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Review Article

Usefulness of Ultrasonography in the Assessment of Peripheral Enthesis in Spondyloarthritis☆

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ABSTRACT

Enthesitis is one of the characteristic etiopathogenic manifestations of spondyloarthritis. However, in clinical practice, its presence often goes unnoticed because of the lack of precision and sensitivity of physical examination to detect it. Viable, valid and reliable imaging tests are needed for early diagnosis, as well as a good sensitivity to change to monitor therapeutic response. In this paper we review the most relevant aspects of current knowledge of the enthesis and discuss the validity of ultrasound for assessing enthesitis in spondyloarthritis and its sensitivity to change to monitor therapeutic response.

Utilidad de la ecografía en la evaluación de las entesis periféricas en las espondiloartritis

Palabras clave:
Entesis
Espondiloartritis
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RESUMEN

La inflamación de la entesis es una de las manifestaciones etiopatogénicas características de las espondiloartritis. Sin embargo, en la práctica clínica, su presencia pasa muchas veces desapercibida debido a la falta de precisión y de sensibilidad de la exploración física para detectarla. Son necesarias pruebas de imagen viables, válidas y fiables para un diagnóstico precoz, y con buena sensibilidad al cambio para monitorizar respuesta terapéutica. En este trabajo, se revisan los aspectos más relevantes de los conocimientos actuales de la entesis y se analiza la validez de la ecografía para valorar entesitis en pacientes con espondiloartritis, así como su sensibilidad al cambio para monitorizar respuesta terapéutica.

Introduction

The enthesis is considered the target tissue for inflammation in spondyloarthritis (SpA) and is key in the pathogenesis of this group of diseases. From a comparative point of view, we can say that the enthesis is for SpA what the synovium is in rheumatoid arthritis (RA). RA is characterized by both arthritis and tenosynovitis, with enthesis involvement being non-existent or very minor. However, in SpA inflammation occurs both in entheses and in the synovial tissue. McGonagle has shown that synovitis that occurs in patients with SpA is secondary to the release of proinflammatory cytokines from the entheses, unlike RA, where a primary autoimmune synovitis[1] is produced. This hypothesis is based on studies of magnetic resonance imaging (MRI) of the knee comparing patients with RA and SpA; patients with SpA had enthesitis and synovitis in the same joint, while patients with RA only had synovitis.[2]

The concept of SpA as a group appears in 1958, advocated by the theory of "separatists", who begin to see it as its own entity, on the basis of common clinical features in the patients with this condition which clearly differed from RA.[3] However, it was not until 10 years later, in 1970, when the involvement of entheses was first described in the pathogenesis of SpA.[4] Subsequently, it has been demonstrated that inflammation of the enthesis is responsible for many of the symptoms, and explains the multitude of locations of pain in these patients. Thus, at an axial level, it is responsible for inflammatory back pain, sacroiliac pain, chest pain, stiffness and

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functional limitation and, at a peripheral level, is responsible for plantar fasciitis and Achilles tendinitis as the peripheral entheses most commonly described as affected, and is even implicated in the onychopathy shown by patients with psoriatic arthritis (PsA).[5]

In 1990, Bernard Amor for the first time explicitly collected the involvement of the peripheral entheses as a sign or symptom in the clinical history: "heel pain or pain of other well-defined enthesis" in their ranking criteria for the diagnosis of SpA. Later, in 1991, the European Group for the Study of SpA included enthesopathy again as one more "item" on their ranking criteria. However, until the development of modern imaging techniques, especially MRI and ultrasound, the diagnosis of enthesitis has been underestimated, mainly by the lack of sensitivity of the clinical examination for their detection. Thus, the involvement of the enthesis has not been properly included in either the evaluation or diagnosis of SpA until today. However, things are changing with the increasingly widespread practice of ultrasound among rheumatologists.[6,7]

Throughout this article, we will review how ultrasound opens new perspectives and possibilities in the field of SpA.

Definition and Overview of Entheses

Enthesis is defined as the region where a tendon, ligament, joint capsule, fascia or muscle attaches to the bone. It is a transition tissue whose function, besides being a soft tissue anchor, is to transfer the stress in these areas of attachment to the adjacent bone, and vice versa.

Histologically, Benjamin et al.[8] distinguished 2 types of entheses in relation to the tissue they have in the anchorage zone: the fibrous enthesis, which binds metaphysis and diaphysis of long bones, and fibrocartilage enthesis, which joins epiphysis and apophysis of long bones, short bones of the hands and feet, and spine. The most common, and the ones of interest because they represent the target organ involvement in SpA, are fibrocartilaginous entheses, although it is unclear if the phenomenon of enthesitis only affects these.

The fibrocartilaginous entheses include 4 histologically distinct areas: (1) a fibrous zone composed of fibers of type 2 collagen and in which versican is the predominant extracellular matrix proteoglycan, (2) uncalcified fibrocartilage zone, in which aggrecan prevails as the extracellular *matrix proteoglycan*, (3) calcified fibrocartilage area and zone and (4) subchondral bone.

The calcified fibrocartilage zone (*zone 2*) of variable thickness and devoid of vessels, is theoretically where enthesis injury initially occurs and where the inflammation extends to the synovium and adjacent bone tissue.[1] Nutrition is believed to come from the entheses vessels in the bone marrow, tendon fibrous region and through the adjacent fat and connective tissue.

In 2001, Benjamin and McGonagle introduced the concept of 'entheseal body',[9,10] considering the enthesis as a body, formed by different tissues, and defining it as a "*collection of related tissues in and around the enthesis, which serve the common function of dissipating tension.*" This attempts to explain why the enthesis inflammation experienced by patients diagnosed with diffuse SpA is associated with changes in the surrounding tissues, both soft tissue (bursitis, edema of subcutaneous tissue) and bony unions (erosions, enthesophytes).[11]

The nail findings (onychopathy) displayed on the SpA are an extension of the changes that occur in the entheses of the distal interphalangeal joints into the matrix and nail bed, as has been shown by MRI.[5,12]

Furthermore, the synovial tissue of the bursa with the entheses forms the so-called "entheso-synovial complex". Healthy entheses, in its fibrocartilage area, is avascular and presents low cell density and no inflammatory cells. Instead, the synovium is a vascularized structure and contains a resident population of immune cells and, therefore, the capacity for hyperplasia and immune response. Moreover, adipose tissue has *a proprioceptive* function by monitoring changes in the angle of insertion of the enthesis, *an immune* function, due to its high content of macrophages, and *a nociceptive* function, participating in the painful entheseal disease.

"Enthesopathy" and "Enthesitis"

The term "enthesopathy" refers to the structural alteration of the enthesis by mechanical, traumatic, metabolic or even inflammatory causes, while the concept of 'enthesitis' is used when there is active inflammation of the entheses, as in SpA, although inflammatory changes may also occur in other, not necessarily inflammatory, conditions. Enthesitis is part of the clinical spectrum of SpA, in all subtypes: ankylosing spondylitis (AS), SpA, Reiter's syndrome, SpA associated with inflammatory bowel disease, juvenile SpA and, more recently, axial and peripheral SpA, and in almost all patients although, in the literature, the percentage of patients with clinical manifestations of enthesitis is variable (10%–60%).

Clinical Evaluation of Enthesis

The prevalence of enthesitis in SpA is not easy to determine for 2 main reasons: on one hand, the possible subclinical involvement of the entheses and, on the other, the diagnostic difficulty of the clinical examination, due to the absence of visible inflammatory signs. Still, indices have been developed to clinically assess entheses in patients with SpA.

There are 3 validated indices for AS (Mander enthesis Index [MEI], Maastricht Ankylosing Spondylitis enthesitis [MASES] and Major) and 2 indices validated for PsA (Glandman and Leeds). The MEI, published by Mander in 1987, evaluates 66 entheses, establishing a pressure pain, ranking making it difficult to apply when in clinical practice.[13] Subsequently the MASES index was published, a simplification of the above, assessing the presence or absence of pain in 13 entheses. The Major index includes 12 entheses in their assessment: iliac, trochanter, epicondyles, epitrochlear, Achilles and plantar fascia. The Gladman index assesses eight enthesis: rotator cuff, anterior tibial tuberosity, Achilles and plantar fascia; Leeds includes 6 entheses in the evaluation: Achilles, medial femoral condyle and epicondyle. The examination is performed by applying constant pressure with the fingertips on the enthesis, which leads to loss of objectivity according to the pain threshold, considering it is not the same for each patient.

Evaluation of Enthesis Through Imaging

The reliability and accuracy of the clinical examination to assess entheses are not satisfactory, so imaging techniques have potential use in their objective assessment. X-rays and computed tomography only detect and evaluate structural bone changes that correspond to past episodes of activity or injury and do not inform us of the presence of inflammatory activity in enthesis at the time of examination. Thus, imaging tests such as MRI and, more recently, ultrasound, have been employed for the diagnosis of active disease in patients with SpA.

MRI has been used in SpA, mainly to assess axial involvement: cervical, dorsal, lumbar and sacroiliac joints. It allows early visualization of Romanus lesions in the spine and enthesitic interspinous and supraspinal ligament injuries, but mostly it has been validated in sacroiliitis. In the swollen entheses, what is detected by NMR is subcutaneous tissue or soft tissue edema (perienthesitic edema) and bone edema; less frequently it detects entheses edema through their connection between fibroblasts and collagen fibers in the