



Editorial

Enthesitis, a clinical manifestation with many unknowns[☆]

Entesitis, una manifestación clínica con muchas incógnitas

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Enthesis makes reference to the site of attachment of a tendon, ligament of muscle fascia to the bone surface,¹ and is considered, currently, as an organ within a functional anatomical concept whose fibrocartilaginous portion: (1) Creates a soft tissue anchor on the bone, (2) Dampens the stress in the anchoring areas and (3) Promotes bone growth.^{2,3} We can find more than 100 entheses in the human body, which are usually structures located extra-articular. The term enthesopathy is used to describe any pathological change in the entheses, while enthesitis indicates the presence of inflammatory changes. There are multiple causes of enthesopathy such as: metabolic diseases, some drugs (fluoroquinolones, retinoids and fluorinated agents) and rheumatic diseases.⁴

We wrote this editorial about enthesitis, taking into account the great lack of knowledge of clinicians on the subject and calling the attention of the medical community to improve the understanding of this frequent manifestation of inflammatory diseases such as spondyloarthritis (SpA) and psoriatic arthritis (PsA). Although in recent years it has been possible to know more in detail some aspects that improve the diagnostic and therapeutic approach of enthesitis, the advances in the knowledge of some molecular, pathophysiological and therapeutic characteristics of this clinical manifestation are insufficient and still do not allow to impact totally on the deterioration of the quality of life that it generates.

During our clinical practice, at some time, every one of us has evaluated and diagnosed a patient with “tennis elbow”

or “golfer’s elbow”, a typical example of isolated enthesitis that is triggered secondary to a sport activity due to repetitive mechanical overload, and which usually resolves spontaneously; however, the enthesitis pathognomonic of PsA and SpA, usually affects more than one entheses and has a chronic behavior; but in this type of patients, it can be generated a speculative hypothesis that the inflammatory threshold is much lower, which would allow to develop an enthesitis even without any mechanical overload, secondary to an exaggerated body response to stress.⁵ This low threshold can be explained by genetic factors such as genes of the major histocompatibility complex class I and polymorphisms in the IL-23 receptor.^{6,7}

Mechanical stress is a central factor in the development of enthesitis, which explains why it occurs more frequently in the lower limbs. The innate immune response also seems to intervene as a trigger for its development, however, the precise molecular process is not known. The adequate response with non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of enthesitis suggests the production of local PGE2 as the early mediator that enables the response to mechanical overload, while the resident mesenchymal cells express cyclooxygenase 2. PGE2 produces vasodilation that widens the trans-cortical blood vessels, which facilitates the recruitment of neutrophils into the bone marrow of the enthesal compartment, and, in addition, PGE2 promotes the production of IL-17, facilitating the inflammatory response, which activates the IL-23/IL-17 pathway.⁸

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Studies in mice show that T cells expressing IL-23R reside in the enthesis and are phenotypically $\gamma\delta$ T cells, which represent the major source of IL-17 and TNF. IL-17 acts as an amplifier of the inflammatory process and induces the production of cytokines and mediators that trigger neutrophil migration. It has also been documented that the uncontrolled activation of myeloid cells or in the absence of A20 protein, signal transducers and activator of transcription 1 (STAT1) promote the release of cytokines that trigger enthesitis.⁹⁻¹²

This enthesal inflammation (enthesitis) is characterized by a pronounced tissue response, considered as an early characteristic of diseases such as PsA and SpA, which subsequently manifests itself with consequences such as enthesophytes, calcaneal spur and plantar fasciitis. These new bone formations are probably initiated by resident mesenchymal cells, which have the potential for proliferation and differentiation within the chondroblasts and the osteoblasts to form cartilage and bone. PGE2 is also an important activator of the differentiation of osteoblasts. On the other hand, it is known that the parathyroid hormone-related peptide is expressed in the enthesis and probably supports the recruitment or the activity of underlying bone cell populations. The bone morphogenetic proteins seem to promote the proliferation of mesenchymal precursors required to form hypertrophic chondrocytes. These cells build the structure for the apposition of new bone by osteoblasts, which forms the enthesophyte. Similarly, Wnt proteins together with their inhibitors, DKK1 and sclerostin, are effector molecules that promote the activity of osteoblasts for the apposition of new bone in the entheses.^{4,5,13}

Enthesitis occurs more commonly in younger, obese patients and in those who have higher disease activity, leading this manifestation to further deterioration in quality of life. In some studies the prevalence of enthesitis in patients with PsA is approximately 35%, being the most frequently involved sites: the Achilles tendon, plantar fascia and lateral epicondyles.⁵ Several indexes have been described for its exploration, including: the Mander/Newcastle enthesitis index (MEI), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), Spondyloarthritis Research Consortium of Canada (SPARCC) index, Berlin (Major) enthesitis index, Leeds enthesitis index (LEI), and University of California, San Francisco (UCSF) enthesitis index. The performance of the MASES, LEI, MEI, Berlin and SPARCC indexes was evaluated in patients with PsA, and the LEI index correlated more consistently with parameters of clinical disease activity; and in a study with patients with SpA, the UCSF index was the most sensitive among these 3 indexes (MASES, Berlin and UCSF).^{3-5,13} Its correct exploration in daily medical practice by the physical examination is limited since the findings are easily confused in those patients with primary or secondary fibromyalgia and in patients with pain amplification syndrome.

Such limitations have led to find imaging techniques for the evaluation of enthesitis. Although there have been recent advances in magnetic resonance, ultrasound (US) seems to be the preferred method to detect enthesitis because it allows an accurate evaluation of the soft tissue components of the entheses and also of the formation of new bone. Hypoechoicogenicity, increased thickness of the tendon insertion,

calcifications, enthesophytes, erosions and Doppler activity have been identified as the most important US characteristics in enthesitis.^{4,5,13} Instruments such as the Glasgow ultrasound enthesitis scoring system (GUESS) or the Spanish enthesitis index (SEI) have been developed to evaluate the presence and severity of enthesitis based on such morphological changes, although these findings are also commonly found in mechanical diseases. More recently, the high-resolution peripheral quantitative computed tomography (HR-pQCT) was introduced to define structural lesions of enthesitis, in particular the quantification of formation of new bone in PsA.⁵

The limitation of knowledge on the enthesitis present in these inflammatory diseases is not only for the pathophysiological mechanisms and the diagnostic methods, but also in terms of the treatment since studies to evaluate the treatment of enthesitis have not been specifically designed; however, the observations about the apparent therapeutic efficacy significantly support the known pathophysiological concepts. In the treatment of this manifestation have been used NSAIDs and local steroids, which demonstrate greater efficacy in the acute stages; no disease modifying antirheumatic drug (DMARD) has been shown to be effective for enthesitis except apremilast (a phosphodiesterase 4 inhibitor). Tumor necrosis factor alpha (TNF- α) inhibitors have demonstrated efficacy on axial and peripheral manifestations associated with enthesitis both in PsA and SpA. In PsA they demonstrate to improve peri-enthesal osteitis detected by magnetic resonance and to increase the vascularization evaluated by Power Doppler US. Ustekinumab, an antibody against the P40 subunit common for IL-12 and IL-23, has also shown efficacy. More recently, medications such as secukinumab and ixekizumab have demonstrated improvement in the indexes for evaluation of enthesitis.^{4,5,14}

Enthesitis is undoubtedly a characteristic finding both of PsA and SpA, for this reason, in our daily practice we must improve our clinical skills to recognize this manifestation, and in case of suspicion and doubtful exploration is necessary to resort to imaging techniques such as US and magnetic resonance to document it, since their finding becomes a factor that negatively impacts the quality of life of patients with these diseases, therefore, it is imperative that the Colombian health system covers the cost of these imaging techniques carried out by qualified and trained personnel, both in rheumatology and in radiology of this type of musculoskeletal manifestations that are so specific of inflammatory diseases, that if are not controlled in a timely and adequate manner, they generate a high economic impact on the system and the society due to the generation of loss of productivity.

Note: An interesting part of the preparation of this manuscript that I would like to share with the readers was the reading of an article published in *Medicina UPB* that guided me in the methodology for writing this editorial.¹⁵

Conflict of interest

The author declares that there is no conflict of interest.

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