023.

The collected information included demographic and anthropometric information, comorbid conditions, medications, body mass index (BMI), and disease-related information including age

at diagnosis of psoriasis; entheseal pain was evaluated with the Leeds Enthesitis Index (LEI)[53], and current psoriasis activity was determined by dermatologist using the Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI) and Dermatology Life Quality Index (DLQI)[54].

Ultrasonographic evaluation

Each patient was evaluated with routine multi-joint bilateral dynamic B-mode and Power Doppler ultrasound (PDUS) examination of joint and entheses in hands, elbows, knees and heels by an expert rheumatologist sonographer. For the purpose of the present study, we retrospectively analyzed the US data of examination of 6 entheseal sites (12 entheses): lateral elbow epicondyle, quadriceps and patellar tendon (proximal and tibial insertion), Achilles tendon and plantar fascia.

PDUS was performed using a Esaote MyLab XP8 machine equipped with 4-15 and 8-24 MHz transducers and standardized B-mode and Doppler settings, which were optimized for all examinations. Doppler parameters were Doppler frequency within 4.2–10 MHz (4-15 probe) and 8.3-16.7 MHz (8-24 probe) and pulse repetition frequency within 720-940 Hz. The Micro-V modality could be used to confirm low velocity entheseal vascularity and to reduce movement artifact.

Enthesitis was defined, for each site, when only mandatory inflammatory lesions (enthesis thickening and hypoechogenicity) were present. Power Doppler intra-entheseal signal was recorded as sign of active enthesitis. Each enthesis was studied as the 2 mm zone of soft tissue adjacent to the bone cortex, based on OMERACT's definition[20]. Structural abnormalities (enthesophytosis and erosions) were also described and recorded. Enthesophyte was defined as a step-up bony prominence at the normal bone profile, and it was further graded by anatomic location and size. Bone erosion was defined as cortical break confirmed with a stepdown defect detected in 2 planes at the cortical bone surface of enthesis (erosions located in bursitic sites, as the superior-posterior corner of calcaneus, were not considered as enthesitic erosions).

The cortical-entheseal bone remodeling has been graded with a novel morphologic gray-scale US score named "CERTUS" (Cortical-Entheseal Remodeling Tuscany Ultrasonographic Score). We used a semiquantitative scale to grade the combination of both enthesophytes (based on their size and anatomic localization) and erosions (based on their presence or absence). In order to specify the anatomic localization of enthesophyte and erosions entheseal surface was divided in three portions: the distal (with respect to the body of tendon)/superficial third, the middle

third, and the proximal (with respect to the body of tendon)/deep third. A 0-3 score was assigned to each enthesis, always studied in two orthogonal scans, where:

0= smooth cortical-enthesal profile (verified in two orthogonal scans), absence of enthesophytes or erosions;

1= single and regular enthesophyte in the distal/superficial third of the entheseal cortical surface, without any detectable erosion;

2= multiple enthesophytes or gross enthesophytosis, extended at least to the middle third of cortical-entheseal surface, without any detectable erosion;

3= multiple enthesophytes or gross enthesophytosis, extended at least to the middle third, with erosion of cortical-entheseal surface (Figure 1).

A variant of CERTUS, with PD, was calculated too. In this scoring system, defined CERTUS-PD, a score 4 was assigned when any grade of pulsing PD signal was depicted exclusively in contact or into the erosion (Figure 2). Any PD signal into tendon or not strictly correlated to a cortical erosion was not considered for this score (Figure 3).

The sum of the scores obtained for each of 12 entheses was used as global score for statistic aims, both for CERTUS (ranging between 0-36) and CERTUS-PD (ranging between 0-48).

The new bone formation at extensor tendon entheses at distal inter-phalangeal (DIP) joints were dichotomously defined (presence/absence) on greyscale US assessment when, in at least one digit, could be observed: abnormally hypoechoic (loss of normal fibrillary sono-structure) and thickening of enthesis of lateral band of extensor complex at its bony attachment on distal phalanx with bony enthesophyte.

The presence of only marginal osteophytosis at DIP joints was dichotomously recorded as DIP osteoarthritis.

The simultaneous presence of entheseal new bone formation and marginal osteophytosis at DIP joint could configure the “three stripes sign” (or “Adidas sign”, remembering the corporate logo) (Figure 4)[55, 56].

Anyway, the US final database also collected data about all evaluated joints and entheses, with calculation of validated US scoring systems as Belgrade Ultrasound Enthesitis Score (BUSES)[57], DACTylitis glObal Sonographic (DACTOS) score[58], and cumulative scores of synovitis (global amount of synovitis with PD>1 for each patient), enthesitis (global number of enthesitis for each patient)[18].

Statistics

Data are reported as mean and standard deviations (SD) for continuous variables with normal distribution (or median and interquartile range [IQR] for data without normal distribution), whereas categorical and dichotomous variables are reported as frequencies and percentages. Student's t-test was used to compare the means of continuous variables between two groups when the distribution of data was normal, and with Welch's correction otherwise. The non-parametric Kruskal–Wallis testing was used to compare the means of continuous variables among groups, with Dwass–Steel–Critchlow–Fligner (DSCF) test for pairwise comparisons. Fisher's exact test was used to compare the percentages between two groups for categorical variables. The non-parametric Spearman rank test was applied in order to correlate variables. Moreover, binomial logistic regression and receiver operating characteristic (ROC) curve analysis were used to determine predictive diagnostic value of both CERTUS and CERTUS-PD for PsA with rheumatologic PsA diagnosis as gold standard. Validity of both CERTUS and CERTUS-PD for diagnosis of PsA was determined by the estimation of sensitivity and specificity of various cut-off points. In particular, Youden's J statistic method was applied to obtain the optimal cut-off value, whereas other cut-off values were chosen as the smallest value with specificity of at least 90% and the smallest value with maximal specificity. Cut-off value of both CERTUS and CERTUS-PD aimed to distinguish patients with PSO and PsA from patients with PSO without PsA. The level of statistical significance was set at a p-level of 0.05. Statistical analyses were performed using Jamovi and XLSTAT2021 statistical packages. Feasibility of both CERTUS and CERTUS-PD was evaluated by recording the time spent by the operator and asking the patient about the comfortability of the examination.

Ethics

The study was conducted in accordance with the tenets of the Declaration of Helsinki, and the use of clinical data for retrospective research purposes was approved by the local Ethics Committee of the University of Siena (Reference No. 22271, "RHELABUS", approval Date 22 May 2022). Written informed consent was obtained for all the procedures according to the local Institutional review board guidelines.

Results

Participants Characteristics and Descriptive Statistics

A total of 119 subjects were included. A subsequent clinical diagnosis of Psoriatic Arthritis with Psoriasis (PsO/PsA) was made in 48 patients (40.3%), (male/female ratio 25/23, males 52.1%,

mean age in years 60.08 ±SD 12.83). All the patient diagnosed with PsO/PsA fulfilling the CASPAR criteria [51], when entry criteria were defined as subclinical but US-verified [52-]. The mean time between the referred onset of musculoskeletal symptoms and the final rheumatological visit was 9.3 months. Demographic, anthropometric, and clinical characteristics of participants and are summarized in Table I.

When patients were subdivided according to the definite diagnosis (PsO or PsO/PsA) no statistically significant difference was evidenced for gender (p=0.675), alcoholic consumption (p=0.111), and single co-morbidities. On the other hand, PsO/PsA showed higher number of cigarettes (p<0.001) and years of smoking (p<0.001), higher BMI (p=0.015) and prevalence of metabolic syndrome (p=0.014), delayed onset and diagnosis of skin psoriasis (p=0.02) and higher frequency of systemic treatment for psoriasis (p=0.023). No type of psoriasis was associated with final diagnosis, even if nail psoriasis seemed more frequent, albeit not significant, in PsO/PsA (p=0.08).

Diagnostic performance of CERTUS and CERTUS-PD

A binomial regression analysis was performed to obtain diagnostic cut-offs of both CERTUS and CERTUS-PD for the diagnosis of PsO/PsA

For CERTUS, an estimated AUC of ROC curve of 0.814 (SE 0.0676, 95% CI 0.5703–0.932, p<0.0001) was obtained. The diagnostic cut-off obtained with Youden J-statistic was 3 (sensitivity 89.7%, specificity 61.9%, accuracy 73.2%). The cut-off with the specificity>90% for PsO/PsA diagnosis was 9 (sensitivity 51.7%, specificity 90.5%, accuracy 74.6%). The cut-off with the higher specificity for PsO/PsA diagnosis was 11 (sensitivity 41.4%, specificity 100%, accuracy 76.1%).

For CERTUS-PD, an estimated AUC of ROC curve of 0.828 (SE 0.05061, 95% CI 0.7292–0.9276, p<0.0001) was obtained. The diagnostic cut-off obtained with Youden J-statistic was 4 (sensitivity 89.6%, specificity 61.9%). The cut-off with the specificity>90% for PsO/PsA diagnosis was 10 (sensitivity 51.7%, specificity 90.4%). The cut-off with the higher specificity for PsO/PsA diagnosis was 13 (sensitivity 37.9%, specificity 100%).

Moreover, an estimated AUC of ROC curve of 0.875 (SE 0.0451, 95% CI 0.7868–0.964, p<0.0001) was obtained for enthesitis (def. EULAR). The diagnostic cut-off obtained with Youden J-statistic was 4 (sensitivity 60%, specificity 97.6%). The cut-off with the higher specificity for PsO/PsA diagnosis was 10 (sensitivity 26.6%, specificity 100%). The AUC of ROC curve for active enthesitis was 0.674 (p<0.001), with a cut-off of highest specificity of 2 (sensitivity 0.2%, specificity 100%).

Differences on CERTUS and CERTUS-PD between PsA/PSO and PSO patients

In patients with final diagnosis of PsO/PsA the CERTUS score resulted significantly higher than in PsO ones (CERTUS PsO/PsA mean 10.9 ±SD 7.91, range 0-28, vs CERTUS PsO mean 3.24±SD 3.59, range 0-11, p<0.001). Similarly, CERTUS-PD score resulted significantly higher than in PsO/PsA patients (CERTUS-PD PsO/PsA mean 11.6 ±SD 8.14, range 0-30, vs CERTUS-PD PsO mean 3.26±SD 3.65, range 0-12, p<0.001).

Osteophytosis at IFD was recorded in 52.8 % of overall population, and in 29.2% of PsO/PsA (p=0.013). Enthesophytosis at IFD was recorded in 29.2 % of overall population, and in 18.1% of PsO/PsA (p=0.025). The "Adidas sign" was recorded in 25% of overall population, and in 40% of PsO/PsA (p=0.011). All the differences on scoring assessment between PsO and PsO/PsA was resumed in Table II.

Correlations among US scores and anthropometric, clinical, laboratory parameters.

In the overall population both CERTUS and CERTUS-PD scores significantly correlated with anthropometric parameters No correlation was observed between US scores and available inflammatory indices (ESR and CRP), NAPSI, PASI and DLQI. Only CERTUS-PD correlated with LEI. Both CERTUS and CERTUS-PD scores correlated with other US available scores (Table III).

Feasibility of CERTUS and CERTUS-PD in the real clinical practice

A time of 10-15 minutes was sufficient for setting the US parameters and for completing the US examination of the twelve entheses. No adverse events occurred during examinations, and all patients considered this examination quick, not painful, and mostly comfortable.

Discussion

Recent studies have described the transition phase from PsO to clinical PsA, suggesting that musculoskeletal nonspecific symptoms and subclinical imaging abnormalities (in particular enthesitis) are present in PsO subjects at high risk for PsA development[2-4]. As subclinical enthesitis diagnosis is tricky and difficult to differentiate from mimickers, we aimed to propose a multi-joint US scoring system of only cortical-entheseal abnormalities, overlooking tendon abnormalities, and to evaluate its diagnostic capability for subsequent diagnosis of PsA, in a cohort of PsO subjects with nonspecific musculoskeletal symptoms.

Our study has identified several risk factors associated to the diagnosis of PsO/PsA. Our PsO/PsA patients showed higher frequency of smoking habit, higher BMI with high prevalence of metabolic syndrome, as reported in previous longitudinal studies[3, 8, 38].

Moreover, a delayed onset and diagnosis of skin psoriasis and older age were associated to PsO/PsA diagnosis. On a theoretical point of view, we may hypothesize that in patients with a genetic predisposition to PsO and/or PsA, the overall presence of non-clinical inflammation during the course of the lifetime may have led to damage accrual: this is also facilitated by the lack of treatment for psoriasis (which theoretically could have reduced the appearance of articular damage) as well as by the biomechanical load and dysmetabolic state over the years, which, in turn, could be associated with microdamage

Our US scoring system of cortico-entheseal abnormalities aimed to describe and grading the continuum of modifications occurring on many entheses by biomechanical stimuli (simple traction enthesophytosis), by ageing and dysmetabolic conditions (gross enthesosphytosis) and ultimately by immune-mediated erosive and vascular enthesitic pattern. Moreover, we have chosen to overlook the tendon description, in order to avoid including characteristics (tendon thickening and hypoechogenicity), that are more variable in the time and that are burdened by high subjectivity and low discriminative value[29] and to reduce the screening examination time.

Our US scores demonstrated a good diagnostic capability for PsA diagnosis, comparable with previous more complex US scores for SpA-related enthesitis. In particular, the AUROC of both CERTUS (0.814, cut-off 3) and CERTUS-PD (0.828, cut-off 4) are superior to the yet published AUROC of BUSES for diagnosis of SpA (0.687) or Ankylosing Spondylitis (0.757) (cut-off 7), and they were also comparable with AUROC of MASEI for diagnosis of SpA (0.82) (cut-off 20)[57, 59].

Noteworthy, the cited previous US enthesitis scores, when tested for maximal specificity (100%), reported respectively very low sensitivities of 9.2% for BUSES (with cut-off 26) and 6.19% for MASEI (cut-off 45), while CERTUS and CERTUS-PD demonstrated higher sensitivities (41.4% and 37.9% respectively) also researching highest specificity (100%, with cut-offs of 11 and 13 respectively)[57, 59].

Similarly, a comparison of CERTUS diagnostic accuracy with the EULAR definitions of enthesitis and active enthesitis shows low sensitivity (26.6% and 0.2% respectively) when highest specificity is researched.

The higher specificity of CERTUS scores for PsA diagnosis is probably related to the fact that cortical-entheseal damage signs and erosive changes at the enthesis, and not the active inflammatory changes, are more frequent and diffuse in patients with pSpA or PsA, as demonstrated in previous imaging studies[39, 49, 60], also independently from the presence of local symptoms[39,45, 38].

Moreover, previous US studies clearly demonstrated that entheseal erosions are the rarest abnormalities in not-SpA related enthesopathy[15-17, 18, 28, 37, 38, 60].

The specificity of the US diagnosis of enthesitis could also be dependent on the number of included entheses. According to our findings, our cut-off values obtained with Youden J-statistic, define a PsO/PsA patient with at least an erosive (CERTUS) or erosive and vascularized (CERTUS-PD) enthesitis, with sufficient accuracy. However, in this peculiar clinical context, we also propose other cut-off values with the highest specificity, as the definition of patient in probable transition from PsO towards PsA could imply subsequent prescription of systemic therapy with proved efficacy also on arthritis and enthesitis domains.

In the context of searching subclinical enthesitis could be relevant how much entheses are considered on the US screening. Previous studies demonstrated how much entheses could show abnormalities on US in ageing or dysmetabolic conditions, but with relative rarity of both diffuse erosive changes and new bone formation. For CERTUS, the highest specificity cut-off (score 11) implies that a PsO patient has a PsA transition when 11 of his 12 entheses has at least a single enthesophyte, or when he has at least 6 entheses with gross new bone formation.

In the present study, the global “damage” score of enthesis has demonstrated a strong correlation with the new bone formation at the dorsal aspect of DIP joints, suggesting a common progression of these aspects in the transition phase of PsO towards PsA. The correlation between enthesitis damage sub-scores and radiographic progression has been suggested in previous studies[46, 47, 49, 50].

Moreover, another interesting correlation of CERTUS has been demonstrated with DACTOS, even if PsO/PsA patients showed low scores of this scoring system (mean score 2.7 in PsO/PsA, 0.92 in PsO) without significant PD activity, suggesting a “cold dactylitis” (defined as a dactylitis without PD signals) not differentiable on US with a stenosing tendinopathy of hand flexor tendons[61], where mechanical and dysmetabolic conditions are the prevalent causative factors.

Overall, subclinical entheseal damages, subclinical cold dactylitis and new bone formation at DIP joints could concur to explain the nonspecific arthralgia of PsO patient in transition to PsA[3].

This retrospective study relies on data from a single-centre cohort of patients, in a scenario of real clinical practice, and has limitations to be disclosees.

The first one is the relatively advanced age of the participants and the relatively high prevalence of metabolic syndrome. Therefore, our US scores could not demonstrate the same accuracy in younger psoriatic patients without dysmetabolic conditions. At the same time, the score should be tested in patients with conditions that could favorite enthesopathy, as highest grades of BMI, presence of diffuse idiopathic skeletal hyperostosis (DISH) and overuse conditions.

Secondly, the definite diagnosis of PsA was based on clinical judgement of the rheumatologist. The application of CASPAR criteria on an asymptomatic or pauci-symptomatic dermatologic population is not fully correct, as CASPAR criteria were derived from patients with well-established disease (disease duration ~12 years in the study subjects)[50]. However, a previous study demonstrated a better diagnostic performance of CASPAR criteria when US integrate clinical examination and/or substitute X-rays in suspected subclinical PsA[52]. The rheumatologic clinical diagnosis of PsA/PsO relied on clinical, US and radiographic available data at the time of the visit; however, the presence of synovitis appears to be the only abnormality that is always absent in PsO without PsA (see Table II). This aspect corroborates the appropriateness of PsA diagnosis, as suggested by EULAR consensus in interception of PsA[4], where the presence synovitis, including synovitis and swelling that accompanies dactylitis, not explained by other diagnoses, should be considered as diagnostic for new-onset PsA, in the setting of clinical trials focusing on prevention and/or interception of PsA[4].

In conclusions, the novel US scoring system named CERTUS (and its variant with PD) is a quick tool to quantify cortical-entheseal bone remodeling process in PsO patients, showing a good specificity to diagnose patients in transition from PsO to PsA. The CERTUS has showed to correlate with anthropometric parameters as age and BMI, duration of exposition to PsO, but also with other US scores and new bone formation on DIP joints, suggesting that enthesopatic burden of PsO patient is strictly correlated (and maybe inseparable) with dysmetabolic, biomechanical and ageing factors, and only a multi-joint imaging evaluation can describe how this diffuse entheseal damage burden is unbalanced towards an immune-mediated etiology, rather than a degenerative one. Further studies are needed to demonstrate the sensitivity to change and diagnostic reliability of CERTUS and CERTUS-PD.

Tables and Figures

Table I. Demographic, anthropometric, and clinical characteristics of the study population.

	Overall population with Psoriasis and non-specific MSK symptoms	Psoriasis without subsequent diagnosis of PsA (PsO)	Psoriasis with subsequent diagnosis of PsA (PsO/PsA)	Statistic significance
Number of subjects	119	71	48	
Male gender (%)	57 (48.3)	32 (46.4)	25 (52.1)	n.s.
Age at baseline in years, mean (SD)	53.41 (14.65)	48.59 (13.92)	60.08 (12.83)	p<0.001
BMI, median [IQR]	26.0 [23.08, 28.85]	25.2 [22.0, 28.2]	27.8 [24.75, 29.77]	p=0.03
Metabolic syndrome (%)	19 (15.8)	6 (8.5)	13 (27.1)	P=0.014
Smoke, cigarettes in die, median [IQR]	10.0 [3.5, 20.0]	10.0 [0.0, 15.0]	15.0 [10.0, 20.0]	p<0.001
Years of smoke habit, mean (SD)	17.73 (13.88)	13.51 (12.47)	26.36 (12.42)	p<0.001
Alcool assumption (%)	20 (18.2)	10 (15.4)	10 (22.7)	n.s.
Type 2 diabetes mellitus (%)	16 (13.3)	7 (9.9)	9 (18.8)	n.s.
Arterial hypertension (%)	34 (28.3)	15 (21.1)	18 (37.5)	n.s.
Cardio-vascular diseases (%)	11 (9.2)	5 (7.0)	5 (10.4)	n.s.
Anxiety/depression (in therapy) (%)	7 (5.9)	2 (2.8)	5 (10.6)	n.s.
Other co-morbidities (%)	6 (5.0)	1 (1.4)	5 (10.4)	n.s.
No co-morbidity (%)	21 (17.8)	14 (19.7)	7 (14.9)	n.s.
Familiarity for psoriasis (%)	49 (41.5)	33 (47.1)	16 (34.0)	n.s.
Mean age of psoriasis onset, years (SD)	33.94 (15.83)	29.83 (14.32)	39.33 (15.71)	p=0.002
Mean age of psoriasis diagnosis, years (SD)	35.25 (15.85)	31.29 (14.45)	40.57 (15.74)	p=0.002
Years of duration of psoriasis, mean (SD)	19.34 (12.32)	19.03 (12.05)	20.12 (12.81)	n.s.
NAPSI_at baseline, mean (SD)	14.17 (17.45)	16.00 (22.63)	15.33 (18.09)	n.s.
PASI_at baseline, mean (SD)	6.66 (4.88)	6.95 (4.71)	6.13 (5.13)	n.s.
DLQI_at baseline, mean (SD)	11.28 (7.52)	11.72 (7.34)	10.56 (7.93)	n.s.
LEI score (range 0-6), mean (SD)	0.403 (0.744)	0.14 (0.472)	0.76 (0.898)	p=0.001

Data are reported as mean and standard deviations (SD) for continuous variables with normal distribution (or median and interquartile range [IQR] for data without normal distribution), whereas categorical and dichotomous variables are reported as frequencies and percentages. The level of statistical significance was set at a p-level of 0.05. n.s.= not significant. PsO=Psoriasis, PsA=Psoriatic Arthritis, MSK=musculoskeletal, BMI=body mass index, NAPSI=Nail Psoriasis Severity Index, PASI=Psoriasis Area and Severity Index, DLQI=Dermatology Life Quality Index, LEI=Leeds Enthesitis Index.

Table II. Differences on scoring assessment in the overall study population and between PsO and PsO/PsA patients.

	Overall population with Psoriasis and non-specific MSK symptoms	Psoriasis without subsequent diagnosis of PsA (PsO)	Psoriasis with subsequent diagnosis of PsA (PsO/PsA)	Statistic significance
Number of subjects	119	71	48	
DACTOS score (range 0-25), mean (SD) [range]	1.67 (2.75) [0-16]	0.92 (1.6) [0-7]	2.7 (3.61) [0-16]	p=0.016
BUSES score (range 0-132), mean (SD)	12.6 (17.9) [0-84]	3.68 (3.86) [0-13]	24.9 (22.1) [0-84]	p<0.001
Joint synovitis (global score>1), mean (SD)	0.153 (0.763)	0	0.367 (0.159)	p=0.094
Enthesitis (def. EULAR), mean (SD)	2.72 (4.07)	0.667 (1.63)	5.60 (4.70)	p<0.001
Active enthesitis (def. EULAR), mean (SD)	0.278 (0.697)	0.238 (0.154)	0.633 (0.964)	p=0.002
CERTUS (range 0-36), mean (SD) [range]	6.39 (6.87) [0-28]	3.24 (3.59) [0-11]	10.9 (7.91) [0-28]	p<0.001
CERTUS-PD (range 0-48), mean (SD) [range]	6.66 (7.16) [0-30]	3.26 (3.65) [0-12]	11.6 (8.14) [0-30]	p<0.001

Data are reported as mean and standard deviations (SD) for continuous variables with normal distribution (or median and interquartile range [IQR] for data without normal distribution), whereas categorical and dichotomous variables are reported as frequencies and percentages. The level of statistical significance was set at a p-level of 0.05. n.s.= not significant. PsO=Psoriasis, PsA=Psoriatic Arthritis, MSK=musculoskeletal, BUSES=Belgrade Ultrasound Enthesitis Score, DACTOS=DACTylitis glObal Sonographic score, PD= Power Doppler.

Table III. Correlations between CERTUS or CERTUS-PD and anthropometric parameters, clinical and ultrasonographic scores.

	CERTUS	CERTUS PD
Age at baseline	r=0.601, p<0.001	r=0.599, p<0.001
BMI (body mass index)	r=0.372 p<0.001	r=0.318, p=0.007
Age at time of visit	r=0.500, p<0.001	r=0.599, p<0.001
Age of psoriasis onset	r=0.274, p=0.004	r=0.268, p<0.006
Age of psoriasis diagnosis	r=0.261, p=0.006	r=0.259, p<0.008
Duration of psoriasis	r=0.232, p=0.015	r=0.228, p<0.018
DACTOS	r=0.234, p=0.05	r=0.257, p=0.031
BUSES	r=0.813, p<0.001	r=0.830, p<0.001
Number of enthesitis (EULAR def.)	r=0.500, p<0.001	r=0.521, p<0.001
Number of active enthesitis (EULAR def.)	r=0.461, p<0.001	r=0.516, p<0.001
Number of joint synovitis (global score>1)	r=0.249, p=0.036	r=0.244, p=0.04
New bone formation at extensor tendon entheses at dorsal aspect of DIP joint	r=0.259, p=0.029	r=0.256, p=0.031
New bone formation (osteophytosis) at dorsal aspect of DIP joint	r=0.570, p<0.001	r=0.580, p<0.001
LEI	Not significant	r=0.444, p<0.001

The level of statistical significance was set at a p-level of 0.05. BMI=body mass index, BUSES=Belgrade Ultrasound Enthesitis Score, DACTOS=DACTylitis glObal Sonographic score, PD= Power Doppler, LEI=Leeds Enthesitis Index.

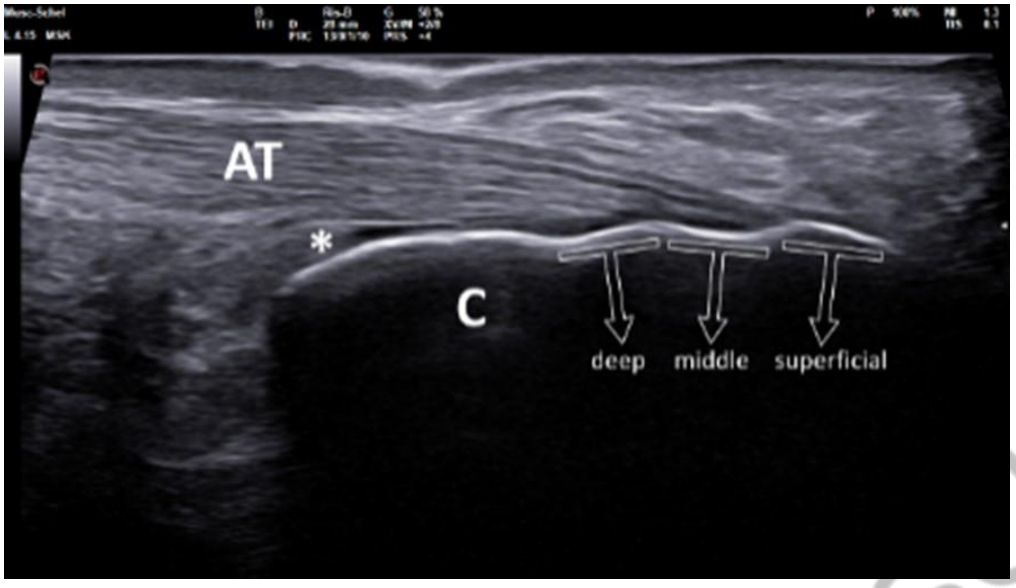

Figure 1. **Scoring method in CERTUS: grade 0.** Longitudinal scan over Achilles tendon (AT) enthesis on calcaneus (C), with a 4-15 linear probe. The cortical-entheseal bony surface has been divided in three portions: the distal (with respect to the body of tendon)/superficial third, where traction forces are more relevant, the middle third, and the proximal (with respect to the body of tendon)/deep third. The image depicts a Grade=0 (absence of enthesophytes or erosions in the three portions). The small amount of fluid in the retro-calcaneal bursa (asterisk) is not relevant for the score.

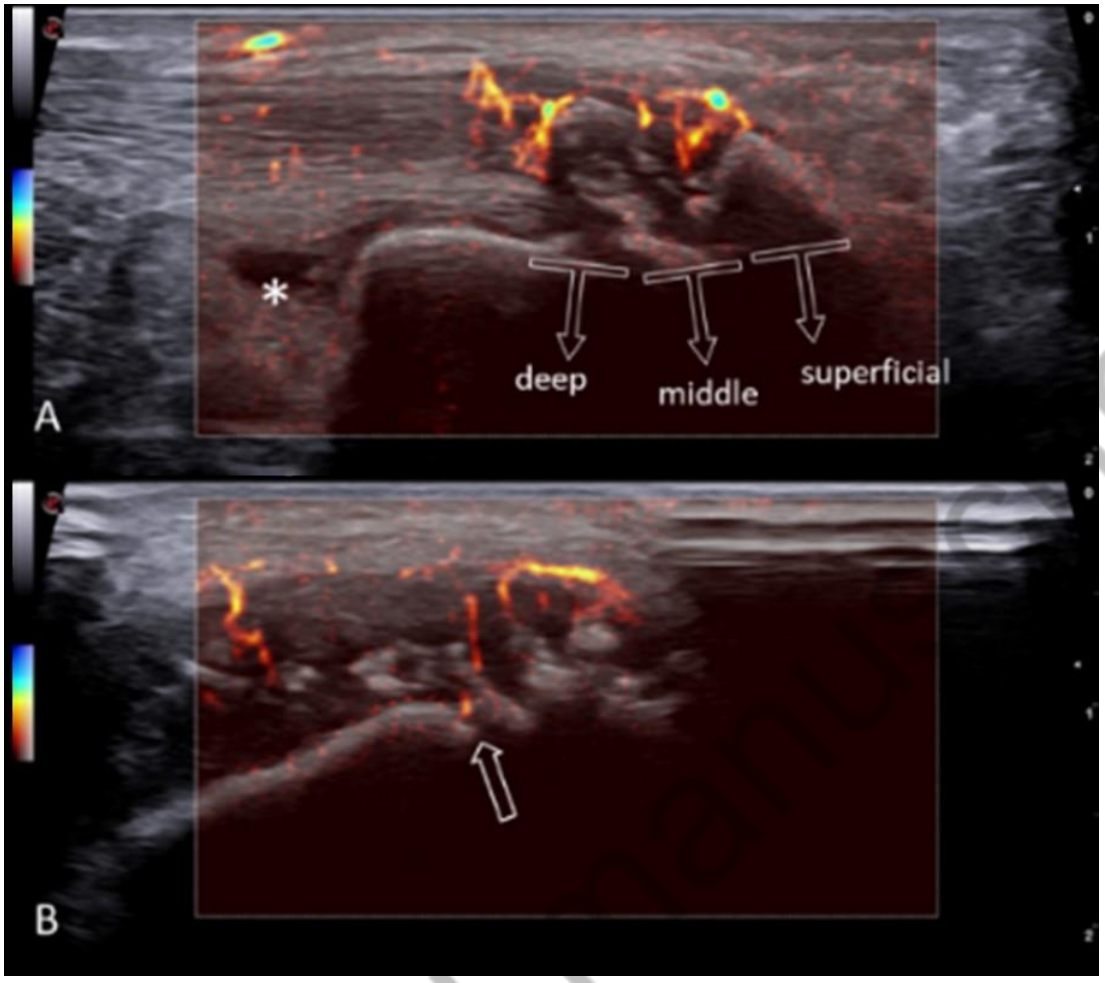

Figure 2. Scoring method in CERTUS (grade=3) and CERTUS -PD (grade=4). Longitudinal (A) and transverse (B) scan over Achilles tendon (AT) enthesis on calcaneus (C), with a 4-15 linear probe. Gross and multiple spurs occupy all the cortical-entheseal bony surface, with at least a small erosion in the free surface (CERTUS: grade=3). Power Doppler shows vascular signals in contact with a retro-calcaneal erosion (empty arrow in B), that are relevant for augmentation of the score grading (CERTUS-PD: score=4). Neither the effusion in the retro-calcaneal bursa (asterisk) nor the thickening and hypoechoic appearance of Achilles tendon is relevant for the score.

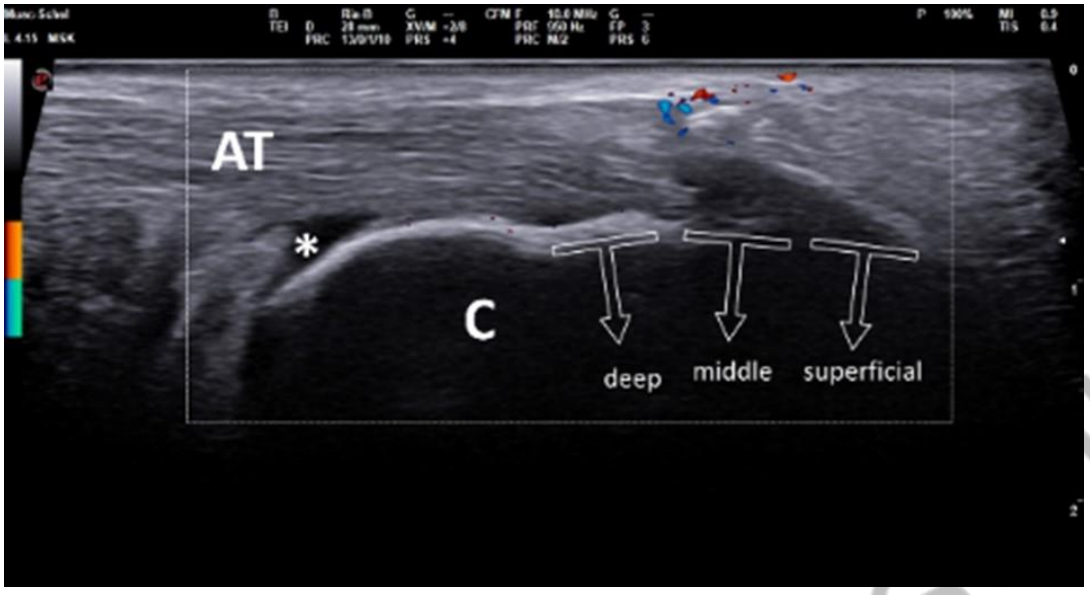

Figure 3. Scoring method in CERTUS and CERTUS -PD (grade 2). Longitudinal scan over Achilles tendon (AT) enthesis on calcaneus (C), with a 4-15 linear probe. A gross spur occupies the distal and middle portions of cortical-entheseal bony surface, with no erosion in the free surface (CERTUS: grade =2). The Power Doppler vascular signals around the spur are not relevant for CERTUS-PD, as they are not in strict contiguity with any erosions (CERTUS-PD: grade=2). The limited amount of fluid in the retro-calcaneal bursa (asterisk) is not relevant for the score.

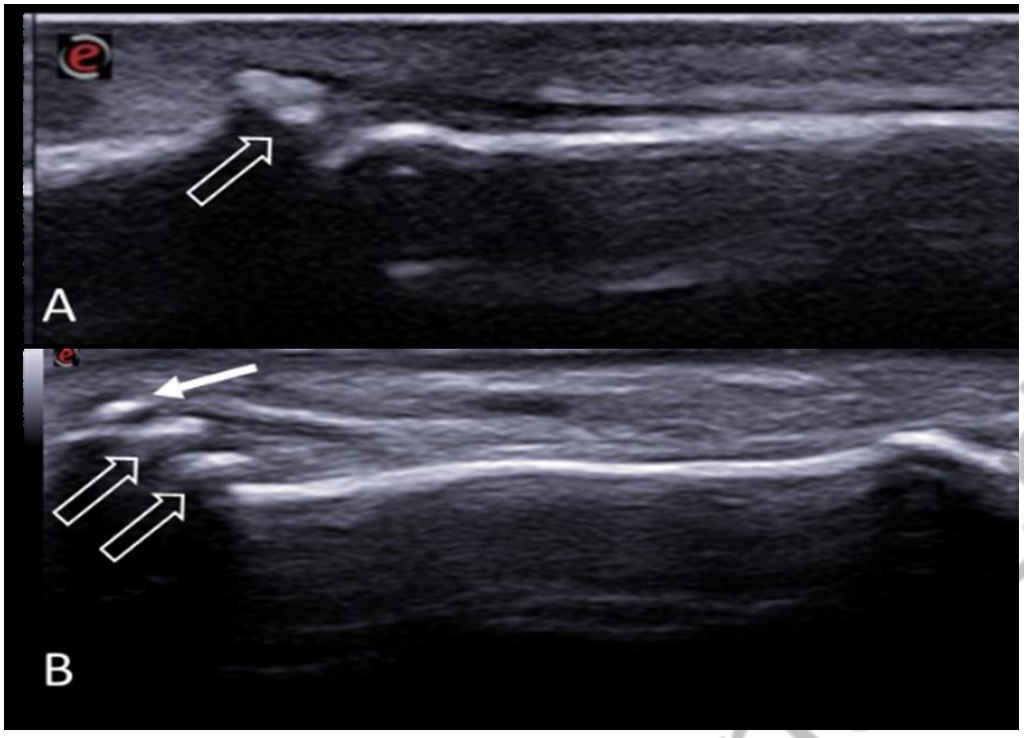

Figure 4. New bone formation at dorsal aspect of distal interphalangeal (DIP) joints of hand. Longitudinal scan over DIP joint of hand with an 8-24 MHz linear probe. A-In a middle-aged patient with PsO and hand nodal osteoarthritis a gross osteophyte (empty arrow) rise over the base of distal phalanx. B-In a middle-aged patient with PsO, hand osteoarthritis and subsequent diagnosis of PsA, the bony profiles of the DIP joint show marginal osteophytosis (empty arrows) both on the head of middle phalanx and on the base of distal phalanx; a third site of new bone formation is visible at the enthesis of extensor complex (thin arrow). The simultaneous presence of entheseal new bone formation and marginal osteophytosis at DIP joint configure the “three stripes sign” (or briefly “Adidas sign”, remembering the corporate logo).

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