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GRAPPA 2023 Debate: Is Psoriatic Disease Really a Primary Enthesitis That Drives Joint Synovitis? The Enthesitis Hypothesis 25 Years On

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ABSTRACT. The enthesitis hypothesis posits that enthesitis is a primary lesion and that inflammation at the enthesis initiates the musculoskeletal symptoms of psoriatic arthritis (PsA) and spondyloarthropathies (SpA). The hypothesis suggested that inflamed entheseal tissue near the synovium could trigger cytokine-mediated synovitis, that enthesis bone anchorage could explain osteitis, and that the location of entheses at the soft tissue interface could explain dactylitis. Advances in imaging techniques that allow better visualization of enthesitis lesions and the development of animal models have allowed evolution of the concept of enthesitis as a central mechanistic driver of musculoskeletal symptoms in PsA and SpA. A debate between Drs. Dennis McGonagle and Bruce Kirkham at the Group for Research on Psoriasis and Psoriatic Arthritis (GRAPPA) 2023 annual meeting discussed the data supporting and refuting this hypothesis in PsA and SpA, respectively. The major points of this debate are summarized in this article.

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

The enthesitis hypothesis of psoriatic arthritis (PsA) and the allied spondyloarthropathies (SpA) celebrated its 25th birthday in 2023,[1] just as its parent concept of the seronegative was approaching its 50th birthday.[2] Briefly, the SpA concept recognized enthesitis as a feature of these diseases but never considered the central role of enthesitis.[3] Based on the presence of clinically unrecognized enthesitis in early PsA and SpA synovial disease using fat suppression in magnetic resonance imaging (MRI), it was proposed that enthesitis was the primary lesion.[4]

Further, a credible link between enthesitis and synovitis was proposed, since at that time it was known that nanomolar quantities of cytokines including tumor necrosis factor (TNF) and interleukin 1 (IL-1) injected into murine joints could trigger synovitis.[1] Hence, it was suggested that inflamed entheseal tissue closely juxtaposed to the synovium could trigger a cytokine-mediated synovitis. Additionally, enthesis bone anchorage could explain osteitis, whereas the location of entheses at the soft tissue interface could explain lesions such as dactylitis.[5] Hence the whole field quickly realized that a synovial-centric pathology underscored rheumatoid arthritis (RA) and an entheseal-associated pathology underscored SpA, including PsA.

Excellent imaging and tissue microanatomy work from the late Prof. Michael Benjamin seemed to refute perceived flaws in the enthesitis theory, including subfibrocartilaginous osteitis in the sacroiliac joint and tenosynovitis at regions of wrap around tendons.[3] In the case of PsA, the enthesitis theory posited that a close microanatomical link between the nail and the distal interphalangeal joint (DIP) enthesis underscored the striking link between PsA and nail disease.[5]

Nearly a decade later, careful high-resolution MRI by Tan et al in collaboration with microanatomy from the Benjamin laboratory clearly showed this link but went further, showing how the nail was directly anchored to the enthesis.[6] Beyond the skeleton, extraarticular manifestations of PsA and SpA—including anterior uveitis and aortic root inflammation—are types of entheses, share repetitive movements and microdamage, and show how the enthesitis concept offers a unified pathology.[7]

Pioneering ultrasound (US) imaging research by several groups, including Gutierrez, D'Agostino, Balint, and colleagues, demonstrated the large subclinical burden of enthesopathy in PsA and SpA, as well as extracapsular inflammation where metacarpophalangeal (MCP) capsules/tendons wrapped around bone at functional entheses.[8-10] In fact, for those undertaking clinical US or anatomy studies, the enthesis model provides a theory to help categorize synovial or enthesitis SpA-associated disease.

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Indeed, if enthesitis was primary in PsA, then it should predate other manifestations. Hot on the heels of the enthesitis theory came the first study with MRI as a primary outcome in axial and peripheral SpA by Marzo-Ortega et al in Leeds, which showed excellent clearance of the enthesitis/osteitis lesions in SpA after treatment with etanercept, thus confirming the enthesitis/osteitis lesion as a key target for outcome science.[11]

Key conceptual underpinnings of PsA and SpA came with the elucidation of enthesis structure beyond just the 4 classical insertional regions of tendon/ligament, fibrocartilage, calcified fibrocartilage, and bone. It was recognized that the enthesis comprises a structure around joints called the synovio-entheseal complex, including bony tuberosities to dissipate stress and fibrocartilage on the bony surface and tendon undersurfaces.[12] This structure is key to understanding why patients with PsA present with joint swelling and not focal-isolated enthesitis (Figure).[13]

Support for the enthesitis hypothesis

Dr. Dennis McGonagle argued that disproving the enthesitis theory of SpA is difficult since enthesitis is incredibly difficult to measure, harkening to a quote attributed to Lord Kelvin, the formulator of the laws of thermodynamics: "If you can't measure it, you can't improve it." In fact, studies explicitly designed to measure enthesitis using secukinumab, a drug with numerically higher responses in PsA compared to TNF inhibitors (TNFi), failed to show improvements in enthesitis on imaging. This is due to the relatively avascular structure of the enthesis, but peri-entheseal innervation leads to pain.[14] A paper from Leeds, including more than one coauthor proponents from the original enthesitis model, claimed that the notion that enthesitis was uncommon in early PsA is an outlier in the entire field[15] and is at odds with numerous other studies including the aforementioned seminal papers.[8-10] The importance of enthesitis as the key PsA lesion is supported by numerous publications from academic sonographers that repeatedly show a large burden of enthesitis in PsA and indeed frequent enthesopathy in psoriasis (PsO).[16-18]

Outside of US, high-resolution computed tomography scanning of the small joints in humans has also shown a large burden of subclinical entheseal changes. Indeed, follow-up studies from the Erlangan group showed that those with the subclinical imaging enthesopathy were the ones who developed clinical enthesitis—a direct confirmation of the original enthesis hypothesis.[19] Work from the same group showed that MRI inflammatory changes in the same group in conjunction with arthralgia were more likely to develop PsA.[20] Further, in subjects progressing to PsA, several other studies have shown an increased burden of enthesopathy and tenosynovitis, likely linked to accessory pulley entheses. So, enthesitis is not only present in PsA but predates it.[21]

The 3 major cytokines that have been successfully targeted to treat PsA, namely IL-23, IL-17A, and TNF, are intricately linked with enthesitis, as has been shown using animal models. Of the many relevant animal models that deserve mention, the DBA/1 mouse model used by Lories et al showed entheseal pathology and DIP nail region disease.[22] Jacques et al in the Elewaut group demonstrated that an SpA-like phenotype started out with enthesitis before spreading to the adjacent tissues.[23] Crucially, these investigators provided the first evidence, to our knowledge, that the suggested joint biomechanics and deep Koebnerisation at insertions may be key to enthesitis since mouse tail suspension completely blocked arthritis. Thus, in a single experiment, PsA shifted from an autoimmune disease to an innate immune enthesis-mediated biomechanical dysregulation problem.

The seminal paper by Sherlock et al, building on the work by Adamopoulos et al on the DNA minicircle model of hepatic IL-23 overexpression, showed that cytokine dysregulation at the mouse enthesis underpins PsA.[24,25] This study showed that the mouse enthesis had IL-23R–positive unconventional T cells close to the insertion.[24] When exposed to systemically circulating IL-23, this appeared to drive an IL-17 pathway–dependent

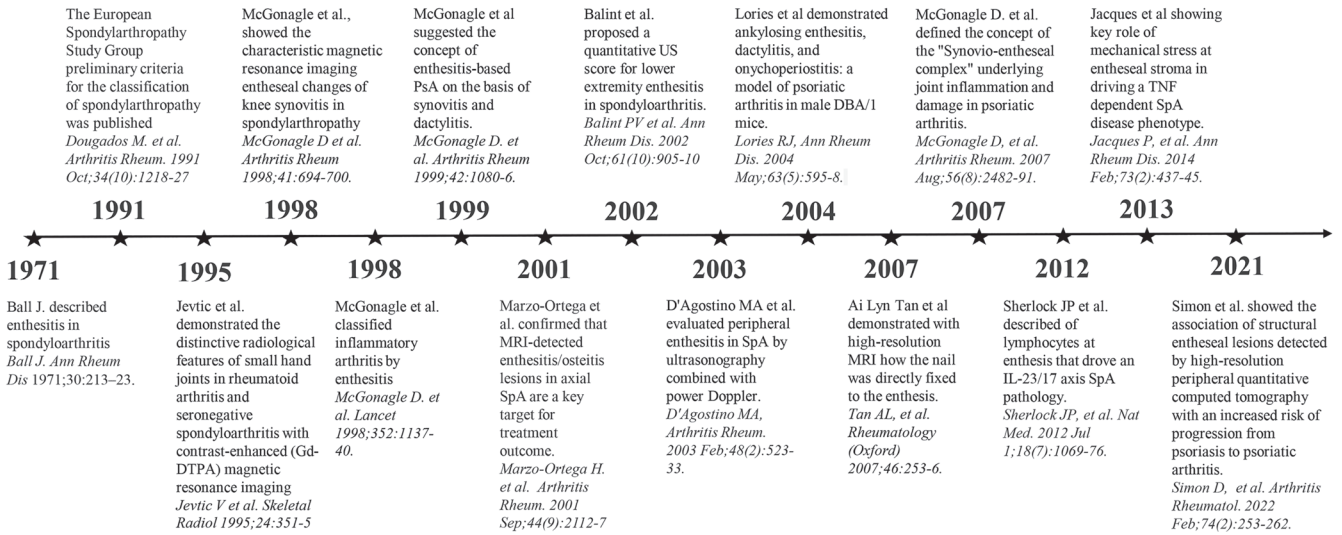

Figure. Some selected milestones in the enthesitis theory of psoriatic arthritis development. Gd-DTPA: gadolinium DTPA; IL: interleukin; MRI: magnetic resonance imaging; SpA: spondyloarthropathies; TNF: tumor necrosis factor; US: ultrasound.

primary enthesitis and aortic root inflammation. A later paper from Reinhardt et al showed that these enthesis and aortic root resident cells were also in the ciliary body (a type of enthesis) and that these were mostly γδ T cells.[26]

These animal studies provided the impetus to explore the enthesis immune system. Smaller entheses around the body lack a thick fibrocartilage and the innate and adaptive immune cells expressed in normal skin and gut are also in the peri-entheseal tissue. The entheses tissue has at least 2 distinct populations of IL-23–producing myeloid cells, including neutrophils as well as resident innate lymphoid cells, mucosal-associated invariant T cells, γδ T cells, and conventional CD4 and CD8 T cells. The enthesis is a good structure to consider translational immunology in humans as, for example, interrogation of the enthesis immune system showed that some enthesis resident γδ T cells produce IL-17A independently of IL-23.[27-29] This again validates the veracity of the enthesis concept.

The enthesitis hypothesis provides a unified concept for understanding inflammation against self, where disease is driven by local immunity at sites of stress rather than the classically described humoral autoimmunity mechanism.[30] The inability to optimally image enthesitis and failure to appreciate its importance is driving novel imaging-based approaches to try and decipher inflammation. The enthesitis model and differentiation between soft tissue entheseal inflammation vs bony anchorage–site inflammation provides a benchmark for understanding chronic axial PsA, where extensive entheseal soft tissue calcification is evident, whereas MRI-determined bone edema is less common compared to ankylosing spondylitis (AS). Exploring enthesis immunology will help unravel the effect of IL-23 blockers in axial PsA in contrast to the unresponsiveness in HLA-B27+ AS. To summarize, the enthesis is an immunologically discrete organ and its clinical relevance is hard to appreciate. It is little wonder that Moll and Wright's seminal article proposing 5 subtypes of PsA did not appreciate enthesitis.[31] The enthesitis theory provides a fundamental clinical and imaging perspective to understand PsA.

Refuting the enthesitis hypothesis

Dr. Bruce Kirkham presented the counterpoint to the argument, starting with the imaging revolution in rheumatology research in the mid-1990s with McGonagle at the forefront. Radiographs and nuclear medicine had proven inadequate,[32] whereas MRI and US were beginning to allow visualization of previously unseen localized inflammation in soft tissues with a notable presence of enthesitis in PsA and peripheral SpA.[33] This led to 2 papers in 1998 from the Leeds group,[1,4] with the Lancet paper[1] proposing that "a primary inflammatory enthesitis could explain all of the rheumatic signs of spondyloarthropathies." It also presciently suggested the way forward to test this hypothesis: "This hypothesis could be tested with specialised MRI techniques and high-resolution ultrasonography to show that enthesitis is ubiquitous in all skeletal lesions of early spondyloarthropathies and by similarly assessing other hitherto unclassified arthropathies." These insights were very important in moving a previously weak PsA/SpA research program forward.

A testable hypothesis does not have to be a correct hypothesis, and evidence against a hypothesis might come at any time.[34] A major defect in the enthesitis hypothesis is the use of the word "all," as terms such as "all" and "never" are not usually plausible concepts in medicine. Kirkham argued that the initial enthusiasm of McGonagle group has since moderated, but the current idea remains that enthesitis underpins most musculoskeletal pathology in PsA.[35] Over the years, the enthesitis concept has grown and been supported by multiple publications.[36] However, other studies have questioned the validity of this as a universal concept.[15,37] Two important issues have been raised: (1) Is enthesitis a true hallmark of SpA compared to the other common inflammatory arthritides (eg, RA)? (2) Is enthesitis really the primary inflammatory lesion in all or most early SpA/PsA cases?

Studying the philosophy and practice of scientific research, it is important to remember that a hypothesis is just a testable statement, not a truth. It is not possible to say a hypothesis is true as there might be a fact that refutes it around the corner, but research can show that a hypothesis is *not* supported. This is explained by the black swan example. In early Europe, if one hypothesized that all swans are white, all their observations would have supported their hypothesis. However, when explorers returned with stories of black swans in places such as West Australia, clearly their hypothesis was disproved.[34]

Studies compared imaging of enthesitis in RA and PsA/SpA. When enthesitis was scored by readers blind to the clinical diagnosis, many patients with RA were reported as having enthesitis at inflamed joints at a similar incidence as patients with peripheral SpA.[37] A study of patients with early PsA in Leeds showed that US did not always confirm enthesitis in patients clinically assessed as having enthesitis.[15]

A study of patients with early PsA has accelerated over recent years with improvements in US machines and agreed reporting criteria.[38] Some patients with arthralgia and PsO are also studied as pre-PsA.[39] A recent comprehensive study reported that patients with US-detected enthesitis made up only 30% of a group of patients with early PsA.[40] Another study of pre-PsA in subjects with arthralgia detected enthesitis in 40% of subjects, in contrast to joint inflammation in 50%.[21] The investigators commented that those with enthesitis were more likely to develop clinical PsA at a later timepoint.

These results show how far we have come from the early days of research into psoriatic disease (PsD). However, they definitely disprove the original hypothesis even though it played an important part in driving increasingly sophisticated research. Enthesitis is now established as an important component of PsD, but its role in the early disease process is just one of several important paths. This new understanding opens broader questions about key pathways in early PsD development.

Conclusion

In conclusion, a lively debate covered the first 25 years of the enthesitis theory encompassing issues such as how the enthesitis hypothesis has resulted in improved understanding of PsA. However, a gold standard for measuring enthesitis does not yet

exist to further buttress the theory. Accordingly, the debate was wide ranging and borrowed from the philosophy of science. The need for further research was recognized.

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