Psoriatic Enthesitis: An Update from the GRAPPA 2013 Annual Meeting

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ABSTRACT. The enthesis, attachment site of ligaments, tendons, and joint capsules to bone, has emerged as a complex structure or entheseal organ that dissipates stress to maintain homeostasis. Entheses are also anatomically and functionally integrated with adjacent bursa, fibrocartilage, and synovium in a synovial entheseal complex that may trigger inflammation in response to biomechanical stress. Recent studies have suggested that inflammation in psoriatic arthritis (PsA) arises in the enthesis based on imaging and anatomical data. In this review, the anatomy of the enthesis from a functional perspective is discussed, and the data that support a central role for enthesitis in PsA are outlined. In addition, new animal models that implicate Th17 and tumor necrosis factor pathways in enthesitis are highlighted along with new data that question the primacy of the enthesis in the early stages of PsA. Finally, future studies that incorporate new technologies are outlined. Those studies may address the contribution of entheseal inflammation to initiation and perpetuation of key pathophysiologic pathways in the psoriatic joint. (J Rheumatol 2014;41:1220–3; doi:10.3899/jrheum.140174)

Key Indexing Terms:
ENTHESIS ENTHESITIS PSORIATIC ARTHRITIS BONE SYNOVIUM

Entheses were strongly implicated in the pathophysiology of spondyloarthritis (SpA) by Ball in his Heberden Oration, delivered in 1970[1]. Based on his review of pathologic tissues from patients with ankylosing spondylitis (AS) and rheumatoid arthritis (RA), he concluded that the synovitis of AS was less destructive than RA, but was notable for the striking presence of a unique inflammatory enthesopathy that may help to explain both the clinical and pathologic features characteristic of SpA. Over 25 years later, Benjamin and McGonagle combined studies of pathologic tissues with imaging data to formulate a unified model of psoriatic arthritis (PsA), in which enthesitis is viewed as an initiating event that triggers synovitis in adjacent tissues, resulting in altered bone remodeling[2,3,4,5]. Over the past decade, data to support this dynamic model have been limited; recently, however, advances in imaging coupled with histopathologic studies on human and murine tissues have provided new insights into the potential role of enthesitis in PsA. Moreover, the enthesis has become a major therapeutic target in PsA clinical trials[6].

At the 2013 annual meeting of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), I updated the members on the anatomy of the enthesis, the central role of enthesitis in PsA, and new data and possible future studies that may address the contribution of entheseal inflammation to initiation and perpetuation of key pathophysiologic pathways in the psoriatic joint.

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The Functional Enthesis

Data from magnetic resonance imaging (MRI) and cadaver studies have dramatically changed the concept of the enthesis from a structure that simply tethers tendon and ligament fibers to bone to a complex of anatomically contiguous structures that continually adjust to changing biomechanical loads[7]. The insertion of tendon and ligament fibers is 1 component of an "enthesis organ," also comprising adjacent tendon, bone fibrocartilage, fat pad, bursa, and synovium. The interaction of these diverse adjacent structures serves to dissipate biomechanical stress away from the insertion site. The entheseal organ is also in close proximity to the synovial cavity; the term synovial-entheseal complex reflects the anatomic, functional, and physiologic interaction between these 2 tissues[5]. Although the normal enthesis is avascular and acellular, in the setting of high biomechanical stress, danger signals released by stressed or damaged entheses may trigger production of cytokines by lining cells and infiltrating monocytes and lymphocytes in the adjacent synovial tissue, resulting in a local periarticular and articular inflammatory response.

Enthesitis: A Cardinal Event in Psoriatic Arthritis?

Inflammation of the enthesis, or enthesitis, is a clinical feature observed in a wide array of disorders (Table 1). Enthesitis has been noted not only in patients with SpA but also in patients with RA and osteoarthritis (OA)[8]. It has also been reported in a variety of endocrine disorders and

Table 1. Disorders associated with enthesitis. Adapted from Slobodin, *et al*. Semin Arthritis Rheum 2007;37:119-26[8]; with permission.

Rheumatic Disorders	Metabolic and Endocrine	Drug-induced
Spondyloarthropathies	Hyperparathyroidism	Fluoride
Rheumatoid arthritis	Hypoparathyroidism	Fluoroquinolones
Chondrocalcinosis	Acromegaly	Glucocorticoids
Osteoarthritis	Hemochromatosis	Retinoids
Diffuse idiopathic skeletal hyperostosis	Diabetes mellitus	

diseases related to altered calcium and phosphate metabolism. Presumably, the pathways leading to inflammation in these diseases differ from a pathophysiologic perspective. Inflammation in the RA joint may spread to involve the adjacent entheses, and metabolic abnormalities may alter the entheseal structure and trigger release of danger signals that generate synovial cytokine release; however, at this time, the events that promote enthesitis in these disorders remain unknown.

A dominant model of PsA pathogenesis proposed that enthesitis is the central lesion in PsA, in contrast to RA where inciting events are thought to arise in the synovial membrane[4]. This hypothesis was based on a cross-sectional MRI study of 10 patients with SpA and 10 with RA that demonstrated entheseal abnormalities and perientheseal bone marrow edema in all 10 SpA patients but in only 4 of those with RA[9]. Subsequent studies by other investigators regarding the specificity of these imaging findings, reviewed recently by Paramarta, *et al*[10], yielded conflicting results. Additional support for the importance of enthesitis in SpA pathology indicated that HLA-B27+ patients with plantar fasciitis demonstrated more severe bone pathology (bone marrow edema) than HLA-B27–negative patients[11]; and in an ultrasound assessment of patients with established RA, the presence of HLA-B27 alleles was not associated with increased prevalence of enthesitis, suggesting that additional factors, not observed in this population, are required for the enthesis phenotype to be expressed[12].

The close association between nail and distal interphalangeal (DIP) involvement has been a well-recognized clinical feature of PsA, but the mechanisms that underlie this relationship remained an enigma. Cadaver studies demonstrated that extensor tendons of the fingers attach to both the distal phalanx and to the nail root and matrix, providing an explanation for the close association between psoriatic nails and DIP involvement in PsA linked by enthesitis of a bridging tendon[13]. Additional confirmation to support the connection between enthesitis and nail involvement in PsA was provided by high-resolution 18F-fluorodeoxyglucose positron emission tomography scans in patients with PsA and OA that confirmed increased bone metabolism in the entire distal phalanx, periosteum, and entheses, which was most notable in patients with PsA[14]. It is also well established that psoriasis precedes PsA by about 10 years and that many patients with psoriasis have subclinical imaging abnormalities. Musculoskeletal power Doppler ultrasound (PDUS) studies recently demonstrated that 23–70% of patients with psoriasis without joint involvement have evidence of enthesitis; these frequencies were significantly higher than observed in healthy controls[15,16,17].

Studies performed over the last several years, however, provide a different perspective regarding the dominance of enthesitis in PsA pathogenesis. Radiological analysis of a large cohort of patients with PsA, SpA, and RA revealed a significantly higher proportion of entheseal involvement in AS compared to RA and PsA, where the frequency of enthesitis was remarkably similar[18]. In a recent MRI and synovial biopsy study of 13 patients with early SpA (4 PsA) and 20 patients with RA, the MRI synovitis score was higher, and more infiltrating cells were noted in SpA peripheral joint tissues; but the number and distribution of enthesitis sites on MRI did not differ between the 2 diseases[10]. Admittedly, conclusions based on 4 patients with PsA must be viewed with caution, considering the clinical heterogeneity in this disorder. In another PDUS study in 42 patients with early PsA and 10 controls, the prevalence of clinical enthesitis was 57% in PsA and 0% in controls, but only 24% of those patients had an elevated power Doppler score. Overall, these studies raise serious questions regarding enthesitis as the origin of inflammation in PsA; however, it is difficult to draw definitive conclusions because of the diversity of disease manifestations, differences in imaging equipment and analysis methods, and the cross-sectional nature of these studies. Enthesitis, like synovitis, may be intermittent, and a snapshot in time may not provide an accurate picture of chronic musculoskeletal inflammation.

Animal Models of Enthesitis

A key principle in the enthesitis model is that biomechanical forces trigger an inflammatory response that drives synovitis and altered bone remodeling. The inflammation is presumably mediated by both innate and acquired immune pathways although data to support this view have been difficult to obtain. Recent studies in animal models, however, have provided a fascinating glimpse into how biomechanical stress and trauma are linked to musculoskeletal inflammation and revealed the identity of inflammatory cytokines at the apex of the tissue response. In the DBA/1 mouse model, male mice housed in crowded conditions became aggressive and developed an arthritis in the hind paws described as an onychoperiostitis that is entheseal but not synovially based[19]. New bone formation was observed in these mice, driven by bone morphogenetic protein signaling. The investigators were able to increase the incidence of arthritis by caging the mice together in crowded conditions; placing them in larger cages with filter tops dramatically decreased the incidence of arthritis[20].

These data suggest that environmental factors can exert a large effect on spontaneous development of arthritis strongly linked to enthesitis. In another biomechanical stress model, hind limb unloading of mice that develop inflammatory arthritis due to overexpression of tumor necrosis factor (TNF) was associated with a significant decrease in Achilles tendon inflammation compared to weight-bearing controls[21]. Extracellular signal-regulated kinases 1/2 signaling mediated the inflammation induced by biomechanical stress (weight-bearing), and new bone formation was present at the sites of enthesitis. These models provide strong evidence to support a direct link between trauma, enthesitis, and new bone formation; however, the relevance of these findings to PsA remains to be established.

The cellular and molecular pathways driving enthesitis and bone formation were recently analyzed using a novel mouse model that implicates interleukin 23 (IL-23) as a key cytokine driving the cascades that lead to inflammation and new bone formation. In the passive transfer model of collagen arthritis, examination of tissues at an early timepoint revealed marked entheseal inflammation[22]. Using 2 photon microscopy and minicircle DNA technology, Sherlock, *et al*[22] demonstrated that the enthesitis was associated with both bone erosion and new bone formation and triggered by IL-23 that bound to a resident entheseal CD3+CD4-CD8-RORγT+ lymphocyte population. They also found that IL-23 promoted inflammation by means of IL-17 and TNF, whereas new bone formation was associated with overproduction of IL-22. These exciting findings underscore a major contribution from IL-23 to inflammation and bone remodeling in SpA. Based on the studies outlined above[5,11,21], a model of the events that favor enthesitis is depicted in Figure 1.

From a translational perspective, agents that block IL-23 have the potential to inhibit both inflammation and altered bone remodeling, although confirmation of murine studies is needed. It should be pointed out that in another murine model, injection of IL-23 minicircle resulted in the development of inflammatory-erosive arthritis by expansion of myeloid osteoclast precursor cells without pathologic bone formation[23]. Thus, it is likely that the arthritis manifestations resulting from expression of a single cytokine can differ between mouse strains and housing environments, which underscores the importance of human studies. Moreover, IL-22 was shown to drive keratinocyte proliferation in animal models of psoriasis and in human psoriasis, yet a recent trial of an anti-IL-22 antibody showed no significant response in patients with plaque psoriasis[24]. These studies highlight the complexity of the microenvironment in humans, where the interplay of cells and cytokines promotes an inflammatory response that is fundamentally different from that observed in cell cultures or animal models.

Studies over the last 15 years have provided new knowledge regarding the anatomy, physiology, and pathology of the enthesis, leaving little doubt that these structures, vastly more complex than originally conceived, are involved in the inflammatory events in psoriatic joint disease and periarticular inflammation. The precise role of the enthesis in the early stages of disease, however, remains an area of contention. To address this important question will require improved imaging modalities such as 3-dimensional and/or contrast-enhanced power Doppler US[25,26] or whole-body MRI[27] to record all the possible enthesitis sites, some of which may be clinically silent. In addition, studies with adequate sample size to address the marked clinical diversity, coupled with instruments that assess for enthesitis at several timepoints, will help to address this important question. Lastly, careful analysis of the effect of IL-22 and IL-23 blockade on bone pathologies in animal models and patients with PsA will provide much-needed information regarding the possible role of the IL-23/Th17 pathway in the generation of synovitis and pathologic bone remodeling in the psoriatic joint.

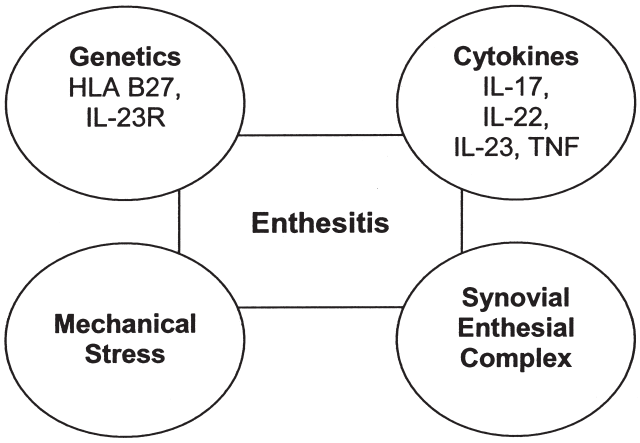

Figure 1. Factors associated with development of enthesitis, based on published studies[5,11,22]. Inflammation at the enthesis is modulated by several interactive events that are present in patients with spondyloarthritis. In this model, patients with certain genetic backgrounds [interleukin 23R (IL-23R), HLA-B27] experience trauma or biomechanical stress that results in damage to the entheses and contiguous structures, triggering an inflammatory response regulated by IL-23 and tumor necrosis factor (TNF). The inflammation is not limited to the entheses but goes on to involve contiguous structures (bursa, fibrocartilage, synovium) in the synovial entheseal complex.

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