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GRAPPA Debate: Be it Resolved That Clinical Enthesitis Indices Do Not Reflect True Enthesitis and Hence Should Be Discontinued

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ABSTRACT. Enthesitis is increasingly recognized as a key manifestation of psoriatic disease (PsD). However, how best to assess enthesitis remains a point of discussion due to limitations of the existing assessment tools, including their inability to differentiate between inflammatory and noninflammatory enthesitis as well as a high placebo response in clinical trials. At the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2024 annual meeting, a debate was held to address whether traditional clinical enthesitis indices should be discontinued for PsD. Dr. Sibel Aydin advocated for their discontinuation, emphasizing that clinical indices often capture "enthesalgia" (pain at the entheseal sites overlapping with pain disorders like fibromyalgia) rather than true inflammatory enthesitis. These clinical indices may lack specificity for detecting inflammation, which can lead to inaccurate assessments. Further, studies show high reports of placebo response when using clinical indices, suggesting their limitations in discriminating active disease from noninflammatory pain mechanisms. Aydin advocated for prioritizing emerging imaging tools over traditional clinical indices. Dr. Atul Deodhar argued against discontinuation of traditional clinical enthesitis indices, highlighting that despite limitations, these indices have been used successfully in multiple randomized controlled trials, leading to approval of numerous treatment options for psoriatic arthritis. Although promising, alternative imaging modalities like ultrasound to evaluate inflammation come with their own challenges, including operator dependency, variability in interpretation, and lack of regulatory approval as a standardized outcome measure. This report presents both perspectives, analyzing the evidence and implications for the future of enthesitis assessment in clinical practice.

Key Indexing Terms: enthesitis, GRAPPA, indices, outcome measures

Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by skin and joint involvement, with enthesitis being a prominent clinical feature.[1] The accurate assessment of enthesitis is crucial for guiding treatment decisions and management. The Group for Research and Assessment of Psoriasis and PsA (GRAPPA)–Outcome Measures in Rheumatology (OMERACT) working group developed a Core Domain Set to specify the key domains to measure in randomized controlled trials (RCTs) for PsA.[2] Although enthesitis is one of the highlighted domains, the optimal assessment method remains unclear.

Clinical enthesitis indices have been developed for use in daily clinical practice as well as in clinical research. However, there has been growing debate about the accuracy of these traditional clinical indices, particularly with the advent of advanced imaging techniques that may be used to evaluate enthesitis. A debate was held to address this controversy at the GRAPPA 2024 annual meeting in Seattle, USA, focusing on whether clinical enthesitis indices should be discontinued. Two rheumatologists, Drs. Sibel Aydin and Atul Deodhar, presented the evidence for and against the discontinuation of clinical enthesitis indices, moderated by Liliana Candia (Table).

Aydin began the discussion by describing the commonly used clinical indices used in clinical trials for PsA (the Leeds Enthesitis Index [LEI], the Spondyloarthritis Research Consortium of Canada [SPARCC] Enthesitis Index, and the Maastricht Ankylosing Spondylitis Enthesitis Score [MASES]), highlighting which entheseal sites are included in the indices, how they were validated, and their sensitivity to change. She noted that all clinical indices primarily focus on large entheses and may overlook more minor, yet clinically significant, entheses.[3] Among the commonly used indices, LEI is the only one that was specifically developed for PsA. The other indices were developed for axial spondyloarthritis or radiographic axial spondyloarthritis. The LEI was developed in 28 patients with PsA, which is a small number to reflect the heterogeneity of PsA.[4] Current evidence highlights significant limitations in the performance of commonly used enthesitis indices. For instance, the LEI has shown improvement in patients treated with agents like methotrexate and leflunomide, which have little to no known efficacy

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Table. Summary of key arguments from the GRAPPA debate on clinical enthesitis indices.

In Favor of Discontinuation (Dr. Aydin)	Against Discontinuation (Dr. Deodhar)
Clinical enthesitis indices often measure "enthesalgia," not true inflammatory enthesitis	Clinical indices have led to approval of 14+ PsA drugs and are recognized by the FDA/EMA
High placebo response rates in trials using clinical indices suggest poor specificity	Indices are validated, reliable, and feasible in clinical trials
LEI and other indices may show improvement with drugs not effective for enthesitis (eg, methotrexate)	US has limitations (eg, operator-dependent, lacks standardization, poor interobserver agreement)
Imaging (eg, US) offers greater specificity and objectivity	Enthesitis-related US findings are common in healthy and obese individuals, limiting specificity
US correlates with neural activity patterns in fMRI, supporting its relevance	No phase III PsA trial has used US-based scores for regulatory approval
Subclinical enthesitis detected by US predicts PsA development and links to nail disease	Clinical indices differentiate active drugs from placebo (eg, ULTIMATE trial SPARCC score[25])
Enthesitis may be a "deep Koebner phenomenon" better captured imaging	Removing clinical indices without replacement would leave a gap in outcome by assessment

EMA: European Medicines Agency; FDA: United States Food and Drug Administration; fMRI: functional magnetic resonance imaging; GRAPPA: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; LEI: Leeds Enthesitis Index; PsA: psoriatic arthritis; SPARCC: Spondyloarthritis Research Consortium of Canada; US: ultrasound.

for enthesitis, raising concerns about the specificity of the index.[4] Conversely, the SPARCC Enthesitis Index failed to demonstrate a superior response with adalimumab compared to placebo, despite established effectiveness of adalimumab in treating enthesitis.[5] This inconsistency—detecting improvement when none is expected and failing to do so when it is—represents a fundamental weakness of current indices.

One potential reason for this discrepancy may lie in the selection of the anatomical sites included in these indices. A posthoc analysis of the ABILITY-2 trial by Mease et al assessed the responsiveness of individual entheseal sites to adalimumab vs placebo.[6] Notably, in the medial femoral condyle, an enthesis that comprises one-third of the LEI, placebo led to greater resolution of enthesitis than adalimumab (70.4% vs 43.8%). Of the 15 entheseal sites tested (all featured in ≥ 1 major index), only 3—the iliac crest and the medial and lateral humeral condyles—showed statistically significant improvements with adalimumab over placebo at 12 weeks.

Further concerns about the lack of specificity of clinical enthesitis indices arise from their inability to reliably distinguish true enthesitis from pain related to fibromyalgia. Roussou et al demonstrated a strong correlation between fibromyalgia tender points and sites assessed in clinical enthesitis indices, highlighting the potential for misclassification.[7] Another study found that higher scores on enthesitis indices were more strongly associated with fibromyalgia than with PsA, raising additional doubts about their diagnostic value.[8]

Aydin has argued that current clinical enthesitis indices may be measuring "enthesalgia" (pain at the entheseal sites overlapping with pain disorders like fibromyalgia) rather than true inflammatory enthesitis, emphasizing their inability to reliably differentiate between inflammatory and noninflammatory pain conditions such as fibromyalgia. This is reflected in RCTs that report high placebo response rates for the resolution of enthesitis—sometimes up to 44%—when using clinical enthesitis indices.[9-14] High reports of response to placebo and the lack of confidence in the accuracy of these clinical indices are the main reasons why enthesitis is not being considered as one of the primary outcomes in clinical trials despite being one of the key manifestations of PsA. These findings underscore the need for more reliable and sensitive tools to accurately measure enthesitis response in clinical trials and practice.

Aydin then argued that imaging modalities may be better than clinical indices for evaluating enthesitis. A study involving patients with PsA with Achilles enthesalgia, categorized by positive or negative ultrasound (US) findings, used functional magnetic resonance imaging (MRI) to show that patients with positive US results (hypoechogenicity and Doppler signals) showed increased neural activity at rest and in response to entheseal pain induction compared to those with negative US findings.[15] This suggests that US can help distinguish between different pain mechanisms in patients with PsA more accurately than the clinical indices.

Aydin and Deodhar previously coauthored an editorial highlighting the subjective nature of diagnosing enthesitis through physical examination.[3] These examinations rely heavily on patient-reported pain responses to pressure, which can be subjective since not all patients report pain to the same extent. Accurately detecting enthesitis is complex due to the involvement of multiple pain mechanisms; thus, physical examination alone is not reliable for diagnosis. Altogether, Aydin argued that clinical indices are inaccurate based on many different types of evaluations and that emerging imaging modalities will perhaps be better able to diagnose enthesitis.

Deodhar began his counter argument by emphasizing that the debate was not about the superiority of US over clinical examination in diagnosing enthesitis, but rather the necessity of clinical enthesitis indices in clinical practice and clinical trials. He argued that although US is useful in diagnosing enthesitis, discontinuing clinical indices would leave a gap in assessment

tools. Deodhar argued for keeping the clinical enthesitis indices due to the rigorous development and validation processes that led to their adoption. These indices were developed from power Doppler and MRI studies as well as the Mander Enthesitis Index.[4,16,17] Substantial to excellent agreement has been shown to exist among observers using these indices, underscoring their reliability in clinical practice.[18]

Deodhar continued by highlighting the limitations of US, including dependency on machine quality, operator skill, and poor interexpert agreement. Additionally, US lacks recognition by regulatory bodies like the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) as a valid outcome tool, whereas more than 14 novel therapies have been approved for treating PsA based on clinical enthesitis indices. A systematic review of sonographic enthesitis instruments exhibited several limitations, including a lack of standardization in the number and location of entheseal sites, reliance on expert opinion, variations in scoring elementary lesions, and the presence of Doppler vascularization grading.[19] Their construct validity was also tested against clinical enthesitis rather than other imaging or biomarkers. The review concluded that none of the sonographic enthesitis instruments met the OMERACT Filter 2.1 in patients with PsA.[20]

US is not specific enough to diagnose enthesitis. Deodhar highlighted studies showing a high prevalence of US-detected abnormalities such as enthesophytes or calcifications in up to 73% of healthy individuals and 76% of dysmetabolic patients with obesity and metabolic syndrome, which are common comorbidities in PsA. These findings illustrate the difficulty in distinguishing between immune-mediated inflammatory enthesitis and mechanical enthesitis using US alone.[21-23]

There are also reliability issues related to US-based assessments for enthesitis, further complicating the adoption of US as a replacement for clinical enthesitis indices. A study completed through OMERACT showed that when 11 sonographers assessed 5 patients with 40 entheses, interobserver reliability was moderate to low, with a prevalence-adjusted and bias-adjusted κ (PABAK) score of 0.6 and a Light κ score of 0.4.[24]

Deodhar shared findings from the ULTIMATE trial, a phase IV study comparing secukinumab and placebo in patients with PsA over 52 weeks.[25] The clinical SPARCC Enthesitis Index showed a significant difference between the 2 groups ($P = 0.03$), successfully differentiating the treatment effects. However, the OMERACT power Doppler US (PDUS) enthesitis scores did not show a significant difference, highlighting the limitations of PDUS in this context.

Further, Deodhar presented data showing that clinical indices like the American College of Rheumatology 20% improvement (ACR20) response can effectively differentiate active treatments from placebos in phase III PsA trials across various drug categories.[26] No phase III studies for biologic or targeted synthetic disease-modifying antirheumatic drugs have used US enthesitis scores for FDA submissions. Instead, all relied on clinical enthesitis indices, which shows the importance of maintaining these established tools.

In her rebuttal, Aydin highlighted the complexity of psoriatic disease (PsD) and the clinically important question whether enthesitis is a standalone domain or linked to other disease domains. She noted that enthesitis detected by US is linked to nail disease, a well-known risk factor for progression to PsA. This connection could not be demonstrated using clinical indices.[27] PsD has long been recognized as a disease spectrum, and physical examination is not capable of capturing the transition from psoriasis (PsO) to PsA.[28] Patients with PsO have repeatedly been shown to have subclinical enthesitis detectable by US, and the subclinical enthesitis was shown to be a risk factor for developing PsA.[29-34] Additionally, a single-arm study showed the responsiveness of subclinical enthesitis in patients with cutaneous PsO treated with ustekinumab, raising the possibility of preventing PsA.[32] Implementing US in enthesitis research has enabled a better understanding of the PsD spectrum.

Aydin also stressed the need to better understand the factors that affect the entheseal changes visible on US. Due to the entheses constantly being exposed to biomechanical stress, entheseal structural changes also occur as a part of aging, and US is sensitive enough to detect these changes that occur with age or physical activity in healthy people.[22] However, patients with PsD have repeatedly been shown to have higher entheseal changes on US when controlled for these factors.[35] Koebnerization—the appearance of skin lesions in response to trauma—is a well-known phenomenon in PsO, and abnormal entheseal findings visible on US in response to mechanical trauma support the idea that enthesitis is a "deep Koebner phenomenon."[36] Interpreting US findings requires consideration of these factors. This is similar to the use of C-reactive protein levels, which, despite known variations with age and sex, are clinically valuable since clinicians can interpret them in context.[37,38] Similarly, US should be a complementary tool that enhances clinical judgment rather than replacing it.

In his rebuttal, Deodhar highlighted differences between the locations used in clinical enthesitis indices and fibromyalgia tender points, emphasizing their distinct purposes. He reiterated that the debate was not about comparing clinical examination and US assessment for enthesitis diagnosis, but about whether to eliminate clinical enthesitis indices. He argued that these indices, developed through data-driven processes and endorsed by the FDA and EMA, are effective in distinguishing active treatments from placebos and should not be discontinued. He emphasized that they have been successfully used in many modern clinical trials for now-approved PsA therapeutics.

DISCUSSION

The debate at the GRAPPA 2024 annual meeting highlighted the complexities in enthesitis and the assessment for PsA and underscored the need for reliable, objective, and comprehensive tools. Both clinical enthesitis indices and US bring distinct advantages and limitations to the assessment of enthesitis. Clinical indices, although limited by their inability to fully distinguish inflammatory enthesitis from overlapping conditions like fibromyalgia, have a well-established history of use in clinical trials and regulatory frameworks. Their role in treatment approvals for PsA highlights their value in both research and clinical practice.

However, US offers the potential to detect underlying inflammatory changes with greater specificity and may provide insight into subclinical enthesitis, which could have implications for early PsA intervention. Challenges remain with US, including variability in interpretation, lack of standardization, and current limitations in regulatory acceptance.

Therefore, although the integration of US as a complementary tool shows promise, existing clinical indices should continue to play a foundational role in enthesitis assessment. The discussion highlighted the importance of continued research in this area. Studies are needed to develop and validate enthesitis indices using US in clinical practice and standardized protocols for use in clinical trials. A GRAPPA-sponsored study, Diagnostic Ultrasound Enthesitis Tool (DUET), aims to take on these studies. Longitudinal studies are also needed to assess whether using imaging for early detection of and intervention in PsA can help prevent long-term structural damage.

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ETHICS AND PATIENT CONSENT

Institutional review board approval and patient consent were not required.

PEER REVIEW

As part of the supplement series GRAPPA 2024, this report was reviewed internally and approved by the Guest Editors for integrity, accuracy, and consistency with scientific and ethical standards.

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