Ultrasound as a tool for the diagnosis of spondylarthritis in women

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SUMMARY

Objective. The journey to a diagnosis of spondyloarthritis (SpA) can be difficult for women, who often experience delays in receiving the correct diagnosis as their symptoms are frequently misinterpreted due to other conditions like osteoarthritis, fibromyalgia, or other psychosomatic disorders. The purpose of this article is to examine the challenges in the diagnosis of SpA in women and the possible role of musculoskeletal ultrasound in early diagnosis and in avoiding misdiagnosis.

Methods. We have performed a narrative review of the currently available literature on the subject.

Results. The complexity of diagnosing SpA in women is compounded by the misconception that the disease predominantly affects men. To facilitate early diagnosis and prevent misdiagnosis, it is crucial not to overlook gender differences in the clinical presentation of SpA. Since women have more peripheral and enthesitic involvement, performing an ultrasound of entheses, tendons, and joints in women with musculoskeletal symptoms that could refer to SpA may help both in the early and differential diagnosis.

Conclusions. There is a need to increase awareness among physicians of the existence of a different clinical presentation of SpA between men and women. The use of musculoskeletal ultrasound, which allows the detection of even subclinical inflammation and structural damage since early disease at the level of joints, tendons, and entheses can help make an early diagnosis and avoid misdiagnosis. Early diagnosis and timely treatment of SpA are crucial to reducing irreversible damage.

Key words: *Musculoskeletal ultrasound, women, SpA diagnosis.*

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INTRODUCTION

Spondyloarthritis (SpA) is an umbrella term that defines a heterogeneous group of chronic inflammatory diseases affecting the spine and/or peripheral joints, often associated with extra-articular involvement such as psoriasis, uveitis, and inflammatory bowel disease (1). Conditions within this group include ankylosing spondylitis (AS), psoriatic arthritis (PsA), enteropathic arthritis, reactive arthritis, undifferentiated SpA, and juvenile SpA.

According to the classification criteria of the Assessment of Spondyloarthritis International Society, SpA can be subdivided into axial SpA (axSpA) and peripheral SpA based on the prevalent joint involvement (2, 3). Moreover, axSpA can be further subdivided into radiographic axSpA (also known as AS), if radiographic sacroiliitis is found, and non-radiographic axSpA (nr-axSpA), if only magnetic resonance evidence of sacroiliitis is present.

Currently, the diagnosis of axSpA is often delayed by an average of 5-8 years from the onset of initial symptoms, especially in cases of young age at symptom onset and HLA B27 negativity (4). In women, this diagnostic delay is even longer than in men (8.8 *versus* 6.5 years), as shown by a meta-analysis involving 42 studies and 23,889 patients (32.3% women) (5). A later survey of 2846 patients (61.4% women) in 13 countries confirmed these data: the average diagnostic delay in women was 8.9 years compared to 7.4 years in men (6).

To achieve an early diagnosis and avoid misdiagnoses, it is important not to overlook sex differences in the clinical presentation of SpA. Women more commonly experience peripheral involvement, widespread

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pain, and fatigue rather than inflammatory back pain. In this context, the use of musculoskeletal ultrasound, which allows the detection of even subclinical inflammation and structural damage since early disease at the level of joints, tendons, and entheses, can be a very helpful tool.

CHALLENGES IN DIAGNOSING SPONDYLOARTHRITIS IN WOMEN

The difficulties in diagnosing SpA in women can be partly attributed to the misconception that this disease is more common in men. While AS is more prevalent in males, with a male-to-female ratio of 2-3:1 (7), recent studies have shown that in nr-axSpA, the gender ratio is close to 1:1 (8). This discrepancy can be explained by the fact that women tend to develop radiographic sacroiliitis, a distinctive sign of AS, less frequently than men. The journey to a diagnosis of SpA can be difficult for women, who often experience delays in receiving the correct diagnosis as their symptoms are frequently misinterpreted due to other conditions such as osteoarthritis.

A recent real-life study, based on a web-based survey answered by 235 AS patients, showed that a significantly higher percentage of women than men had previously been misdiagnosed with fibromyalgia, depression, and psychosomatic problems (9). Moreover, before being diagnosed, women have a higher number of visits to general practitioners (82.1% *versus* 74.7%), osteopaths (24.4% *versus* 13.3%), and physiotherapists (49.5% *versus* 34.5%) than their male counterparts (10).

Women with SpA experience widespread pain and fatigue more frequently than inflammatory back pain and report higher pain scores in questionnaires than men. Diffuse pain doubles the delay in the diagnosis of SpA in women and increases the risk of being misdiagnosed (11).

This difference in pain experience between men and women is related to genetic, hormonal, and immunological factors. Testosterone is known to reduce the immune response and increase the pain threshold, while literature data on estrogen and progesterone are conflicting (8).

Pain perception differences are not solely related to sex but also to socio-cultural factors linked to gender; for instance, men may tend to suppress or resist pain to adhere to stereotypes of masculinity (12). Several studies have shown that women with SpA have more peripheral involvement and more enthesitis than men (13), which has been found to be a predictor of lower efficacy of biologic therapy (14).

THE ROLE OF MUSCULOSKELETAL ULTRASOUND

Since women have more peripheral and enthesitic involvement, performing an ultrasound of entheses, tendons, and joints in women with musculoskeletal symptoms that could refer to SpA may help both in the early and differential diagnosis. Nowadays, thanks to the availability of increasingly sophisticated equipment, ultrasound is a cost-effective and non-invasive imaging method that allows the presence of inflammation in joints, enthesis, tendons, bursae, and structural bone damage to be detected (15). Moreover, the application of the power Doppler mode allows the estimation of pathological vascularization in active disease. According to the European Alliance of Associations for Rheumatology (EULAR) recommendations for the use of imaging in the diagnosis and management of SpA in clinical practice, ultrasound is a useful imaging tool to support the diagnosis of SpA by detecting enthesitis, peripheral arthritis, tenosynovitis, and bursitis (16).

Enthesitis, which is a landmark of SpA, is difficult to diagnose clinically. The clinical diagnosis of enthesitis is frequently unreliable and subject to high variability, relying on pain elicitation in the entheseal region and potentially influenced by concomitant fibromyalgia. Ultrasound evaluation of entheses is relatively more objective and sensitive than clinical examination. By combining gray-scale ultrasound and power Doppler, SpA enthesitis can be distinguished from mechanical enthesopathy as

well as from entheseal symptoms due to fibromyalgia.
In 2019, Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) published consensus-based definitions of enthesitis: "hypoechoic and/or thickened insertion of the tendon close to the bone (within 2 mm from the bony cortex) which exhibits Doppler signal if active and that may show erosions, enthesophytes/ calcifications as sign of structural damage" (17). This definition allows for the identification of active enthesitis *versus* enthesopathy, defined as "an abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment, viewed in two perpendicular planes, which may show Doppler signal and/or bony changes including enthesophytes, erosions or irregularities" (18).
Ultrasound is also a very useful tool for its high sensitivity to detect tendon or joint inflammation, even in subclinical stages. For both those lesions, well-established definitions have been produced and can be applied in different contexts, including SpA. Ultrasound synovitis is defined as the "presence of a hypoechoic synovial hypertrophy regardless of the presence of effusion or any grade of Doppler signal", and tenosynovitis as "abnormal anechoic and/or hypoechoic (relative to tendon fibers) tendon sheath widening, which can be related both to the presence of tenosynovial abnormal fluid and/or hypertrophy; Doppler signal can be considered if seen in two perpendicular planes, within the peritendinous synovial sheath, excluding normal feeding vessels" (17).
Dactylitis, one of the characteristic SpA features, is common in patients with PsA and is characterized by the involvement of different digital anatomical structures: joints, tendons, and soft tissues. The diagnosis of dactylitis is based on clinical examination; however, ultrasound is a useful tool to support the diagnosis, especially in doubtful cases such as patients with a high body mass index or in cases of subclinical dactylitis. The recently published global sonographic score for dactylitis is able to discriminate between dactylitic and normal fingers and assess the severity of the pathology. It consists of a composite score for each elementary lesion: peritendinous inflammation of the extensors assessed in B-mode and power Doppler at the metacarpophalangeal and proximal interphalangeas joints; soft tissue edema; tenosynovitis of the flexors assessed in B-mode and power Doppler at the most severely affected area of the finger; and a combined EULAR-OMERACT score for synovitis assessed at the individual finger joints (19).

CONCLUSIONS

There is a need to increase awareness among physicians of the existence of a different clinical presentation of SpA between men and women. Women more often have peripheral involvement, widespread pain, and fatigue, symptoms that may lead the clinician to misdiagnosis.
Musculoskeletal ultrasound, which allows the detection of subclinical inflammation in joints, tendons, and entheses, as well as structural abnormalities since early disease, can help make an earlier diagnosis and avoid misdiagnosis. Early diagnosis and timely treatment of SpA are crucial to reducing irreversible damage.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

Conflict of interest
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