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The Role of Ultrasound in Research and Clinical Practice in Psoriatic Arthritis: Highlights From the GRAPPA Ultrasound Workshop

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ABSTRACT. Ultrasound (US) is a valuable imaging modality that can accurately identify relevant features of psoriatic arthritis (PsA), such as synovitis, tenosynovitis, and enthesitis. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Ultrasound Committee ran a workshop during the annual GRAPPA meeting that was held in July 2020. The group presented the following 3 topics: (1) the transition from psoriasis to PsA and the role of US; (2) the effect of biomechanical forces on the entheses in health and disease, and insight for PsA pathogenesis; and (3) differentiation of enthesitis from pain sensitization: use and limitations of clinical and sonographic evaluation of enthesitis. This article summarizes the key messages from this workshop.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis, ultrasound

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) Ultrasound Committee, led by Lihi Eder, Sibel Aydin, and Gurjit Kaeley, had a live ultrasound (US) workshop during the annual GRAPPA meeting held virtually in July 2020. With 82 participants, the workshop was one of the most attended sessions during the annual meeting. The group presented 3 topics: (1) the transition from psoriasis (PsO) to psoriatic arthritis (PsA) and the role of US; (2) the effect of biomechanical forces on the entheses in health and disease, and insight for PsA pathogenesis; and (3) differentiation of enthesitis from pain sensitization: use and limitations of clinical and sonographic evaluation of enthesitis.

The Transition of PsO to PsA

The first topic presented in the workshop by Lihi Eder was the role of musculoskeletal (MSK) US in studying the transition from PsO to PsA. The possibility of PsA prevention has recently gained attention with the advent of effective targeted treatments for PsO. However, since the annual conversion of PsO to PsA remains low, it is important to identify high-risk individuals that can be the target of such interventional trials. US can identify relevant abnormalities, such as enthesitis, synovitis, and tenosynovitis among patients with PsO who do not have any MSK symptoms. A significant proportion of patients with PsO have subclinical enthesitis and synovitis.[1,2] Similar to findings in other rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus, these findings suggest that the inflammatory process is initiated prior to the development of MSK symptoms and may provide a window of opportunity for early intervention. Emerging evidence from 2 small prospective cohort studies suggest that such subclinical sonographic inflammatory findings are associated with a higher risk of future development of PsA, especially when they occur with MSK symptoms.[2,3] Moreover, another recent study showed that treatment of subclinical sonographic enthesitis with targeted biologic therapy resulted in a reduction of enthesitis activity, highlighting the reversibility of inflammation and raising the possibility of prevention of PsA using effective therapies in high-risk patients.[4]

In addition, MSK US could potentially help the rheumatologist diagnose PsA earlier. Recent studies showed that many patients with PsA develop nonspecific MSK symptoms several years prior to the diagnosis of the disease.[5] In the absence of overt findings on physical examination, US holds a significant potential to establish an earlier diagnosis of PsA. In a rapid access clinic, 48% of the patients with PsO who presented with MSK symptoms and were thought not to have PsA after a rheumatologist assessment were found to have at least 1 site with active inflammation by US (joint or enthesis with positive Doppler signal).[6] Overall, these data highlight the potential role of US in identifying patients with PsO at high risk for PsA who can be

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potential candidates for interventional trials, as well as support the use of US at the point of care to optimize earlier diagnosis of PsA.

The Effect of Biomechanical Forces on the Entheses in Health and Disease

The second workshop topic was presented by Sibel Aydin and was on the effect of biomechanical forces on the entheses and insights for PsA pathogenesis. Three recent studies specifically looked at the entheseal changes detected by US and described frequencies and/or severity of the elementary lesions, as well as factors leading to these changes.[7,8,9] The entheses are continuously exposed to biomechanical forces during daily activities, causing increased changes in the echogenicity and increased vascularity, as shown with the presence of Doppler signals. In addition to these inflammatory changes, abnormalities of the bone profile, such as bony spurs at the insertions (enthesophytes), are also very common in the general population. Increased age, higher BMI, male sex, and higher intensity physical activities are associated with these inflammatory and physical damage signs.[7] Understanding the changes within the enthesis is important for 2 reasons. First, it is important to understand what is normal and acceptable in different demographic groups. This information is crucial so that enthesitis due to spondyloarthropathy (SpA) is not over diagnosed using US. The second reason is to explain the pathogenesis of SpA. The defense mechanisms within the entheses may be the key to understand what fails in SpA and whether these are the initial steps pulling the trigger. After reviewing the evidence during the workshop, the participants discussed how they approached entheseal findings clinically. There was a consensus that there is not one finding leading to a diagnosis of SpA/PsA, despite the Doppler signals and erosions being relatively more specific to the disease state. The participants declared they usually seek a combination of these findings. Also, another clue is that patients with SpA generally have more than one entheseal site, whereas healthy people generally have only one site. Overall, there is not a fixed definition of inflammatory enthesitis using US yet and entheseal findings still need to be interpreted by an expert, taking into consideration the patients' age, BMI, sex, and physical activity, as well as other clinical findings.

Differentiation of Enthesitis from Pain Sensitization: Use and Limitations of Clinical and Sonographic Evaluation of Enthesitis

Gurjit Kaeley presented the third topic, which addressed the use and limitations of entheses US to differentiate enthesitis from pain sensitization in subjects with PsA. Fibromyalgia (FM) is a common problem encountered by rheumatologists. Pain is its hallmark with coexisting somatic symptoms such as fatigue, sleep disturbance, and impaired cognition. The prevalence of FM and PsA is estimated to be between 15–25%.[10,11] The classification criteria for FM have increasingly recognized the importance of somatic symptoms. The 2010 American College of Rheumatology classification criteria used the widespread pain index and somatic scores to classify subjects with FM instead of widespread pain and tender points used in the 1990 classification criteria.[12,13] Notably, the 1990 FM tender points are at or near entheseal sites that are used to assess disease activity in PsA. Therefore, entheseal examination is clinically subject to pain sensitization. Subjects with coexisting PsA and FM report a higher disease activity, worse functional deficit, and are less likely to achieve minimal disease activity than patients with PsA or FM alone.[10,11] The prevalence of both FM and obesity increases with age, and may result in a higher prevalence of degenerative changes and associated pain.

Marchesoni, *et al* suggested that patients with FM could be distinguished from those with PsA when > 6 FM-associated symptoms and > 8 tender points were present.[14] An imaging substudy from the same cohort examined 7 pairs of entheses and found that the classification of more than 3 involved sites had 72% sensitivity and 76% specificity to predict PsA.[15] Macchioni, *et al* compared patients with PsA, PsO, and FM, and found that clinical enthesitis median scores were highest in the FM group.[16] In contrast, B-mode and Doppler sonographic findings were higher in the PsA and PsO groups compared to the FM patients. The FM group was imbalanced with a much higher number of females and a lower BMI.[16] The clinical conundrum often facing the practitioner is distinguishing the source of pain in a PsA patient from uncontrolled disease activity vs regional pain and central pain sensitization.

Fiorenza, *et al* compared patients with FM only, PsA only, and patients with both PsA with FM.[17] As seen in previous studies, clinical enthesitis scores were highest in FM patients, followed by FM patients with PsA. Entheseal evaluation using the Glasgow Ultrasound Enthesitis Scoring System (GUESS) distinguished the PsA groups from the FM group. However, PsA alone or PsA with FM could not be differentiated. An intriguing recent study by Martinis, *et al* suggested that the GUESS scoring system may not distinguish inflammatory bowel disease (IBD)-related SpA patients with or without FM.[18] The Madrid Sonography Enthesitis Index, which includes 1 upper extremity enthesis site and incorporates Doppler findings, was able to discriminate patients with IBD-related SpA from those with IBD and FM.

In summary, US using indices such as GUESS does not distinguish active enthesitis from pain sensitization in patients with PsA. Polling of workshop participants indicated that the majority scanned clinically painful areas, whereas others also included standard lower extremity entheses and hand entheses. Further studies with a choice of entheses that limit biomechanical confounders are warranted.

Conclusion

Overall, these topics triggered interactive discussions regarding the role of US in rheumatology and dermatology practice. During the panel discussion part, the group conducted a poll to inform future directions of the GRAPPA Ultrasound Working Group. Most participants were interested in research aimed at developing a prediction model for PsA and, in second place, in studies that assessed the effect of point-of-care US on PsA outcomes (e.g., early diagnosis, achieving remission). This

feedback will guide the development of the research agenda by the US working group.

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