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INTEGRATED STUDY MASTER'S FINAL THESIS

Diferential Diagnosis Between Fibromyalgia and Widespread Enthesitis in Inflammatory Spondyloarthropaties

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1.1 Abstract:

The goal of this paper is to go through the differential pathophysiology of peripheral Spondyloarthropathies (pSpA) and fibromyalgia (FM) (the subject of peripheral and axial Spondyloarthropathies (axSpA) will be discussed in this extended literary review, but the emphasis mostly being on the pSpA which might present itself in the form of enthesitis; a crucial symptom to be distinguished from the widespread pain present in fibromyalgia), as well as going through the differential diagnoses under the umbrella term, inflammatory Spondyloarthropathies (SpA). After the author has done this by using current and reliable sources, the paper aims to show the differences in these two broader categories and the pitfalls that a clinician can fall into when diagnosing the patient. After all of this has been conducted, the paper turns its aim towards the usage of currently available indices and radiological tools (such as ultrasound and magnetic resonance imaging (MRI) for the differentiating of spondyloarthropathies from fibromyalgia, mostly concerning the symptom of widespread pain. Unfortunately, this review will not focus on the medication and treatment of the diseases in question, and for that information other sources are recommended.

1.2 Keywords:

Spondyloarthropathies; Spondyloarthrites; pSpA; Fibromyalgia; Differential diagnosis; MASES; LEI; SPARCC; MRI; ultrasound; enthesitis; widespread pain

1.3 Introduction:

The paper presented here is directed, towards the physicians and other field professionals, to work as a general overview of the subject matter of differentiation between the similar symptoms of fibromyalgia and widespread enthesitis in pSpA, and the aim of the overview is to work as an adjuvant for a clinician working with these two patient groups, helping them to more easily and with confidence to place the patient in either category, this being of utmost importance, as there is a real urgency for early treatment of pSpA, which has a positive effect on the prognostic outcome of the disease, as compared to the more stagnant diagnosis of fibromyalgia.

In this extend literary review my task is to explain the general hypothesized pathophysiological processes of fibromyalgia and pSpA, the similarity of their symptoms, such as widespread pain, and the consequences of improper diagnosis, as well as the pitfalls of making the early diagnosis. In addition to the aforementioned, I will try my best to clarify the two common classification systems of SpA: the axial and peripheral distinction, concerning the clinical presentation of the patient & the

classification into diagnostic subgroups, such as ankylosing spondylitis (AS), Psoriatic arthritis (PsA), Reactive arthritis (ReA), Arthritis associated with IBD, Undifferentiated spondyloarthritis.

The differential diagnosis of widespread enthesitis in pSpA and fibromyalgia is conducted through the help of imaging modalities, like, MRI and ultrasound, through physical evaluation and by laboratory tests. In this overview, I'm going to evaluate all three of these systems, but will be mainly focusing on imaging modalities, mostly the MRI and ultrasound. Additionally, I will also be explaining certain indexes used in the diagnosis of Spondyloarthropathies, such as MASES index, SPARCC index and LEI index.

One of the important goals of this overview is also the critical evaluation of the reliability, sensitivity and specificity of the different radiological modalities and the consequent finding on them.

To guarantee that the reader has enough knowledge concerning the different autoimmune arthropathies and fibromyalgia, and the differences between the two, this paper will start by going through the separate entities of fibromyalgia, SpA, and their distinction into subcategories and trying to explain the most common diagnoses expressing the symptom of widespread pain. It will also explain the multitude of processes connected to the differential diagnoses, building the foundation for the upcoming discussion on the subject.

2. Methodology:

For the articles provided in this extended literary review, an iterative literary search strategy was employed, as the search for two very niche subjects was needed. As the main database, PubMed, was used, and the articles were delimited to contain only articles 10 years or newer, with the exception of the groundwork articles for pathophysiology of the disorders and so on.

The initial search focused on articles concerning keywords, fibromyalgia and widespread enthesitis/pain. *Fibromyalgia: Pathogenesis, Mechanisms, Diagnosis and Treatment Options Update,* was used for the general information on FM

For the information on widespread enthesitis, the literature search proved more complex, as the process of enthesitis is common on many different arthropathies, and widespread enthesitis being considerably less frequently discussed in the literature than localized enthesitis, the searching had to be started with the division and explanation of inflammatory spondyloarthropathies in general.

The spondyloarthropathies, also called spondyloarthritides, being divided by the classification, based in axial and peripheral forms, and also in diagnostical categories created conceptual

challenges in structuring the review, so at this review I mainly focused on the diagnostic classification, containing diagnoses but it is also of utmost importance to explain the distinction of two classification systems.

Concerning the diagnosis of FM, it was decided that the only the more general term, fibromyalgia, would be used concerning the literary overview, as this would offer more informative articles on the subject, whereas the application of only concerning on primary or secondary fibromyalgia would have narrowed down the availability of usable information tremendously.

For the diagnostic approach to spondyloarthropathies it was decided to exclude diagnoses such as undifferentiated spondyloarthropathy (due to the limited amount of relevant literature available), and acute anterior uveitis, as its predominant clinical manifestations differ substantially from the symptom profile discussed in this review. So, the diagnoses being investigated in more detail were Psoriatic arthritis (PsA), Ankylosing spondylitis (AS), Reactive Arthritis (ReA), IBD-associated arthritis and Enthesitis related arthritis (ERA) under the umbrella term “juvenile arthritis”.

Older than 10 year articles have been used in historical context and when associated with studies from the last 10 years.

Most of the articles used were concerning axial/peripheral SpA and PsA out of the spondyloarthropathies, as these subgroups were the most extensively represented in the available literature.

FM was discussed in the context of primary and concomitant, depending on the accumulated studies, taking into consideration the challenge of diagnosing as FM frequently coexists with SpA, complicating both diagnosis and differential diagnostic evaluation. A big problem searching the articles was that the findings of the reviewed studies often differed considerably when FM was thought of its own entity, and when thought of as occurring concomitant to SpA.

The review also discusses commonly used clinical enthesitis indices, mostly MEI, LEI, MASES and SPARCC, as these appear to be among the most commonly used indices in current clinical practice and research. But mostly my review focused on the more objective indicators of enthesitis, the radiological instruments, and out of these X-ray and CT are only discussed briefly in the context of accidental findings and historical sense. Particular emphasis is placed on MRI and especially ultrasound, for its ease of use and relatively low cost in the clinical practise.

Many schemes and tables have been made specifically for this paper, using as inspiration work done by other authors. These schemes and tables were done using the image generation tool of ChatGPT by OpenAI (with combination of the author’s own suboptimal image processing skills)

and Microsoft's excel tool. All of these additional figures have been embedded within the text for ease of reading, so that they do not need to be accessed through supplementary material.

All of the article searching was made using PubMed, and going through their site to respective secondary sources. The multitude of keywords used to search for articles in PubMed were thus: "widespread enthesitis in inflammatory spondyloarthropathies", "inflammatory spondyloarthropathies", "inflammatory spondyloarthropathies", "widespread enthesitis", "enthesitis", "fibromyalgia", "inflammatory spondyloarthropathies classification", "SpA classification", "diagnosis of spondyloarthropathies", "diagnosis of spondyloarthritis", "psoriatic arthritis", "psoriatic arthritis differential diagnosis", "fibromyalgia diagnosis", "fibromyalgia diagnosis criteria", "SpA diagnostic approach", "psoriatic arthritis differential diagnosis", "ankylosing spondylitis", "ankylosing spondylitis diagnosis", "ankylosing spondylitis radiology", ankylosing spondylitis enthesitis", "reactive arthritis", ibd associated arthritis", "juvenile SpA", "enthesitis related arthritis", "acute anterior uveitis", "acute anterior uveitis enthesitis", "undifferentiated SpA", "SPARCC index", "The Leeds enthesitis index", "enthesitis mri", "axial spondyloarthritis", "achilles trial", "SPARCC LEI MASES", "enthesitis radiology", "SpA mri", "mri spondyloarthropathy", "mri spondyloarthropathy fibromyalgia", "mri fibromyalgia", "ultrasound enthesitis", "ultrasound enthesitis fibromyalgia",

A broad range of search terms was utilized and overlapping or non-relevant search terms were excluded from the final review process. A significant proportion of the used words wasn't useful exactly for the subject at hand but helped provide broader contextual understanding of the subject area and supported interpretation of the reviewed literature.

Also, one thing representing a limitation of this literature revieware the absence of rights to certain articles that would've been highly relevant considering the subject in question, and due to this mishap certain papers could not be read in their entirety, but only in a much more condensed form.

2 Diagnoses

2.1 Fibromyalgia

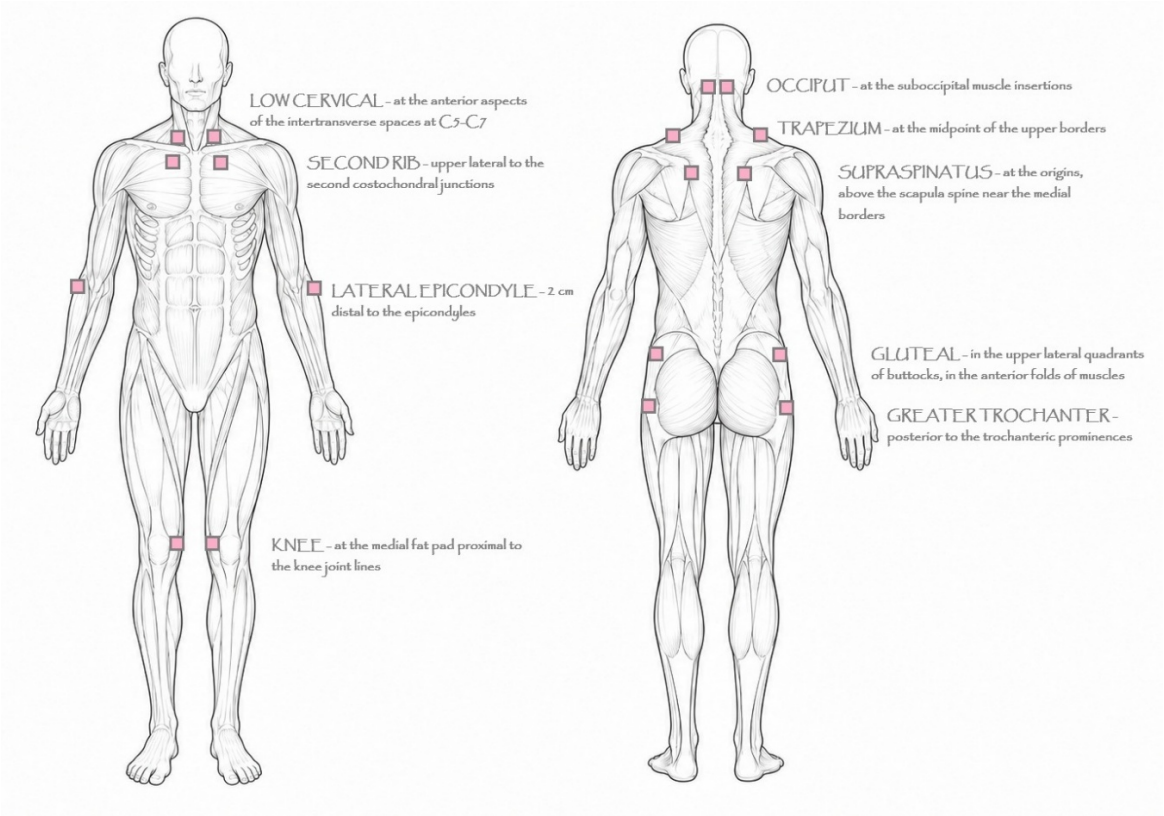
Fibromyalgia (FM) is characterized by chronic musculoskeletal pain; the main symptoms being muscle- and joint stiffness, insomnia, fatigue, mood disorders, cognitive dysfunction, anxiety, depression, general sensitivity and inability to carry out normal daily activities. It is unclear as of date whether the associated mental manifestations caused by the constant feeling of pain or the disease itself. The disorder affects approximately 5% of the world population, being more common in females and generally appearing between the age of 30 to 35 years. [1]

FM was first described in the 19th century, but only at a later date, in the 1970s/1980s, when etiology of central nervous system involvement was discovered, the term ‘fibromyalgia’ started to be used to describe the disease itself. The term was invented by Smythe and Moldofsky, and they used the identification of certain ‘tenderness points’, areas of hyperalgesia or allodynia, around the patient’s body, for the application of said diagnosis. [1]

According to the American College of Rheumatology (ACR), the diagnosis of fibromyalgia is made through two distinct criteria: *1) bilateral pain above and below the waist, characterized by centralized pain, and 2) chronic generalized pain that lasts for at least three months, characterized by pain on palpation in at least 11 of 18 specific body sites.* However, even with the aforementioned criteria, fibromyalgia remains a hard condition to diagnose, taking into consideration the lack of any specific laboratory markers, and its similarity with many Spondyloarthropathies (SpA). [2]

Underneath a figure has been applied, indicating the 18 tender points essential for diagnosing fibromyalgia clinically. It is worth noting that this figure should not be taken as a factual presentation of the exact anatomical locations, as the pink squares are only approximations of these locations, which are also described (in writing) in the figure 1.

Figure 1.



The pathophysiology of fibromyalgia is not entirely known, but it has been proposed that the disorder rises from the processing of pain stimuli inside the person's central nervous system (CNS), through the elevated levels of excitatory neurotransmitters, glutamate and substance P and decreased levels of serotonin and norepinephrine in the descending anti-nociceptive pathways of the spinal cord. It is also assumed that dopamine dysregulation and endogenous cerebral opioids might have a summative effect on the incidence of the disorder, as well as anomalies of the peripheral nervous system, neuroendocrine factors, genetic predisposition, oxidative stress and environmental and psychosocial factors. The unknown summation of these preceding factors ultimately making the patients hypersensitive to pain, giving rise to a central sensitivity syndrome called FM. [2]

In the 2010/2011 criteria by ACR (concerning FM) it was concluded that, FM could be defined using a combination of widespread pain index (WPI) and a symptom severity (SS) scale. SS taking into consideration cognitive symptoms, the level of freshness of the patient's sleep, reported fatigue and the number of somatic symptoms. According to this definition, FM was deemed to be present when either [3]:

1) the WPI was ≥7 with a concurrent SS ≥5

OR

2) the WPI was 3-6 in combination with an SS ≥9.

It was also demonstrated that these new criteria correctly classified 88.1% of the cases and did not require examination of the tender points. [3]

In 2016, the criteria were revised by Frederick Wolfe's team, and they concluded that the ACR criteria showed great sensitivity and specificity, reduced misdiagnosis of localized pain and clarified diagnostic exclusions. The updated criteria were deemed to be suitable for both diagnosis and classification of FM [2]

So, taking into account the findings of the revision of the new criteria, it is still favorable to use the WPI and SS scale for the diagnosis of FM. There are no specific biomarkers to use in aid of the diagnosis despite several attempts, thus the WPI and SS, with the aid of exclusion of other diagnoses, are really the only diagnostical instruments in an aspiring physician's toolkit. For more information on pathophysiology and diagnostical experiments on FM, I suggest the reader visit the paper constructed by Rosalba Siracusa and her team on the subject. [1]

2.2 Spondyloarthropathies

In SpA, two distinct classification approaches can be distinguished: a diagnostic approach base on the patients' individual clinical manifestations and a classification approach based on the standardized division into two principal subcategories, also called Assessment of SpondyloArthritis international Society (ASAS) classification criteria. Concerning these classifications, it is detrimental to understand the primary goal of these distinct classification systems before delving deeper into the subject of this extended literary review. [4]

The most accessible explanation of the two SpA classification systems comes from a literary review by Denis Poddubnyy. According to his paper**,** diagnostic and classification methods differ in concept and application. A diagnostic approach being useful to assess the likelihood of a patient having a certain disease, whereas the classificational approach is only used after a diagnosis has already been made, and is used in order to group patients for future research purposes. [5]

In the following subheading, we first examine the assessment of ASAS classification criteria, and subsequently provide a more detailed discussion on the diagnostic classification system in a later subheading.

2.2.1 ASAS Classification criteria

SpA is a group of diseases with similar clinical and genetic characteristics. These characteristics cover qualities, such as, involvement of axial skeleton, HLA-B27 antigen association, typical involvement of peripheral joints, more specifically of asymmetric oligoarthritis, dactylitis, enthesitis and extra-musculoskeletal manifestations, such as acute anterior uveitis (AAU), psoriasis and inflammatory bowel disease (IBD). [4][5]

Based on the most expressionistic symptoms of the ones mentioned above, the SpA patients can be divided into two distinct groups of clinical presentation: 1) axial spondyloarthropathies (axSpA), mostly expressing axial symptoms, such as back pain and morning stiffness or 2) peripheral spondyloarthropathies (pSpA), mostly expressing more peripheral symptoms, such as peripheral arthritis, enthesitis or dactylitis. It is worth noting, however, that before mentioned symptoms do not exclusively belong to one category or the other, as there can be overlapping between the two groups. [5]

Considering that this paper focuses on widespread pain, the main emphasis will be placed on the subgroup of pSpA, in accordance with the distinction described above.

Unlike rheumatoid arthritis (RA), SpA-related symptoms are usually mono- or oligoarticular and usually affecting the lower limbs. The inflammation in SpA is typically non-erosive and is thought to result secondary to the inflammation of tendon- and ligament insertions, or entheses; the inflammatory reaction being known as enthesitis. [3]

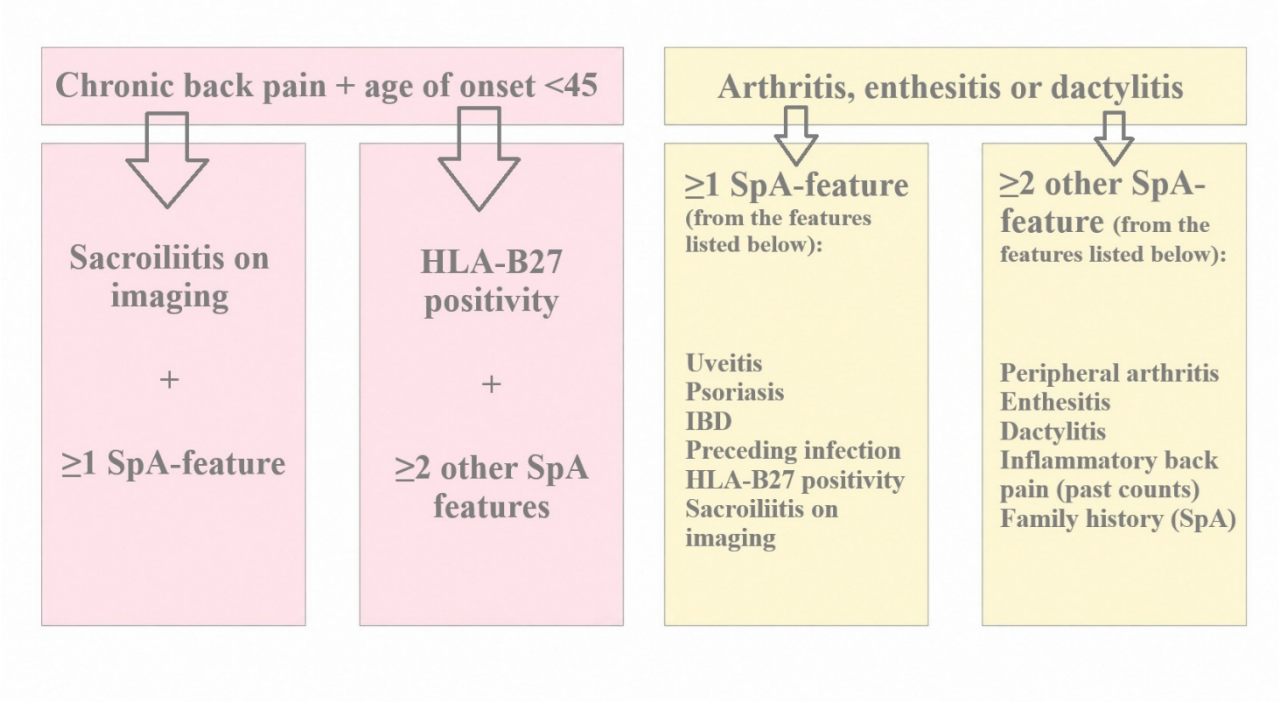
Enthesitis can affect any structure containing ligaments or tendons; however, within the diagnostic and classification framework of SpA, the main focus is placed on peripheral enthesitis, as this is represents one of the most accessible locations for clinical examination. Nevertheless, clinical identification of enthesitis can be challenging, and imaging techniques such as ultrasound and MRI are yet crucial for the objective confirmation of entheseal inflammation, as the specificity of these methods are rather high, approximately 90%, at least, in the context of heel enthesitis of SpA.

In 2009 ASAS group developed the criteria of axSpA and pSpA. Underneath (figure 3), I have attached the said clinical classification system in a simplified form. The one on pink concerning axSpA and the yellow, psSpA. [6][3]

Given the simplification of the original table, the table below requires further explanation: The two columns represent two alternative diagnostic pathways, of which only one must be fulfilled to establish a diagnosis.

The original table also included a separate textbox on the axSpA side (pink), indicating all features of SpA. This was omitted on the grounds that most of the information is already presented elsewhere in the table, with the only exceptions, being *elevated CRP* and *good response to NSAIDs*. These two findings should therefore also be regarded as possible features of SpA.

Figure 3. Clinical classification system of SpA into axSpA (pink) and pSpA (yellow) according to patient's symptoms, imaging modalities and blood tests.



For the ASAS criteria of axSpA to come into effect, the patient has to have chronic back pain (duration >3 months), with the onset of the pain starting before the age of 45 years. The criteria can be approached from two directions, either through the imaging pathway or the clinical pathway (as can be seen on Figure 2A). The overall sensitivity of the criteria is 82.9%, and the specificity, 84.4%, going through the imaging pathway faring slightly better in the original study. [7][3]

The ASAS criteria for peripheral SpA apply to patients with predominantly peripheral symptoms, such as arthritis, enthesitis, or dactylitis. The peripheral criteria additionally include preceding infection to capture reactive arthritis, with the other factors greatly overlapping with the axial SpA criteria. [3]

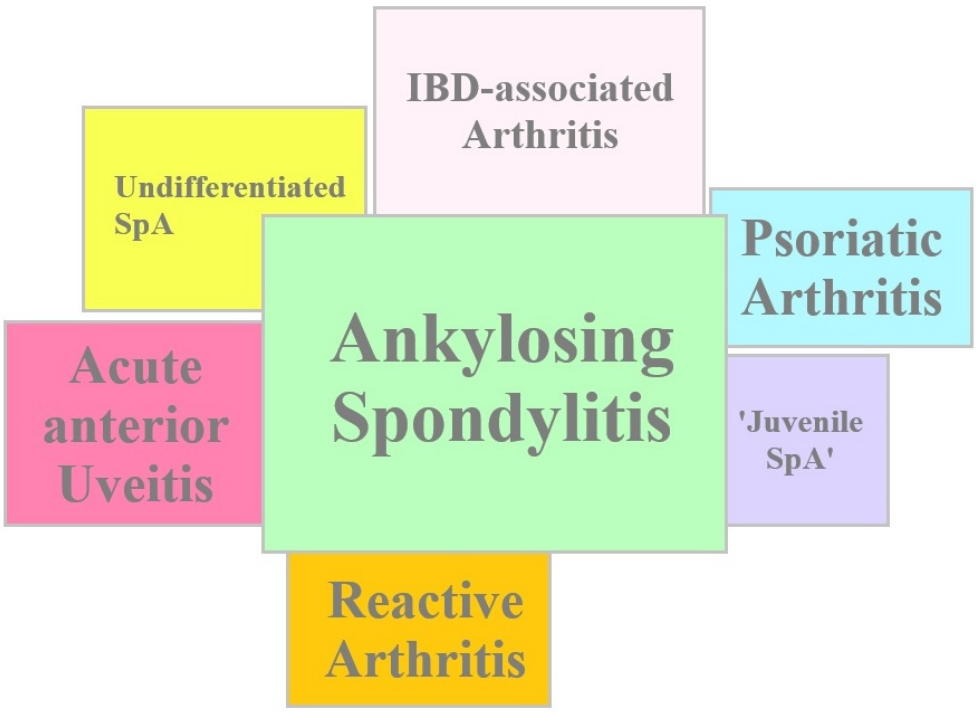
A diagnosis of pSpA is made when arthritis, enthesitis, or dactylitis is present together with one or two other SpA features. The peripheral criteria's sensitivity being of 77.8% and specificity of 82.2%, slightly lower when compared to the axSpA criteria. [3]

I must once again underline that the classification into these peripheral and axial subgroups are mainly used for research purposes, and for clinical practice, diagnostic approach is preferred. Also, the two distinctions usually have different starting points, the diagnostic approach starting at the suspicion of a disease, whereas the classification approach emerges only after a diagnosis has been established, and is, in most cases, used to group patients into more homogenous groups for research purposes. [5]

In summary, the diagnostic approach belongs to clinical practise and must be performed initially (whether the patient participates in a study or not), whereas the classification approach is useful in research. [5]

2.2.2 Diagnostical criteria

Figure 2. Diagnostic classification of SpA



It is anticipated that the reader of this article is now familiar with the ASAS classification system. However, as the diagnostic approach to SpA differs in both concept and application – considering pre-test probability, interpretation of test results and exclusion of alternative diagnoses prior to reaching a conclusion – the discussion will now focus on the diagnostic classification of SpA, addressing the diagnoses in sequential manner. Exception are made for acute anterior uveitis and undifferentiated SpA, either because the symptoms were sufficiently distinct from FM (in the case of AAU) or due to a lack of sufficient usable literature (in the case of undifferentiated SpA). It is

also worth noting that, regarding ‘Juvenile SpA’, the focus is primarily on the subcategory of enthesitis-related arthritis (ERA). [5]

With the paper’s approach to diagnostics of SpA now outlined, the focus will turn towards the individual diagnostic entities themselves, starting with PsA.

2.2.2A Psoriatic arthritis (PsA)

According to a paper by Douglas J Veale and Ursula Fearon, PsA is a complex disease with varied clinical features affecting joints, skin, nails, entheses, and other tissues. They report that the genetic factors associated with articular disease in PsA differ from those associated with cutaneous manifestations of PsA. Gene–environment interactions — such as smoking, trauma, and infections — appear to contribute to disease development (the potential roles of skin and gut microbiota being still under investigation). [8]

Immune-mediated inflammation also plays a central role, particularly involving CD8+ memory T cells and the TNF and IL-23/Th17 pathways. Insights into these mechanisms have led to effective targeted therapies. Although the precise etiology of PsA still remains unclear. [8]

Despite progress in molecular technologies, validated biomarkers for diagnosis, prediction of therapeutic response and remission are still lacking. Emerging tools such as single-cell sequencing, mass cytometry, and advanced imaging may help address these limitations. [8]

PsA accounts for about 20% of early arthritis clinic referrals and poses notable diagnostic and therapeutic challenges. Early recognition is crucial to prevent long-term disability and to manage both joint disease and associated comorbidities. The differential diagnosis includes RA, gout, and other inflammatory arthritides. Only once the diagnosis is consolidated, a comprehensive assessment of peripheral arthritis, enthesitis, dactylitis, skin and nail involvement, and possible axial disease can be conducted. [9]

Early diagnosis of PsA is crucial, as appropriate treatment can significantly improve long-term disease outcomes; however, nearly 50% of PsA cases in both primary and secondary care settings remain unrecognized, and this delayed or missed diagnosis is particularly concerning given the associated burden of metabolic comorbidities and the increased risk of cardiovascular morbidity and mortality. [9]

Although PsA was once considered a relatively mild condition, registry data have demonstrated that it can be progressive and destructive, with a burden on function and quality of life comparable to that of RA. [9]

When considering the diagnosis of PsA, a clinician must be able to differentiate it from other similar conditions, such as RA, with it being a common cause of diagnostic misclassification in practice. A comparative table is provided below. Of note, the reported 60-80% prevalence of enthesitis in PsA (Table 1.) is derived from imaging modalities, whereas clinically overt enthesitis is significantly less prevalent (approximately 34%). [9][10]

Table 1. Differential diagnosis of PsA and RA

Features	Psoriatic Arthritis (PsA)	Rheumatoid Arthritis (RA)
Number of joints involved	30-50% **oligoarthritis**	Mostly **polyarthritis**
DIP-joint involvement	**Affects** distal interphalangeal joints (DIP)	**Doesn't affect** distal interphalangeal joints (DIP)
Enthesitis	Present in 60-80%	
Dactylitis	Present in 30%	
Skin manifestations	Psoriasis 80%	
Nail manifestations	Nail disease 60%	
Serology	Usually **RF** and **CCP (-)**	Usually **RF** and/or **CCP (+)**
Typical radiographic changes	**Periosteal new bone formation**	**Erosion** and **osteopenia**

CCP = cyclic citrullinated peptide; RF = rheumatoid factor

So, considering our diagnosis of PsA it seems important to note that large part of the expression of the disease is oligoarthritic, any joints can be affected, typically comes with enthesitis, can have dactylitis, has skin psoriasis, is usually RF- and CCP-negative and its typical radiological findings being those of periosteal new bone formation, (instead of the erosion and osteopenic findings in RA). Although early diagnosis is clinically desirable, it remains challenging, given that radiological changes are generally not yet evident in the early stages of either PsA or RA. [9]

Ultrasound studies suggest that enthesitis in PsA most frequently involves the lower limb entheses; the most common areas of enthesitis being proximal patellar ligament (58%), followed by Achilles tendon (49%), Quadriceps tendon (48%), Distal patellar ligament (47%) and plantar fascia (18%) [11]

As can be seen in the table above, enthesitis is also a huge contributor to the symptom burden of PsA, with 60-80% of patients with the diagnosis, having, at least, radiological enthesitis, which

might also be misclassified as widespread pain associated with FM, thus a study by N. Bibas and colleagues is quoted underneath for better understanding on the subject. [10]

In their meta-analysis they set out to evaluate the differentiation of enthesitis in PsA from other widespread pain sources and diagnoses, using ultrasound. Their findings indicated that the use of ultrasound alone in the diagnosis of PsA is suboptimal (with a sensitivity of 62% and specificity of 73%), and that it's most appropriately used as an adjuvant tool, rather than for the confirmation or exclusion of the diagnosis. With the addition of Power Doppler, specificity increased markedly (98%), but at the cost of sensitivity (15%). [10]

In conclusion, as an adjuvant for the diagnosis of PsA, ultrasound is useful when first used in grey-scale to detect structural entheseal abnormalities such as erosions, and subsequently combined with Power Doppler, to increase diagnostic confidence by identifying active inflammation, particularly in the assessment of Achilles tendon enthesitis. [10]

However, one important limitation of this method is that many patients may already be receiving DMARD therapy, which can reduce inflammatory activity and consequently diminish Power Doppler signal detection. This may lead to underestimation of disease activity. Additionally, ultrasound entheseal abnormalities are not specific to PsA and may also be seen in mechanical stress, obesity, and physically active individuals, as well as in other forms of SpA. [10]

As PsA also involves articular manifestations, it is important to consider the relationship between joint inflammation (synovitis) and enthesitis. A study conducted by G. Ayan and colleagues investigated this in their study of 126 PsA patients, using ultrasound examination of 46 joints and 12 large entheses. The study demonstrated a moderate positive correlation ($r = 0.410$) between joint inflammation and enthesitis severity, leading the authors to conclude that articular and entheseal inflammation are biologically linked in PsA. [11]

As PsA also affects joints, I find it important to note that some studies like, the one by G. Ayan and their team, has set out to find consistencies with articular inflammation and enthesitis.

There have been also studies conducted concerning the subclinical froms of enthesitis, even though, these are rarer and, usually, have quite small sample sizes. One example is an observational study by Anna E. F. Poulsen and her team, in which they tried to observe how reliable would a whole-body MRI (WBMRI) in detecting inflammatory arthritis (the participants were PsA and RA patients and healthy controls) and they found out that WBMRI was a reliable and reproducible across repeated scans of patients. [12]

To assess reliability, the researchers compared repeated MRI scans and evaluated how consistently inflammatory lesions were identified. The most reproducible findings were seen in inflammation of the axial skeleton, particularly the spine, while peripheral joints and entheses also showed consistently good reliability across repeated examinations. [12]

These findings suggest that WBMRI may become a valuable future tool for monitoring inflammatory arthritis and enthesitis, as it can reliably assess both axial and peripheral inflammation throughout the body in a single examination. [12]

Although the study primarily focused on the reliability and reproducibility of WBMRI, its findings further support the utility of the method in detecting subclinical inflammatory changes, particularly enthesitis, and highlight its potential value in the early assessment and monitoring of inflammatory disease progression. [12]

2.2.2B Ankylosing spondylitis (AS)

Ankylosing spondylitis is a form of chronic arthritis affecting the axial and peripheral joints (e.g., sacroiliac joint, spine, hip, knee) and entheses. It oftentimes is also accompanied by extra-articular symptoms, such as, IBD, AAU, psoriasis, cardiovascular diseases or osteoporosis. AS is commonly starts withing the third decade of life, being more prevalent in the male population (2:1 ratio) [10]

The pathogenesis of ankylosing spondylitis is multifactorial, involving interactions between genetic predisposition, immune mechanisms, and the gut microbiota, along with a close link between inflammation and abnormal bone formation. More on this subject can be learned through an overview by Yuxiao Wei and his team. [13]

The diagnosis of AS depends on typical symptoms, positive findings in X-ray, CT or MRI scan of sacroiliac joint, and it typically affects axial skeleton, especially sacroiliac joints and spine. In AS the main site of inflammation is, similarly to the aforementioned diagnoses, entheses but also, the junction site between articular cartilage and subchondral bone, and bone marrow located beneath the joint cartilage. [13][14]

The manifesting enthesitis in AS involves inflammatory changes at the insertion points of spinal ligaments, annulus fibrosus fibers and vertebral entheses, these sites being most likely the primary high-incidence areas due to the mechanical stress. [13]

An interesting paper by D. Poddubnyy and P. Miossec, published in 2019, also emphasizes the importance of IL-17 pathway in the pathogenesis of AS. In their clinical trials, the authors' noted that, contrary to expectations, the use of IL-17 inhibitors showed clear efficacy in the treatment of

AS, whereas Il-23 inhibitors did not, suggesting that axial enthesitis is likely predominantly IL-17 driven (as opposed to the IL-23 predominance in peripheral enthesitis). [14]

2.2.2C Reactive Arthritis (ReA)

Reactive arthritis (ReA), formerly called Reiter's syndrome, now considered SpA, is an infection-triggered systemic condition marked by sterile synovitis in genetically susceptible individuals, typically following a genitourinary or gastrointestinal bacterial infection. There are a lot of organisms associated with ReA; the commonality between these pathogens being, their intracellular nature.[15]

Underneath the author has listed (in no general order) some of the more commonly known causative agents of ReA, as it might be of help when considering the possibility of such disease. The majority of such associations are between ReA and either enteric or urogenital infections, but there are also exceptions to the rule as will be seen below.

Enteric infections: Salmonella species, Shigella species, Yersinia species, Campylobacter species, Clostridium difficile, Escherichia coli, Bacillus cereus, Amoebae species, Cryptosporidium species, Giardia lamblia, Helicobacter pylori, Strongyloides species, Tropheryma whippelii. [15]

Urogenital infections: Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma genitalium, Neisseria gonorrhoeae, Gardnerella vaginalis. [15]

Respiratory infections: Chlamydia pneumoniae, Streptococcus pyogenes. [15]

Others: HIV, B-19 parvovirus, Borrelia burgdorferi, Brucella abortus, Calmette-Guerin Bacillus, Chikungunya virus. [15]

ReA typically manifests 2-4weeks following a genitourinary or gastrointestinal bacterial infection, the main symptom being arthritis. The relationship with certain bacterial infections has been linked with genetical factors since 1973 (the HLA-B27 being most commonly associated with the diagnosis). It is often noted to be more common in males, but there has been some conflicting findings concerning this finding. [15]

ReA has a highly variable clinical presentation, ranging from no symptoms to acute asymmetric oligoarthritis, with or without extra-articular manifestations. The condition most often affects lower limbs and may also have additional musculoskeletal features such as enthesitis and dactylitis. ReA, like the other SpA has no specific laboratory biomarkers; CRP and ESR can be elevated in ReA, as in a multitude of different diagnoses. The principal differential diagnosis ReA should be

differentiated from being septic arthritis, which has similar symptoms, and also elevated CRP and ESR, makes the distinction, at best, challenging.

There are also no specific imaging studies for ReA, but recently there has been some research conducted on the value of ultrasound in rheumatic diseases in general (including spondyloarthritides). Ultrasound can detect abnormalities in joints, tendons, and entheses, such as synovitis, effusions, erosions, tenosynovitis, and enthesitis. [16]

These findings have been reported in 13–32% of studied cohorts, particularly for sacroiliitis and syndesmophytes. In clinical investigation, also conducted by Abraham Garcia-Kutzbach, it was noted that the method of ultrasound identified bilateral sacroiliitis in 15% of patients and Achilles tendon enthesitis in 39% in the Guatemalan sub-group at least. It has to be taken into account that this prevalence is of course not nearly high enough to confidently exclude the diagnosis of enthesitis [16]

The diagnosis of reactive arthritis is most reliably made by identifying the triggering infection in a genetically predisposed individual who presents with a compatible clinical picture. Underneath I have attached a table for the differential diagnosis of ReA and septic arthritis, having bolded the most noticeable differences between the two, as this knowledge is very important for any aspiring clinician [17]

Table 3. Differential diagnosis of ReA and Septic Arthritis [18]

Features	Reactive Arthritis (ReA)	Septic Arthritis
Joint involvement	**Oligoarthritis** (sometimes polyarthritis); acute onset, often asymmetrical, **migratory**, lower extremity predominance	Usually **monoarthritis**; acute onset, most commonly affects knee joint
History of previous infection	Gastrointestinal or uritogenital infection (**latency period of 1-4 weeks**)	Hematogenous spread from **current** infectious site, direct contamination (iatrogenic, trauma) or local spread
Associated symptoms	Sacroiliitis, Enthesitis, Dactylitis, Ocular inflammations, Dermatologic manifestations, Urethritis, Oral ulcers, Cardiac manifestations, Symptoms from preceeding infections (diarrhoea, dysuria, pelvic pain, prostatitis)	**Classical triad: fever, joint pain, restricted range of motion** *(on the affected joint)*
Synovial fluid analysis	Leukocyte count: **5000-50,000** (neutrophil predominance)	Leukocyte count: **>50,000** (neutrophil predominance)

Other laboratory values	Elevated leukocytes, platelets, CRP, ESR	Elevated leukocytes, platelets, CRP, ESR

2.2.2D IBD-associated arthritis

Inflammatory bowel diseases affect not only the gastrointestinal tract but can also involve multiple extraintestinal organs. This involvement of extraintestinal organs is often termed extraintestinal manifestations (EIMs), not to be confused with extraintestinal complications, which arise from the inflammation caused by the IBD itself. [19]

In both ulcerative colitis (UC) and Crohn's disease (CD), the EIMs most commonly are associated with musculoskeletal system, skin, hepatobiliary tract or eyes. The distinction of musculoskeletal system, including the worthwhile symptoms for this overview, such as peripheral-, axial arthritis and enthesitis. The IBD-related arthritis being prevalent in 10-20% of CD patients and in 5-14% of UC patients, according to a study conducted by Gerhard Rogler and his team. The frequency of EIMs may be higher in the early onset disease, and in younger patients, but the evidence concerning this has been conflicting. [20][19]

The role of genetic susceptibility in the development of EIMs is supported by studies showing concordance rates of 70% in parent–child pairs and 84% in siblings. Moreover, there is considerable overlap between the genetic risk loci associated with EIMs and those linked to inflammatory bowel disease. Smoking also seems to play some role, as patients with CD who smoke have a higher likelihood of developing extraintestinal manifestations compared with non-smokers. It remains unclear whether this association is related to smoking-induced alterations in the intestinal microbiota. [19]

The most common EIMs out of the four noted systems are the musculoskeletal manifestations, affecting up to 46% of IBD patients (reported range: 6-46%), the dispersion being attributed to the prevalent clinical and radiological criteria, and also being hypothesized to geographical differences. [19]

Musculoskeletal ultrasound and MRI can aid in diagnosis by demonstrating characteristic features such as arthritis, enthesitis, tenosynovitis, and bursitis in IBD-associated arthritis, as well as other spondyloarthropathies manifesting these symptoms. [20]

Enthesitis is reported by several studies to be prevalent in 7–50% of adults with IBD. When chronic, it may cause functional impairment and structural damage, such as bone loss, erosions, calcifications, and abnormal new bone formation. Ultrasound can detect enthesitis at earlier stages,

but, alas, is often overlooked on clinical examination. It is also wort noting that MRI with short-tau inversion recovery (STIR) sequences is highly effective for detecting sacroiliitis and enthesitis, as it can reveal inflammation, bone marrow edema, and early bone erosions that are not visible on standard radiographs. [20]

2.2.2E Juvenile arthritis: Enthesitis related arthritis (ERA)

Juvenile idiopathic arthritis (JIA) is defined as arthritis of unknown cause beginning before age 16 and persisting for at least six weeks. JIA is divided into subtypes, one subtype being, enthesitis-related arthritis (ERA), which may progress to adult ankylosing spondylitis. It is worth noting that distinction between juvenile and adult forms are not always clear cut, and reclassification may occur after the age of sixteen. [21]

Although the precise pathogenesis of ERA is unclear, it is thought to result from interactions between genetic susceptibility, changes in the gut microbiome, and mechanical stress, leading to immune activation and the development of synovitis, enthesitis, and spondylitis. As we have talked about HLA-B27 and its importance in the pathogenesis of SpA, it is worth noting here also, that HLA B27 is prevalent in 40-90% of children expressing the diagnosis of ERA. [22]

Enthesitis-related arthritis (ERA) typically affects boys older than six years and presents with asymmetric oligoarthritis of the lower limbs, with or without enthesitis. The most commonly involved entheses are the Achilles tendon, plantar fascia, knee region, and pelvic sites, while upper-body entheses are less often affected. [22]

Compared with adults with ankylosing spondylitis, children show predominantly peripheral arthritis rather than axial disease. Oligoarthritis is the most frequent pattern, and midfoot involvement (tarsitis) is common. Hip involvement occurs early in a subset of patients and is associated with more severe disease and poorer long-term outcomes, with sacroiliitis and hip arthritis becoming increasingly prevalent over time. [22]

It is worth noting, that low-grade fever can also be present, but the symptoms such as weight loss, bone pains, sternal tenderness, hepato-splenomegaly, dactylitis, nail changes, moderate to severe anemia, cytopenia, hypertension and proteinuria are not generally linked with ERA. [22]

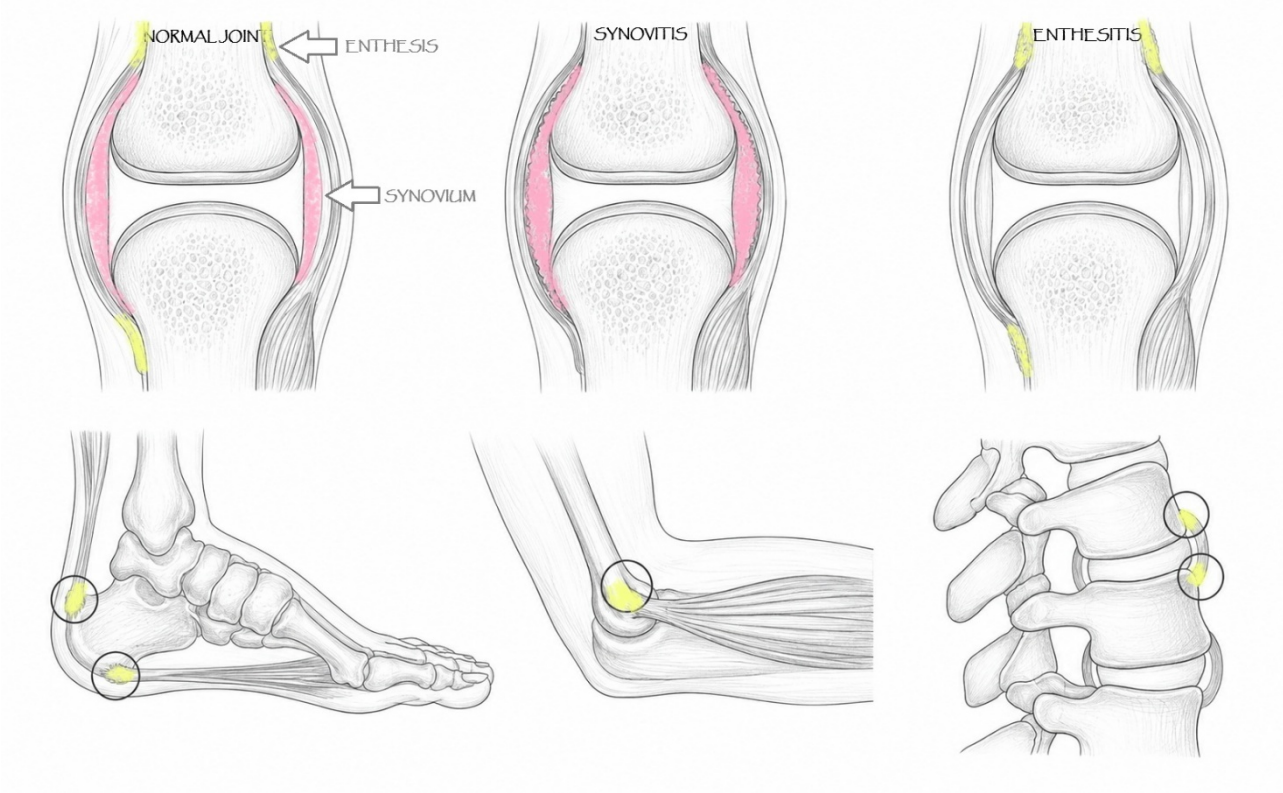
According to a paper by Sajjan Shenoy and Amita Aggarwal, ultrasound can identify subclinical enthesitis and shows high concordance (89%) with clinical findings. [23]

3. Enthesitis

3.1 General information

The term enthesis derives from Greek word for insertion, and in medical context, the term enthesitis is used to describe the inflammation around the area where the tendons and ligaments attach to bony surface; this can happen either locally in periarticular sites or at distant sites, such as Achilles tendon, or the plantar fascia. It is essential to know how to differentiate enthesitis from synovitis. The two can exist independently but it is worth noting that, synovitis can also occur secondary to enthesitis. Underneath, schematic picture has been provided to help in this differentiation of enthesitis and synovitis (Figure 4.) [24]

Figure 4. Differentiation of enthesitis (locally and peripherally) and synovitis



Historically, enthesis has been thought of as a tiny solitary attachment site, before the hypothesis of an enthesitis organ concept, by Benjamin and McGonagle. Which proposed that the enthesis should be viewed as a functional unit formed by not only the entheses but also the adjacent fibrocartilage, bursae, fat pads, and nearby bone. [25]

This concept explained how mechanical stress at insertion sites could induce tissue microdamage and repair responses that triggered inflammatory activation in genetically susceptible individuals, due to the mechanical load being concentrated at and around the entheses themselves. This proposal positioned the enthesis as a primary site in SpA pathogenesis rather than a secondary target, as had been thought in the past. [25]

Complementing this, the synovio-entheseal complex (SEC) concept emphasizes the anatomical and functional continuity between entheses and adjacent synovial sites. [25]

It noted a few differences between the two organs; entheses being more susceptible to mechanical microdamage, while the adjacent synovium was regarded as more immunologically reactive and prone to inflammation. Thus, the SEC hypothesis corroborates with the concept of enthesis as an organ concept, the enthesis being the potential 'initiator' through trauma, and the adjacent synovium escalating and sustaining the inflammation. [25]

Together, these two concepts explain why SpA often presents with both enthesitis and synovitis, and why enthesitis is considered a key initiating and organizing lesion in the disease process rather than an isolated structural abnormality. [25]

3.2 Pathophysiology

Enthesitis can be a symptom of multitude of diseases, many of them under the classifications, such as SpA, but they can also develop from repeated mechanical stress, even in healthy people. Common examples include "tennis elbow" and "golfer's elbow," which manifest as isolated enthesitis, due to overuse, with obesity further increasing mechanical load and susceptibility of the enthesis to inflammation. In cases of enthesitis in healthy people it is worth noting that the affected enthesis is typically singular, the scope of inflammation involving also the body of tendon, and the condition resolves spontaneously.[24]

There is no clear evidence that enthesitis in PsA or other SpA differs fundamentally from mechanically induced enthesitis. However, it is hypothesized that patients with PsA or SpA may have a lower threshold for inflammation, so enthesitis can develop with minimal or normal mechanical stress, as if the tissue overreacts to minor strain.[24]

Possible causes for this lower threshold for inflammation include genetic factors (MHC class I, IL23R variants) that boost immune activation, and impaired epithelial barriers in psoriasis or colitis that increase microbial exposure and sustain inflammation.[24]

3.3. Diagnosis

3.3.1. Clinical findings

In 2016, Ari Polachek and his team conducted a study, in which they analyzed >800 patients with PsA. They defined enthesitis as a sensation of pain at a specific tendon insertion sites. In their review of the patients they concluded that clinical enthesitis was frequently observed, affecting approximately 35% of PsA patients, and typically involving one to two sites simultaneously, the

most common of these sites being, the insertions of Achilles tendon, plantar fascia and lateral epicondyles. They also noted that enthesitis was associated with higher disease activity and increased pain perception. [26][24]

As we have discussed earlier, enthesitis can also appear without symptoms and it is hypothesized by Georg Schett and his colleagues in their paper that the prevalence of enthesitis in PsA patients might be higher, due to two factors: [24]

1) The multitude of entheseal sites in the human body when considering only the small sample taken into account on Polachek's study (the earlier MRI studies conducted by D McGonagle and his team supporting this hypothesis, their studies revealing enthesitis in the imaging studies, excluded by the clinical definition of arthritis. [27][24]

2) Using imaging instead of physical examination reveals enthesitis in a much higher proportion of patients, affecting about 70% of those with PsA. [28]

Table 4. Comparison of enthesitis distribution in SpA

	Patellar ligament	Achilles tendon insertion	Quadriceps tendon	Plantar fascia	Spinal ligament insertions	Annulus fibrosus insertions	Vertebral entheses	Midfoot entheses
Psoriatic Arthritis (PsA)								
Ankylosing Spondylitis (AS)								
Reactive Arthritis (ReA)								
IBD-associated Arthritis								
Enthesitis related arthritis (ERA)								

Before moving towards the explanation of enthesitis indexes, I have provided a table here, for the differentiation of SpA clinical diagnoses, comparing them by their most common enthesitis locations. For the information on PsA and AS, the knowledge has already been provided in the earlier chapters, but for the diagnoses, ReA, IBD-associated enthesitis and ERA, supplementary source has been used. In the table, green highlights the more common sites involved. [29]

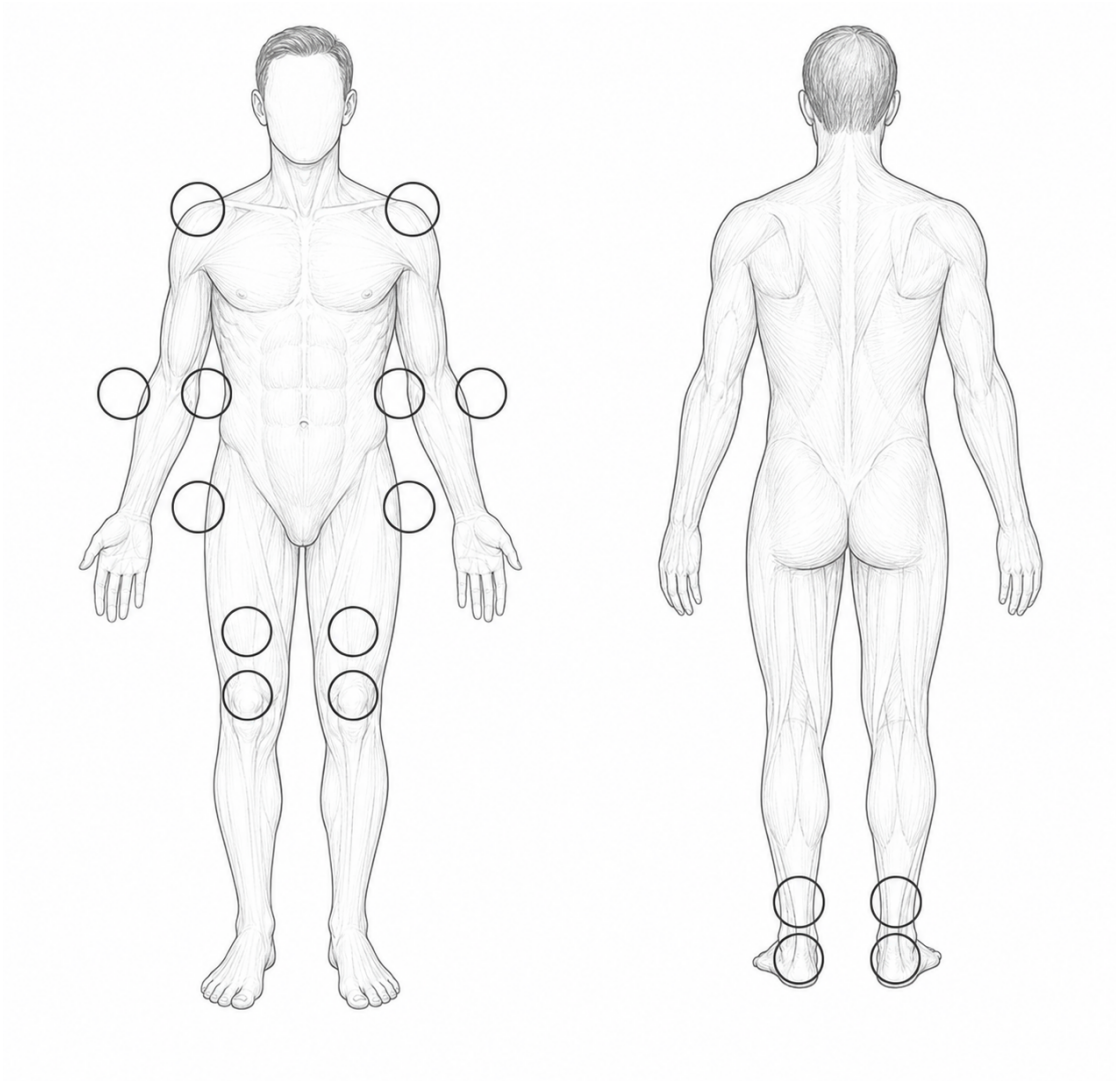
3.3.2 Indices

Traditionally, enthesitis is still diagnosed clinically, but as we can see through the hypothesized pitfalls above, the diagnosis through only clinical examination is far from perfect. One of the notable problems being that tender tendon insertion sites are hard to distinguish from the myofascial pain of FM. However, there are a few clinical adjuvants that have been developed to help in this diagnosis, The spondyloarthritis Research Consortium of Canada (SPARCC) index, The Leeds enthesitis index (LEI) and Maastricht ankylosing spondylitis enthesitis score (MASES). [30]

3.3.2A SPARCC index

The SPARCC index was developed by W P Maksymowych and his team in the year 2009. They demonstrated that a 16-site enthesitis index is practical to use and produces consistent, reproducible results. Underneath a picture is attached, embodying these 16 locations (Figure 5.) [31]

Figure 5. The 16 assessment sites of SPARC index



3.3.2B LEI

The LEI index was developed by Paul J. Healy and Philip S. Helliwell, in 2008, using data they gathered from using Mander Enthesitis Index (MEI), the Maastricht Ankylosing Spondylitis Enthesitis Score, The Major Index and the Gladman index, assessing the treatment regimen with disease-modifying drugs used on twenty-eight patients ailed with PsA for a length of six months. [32]

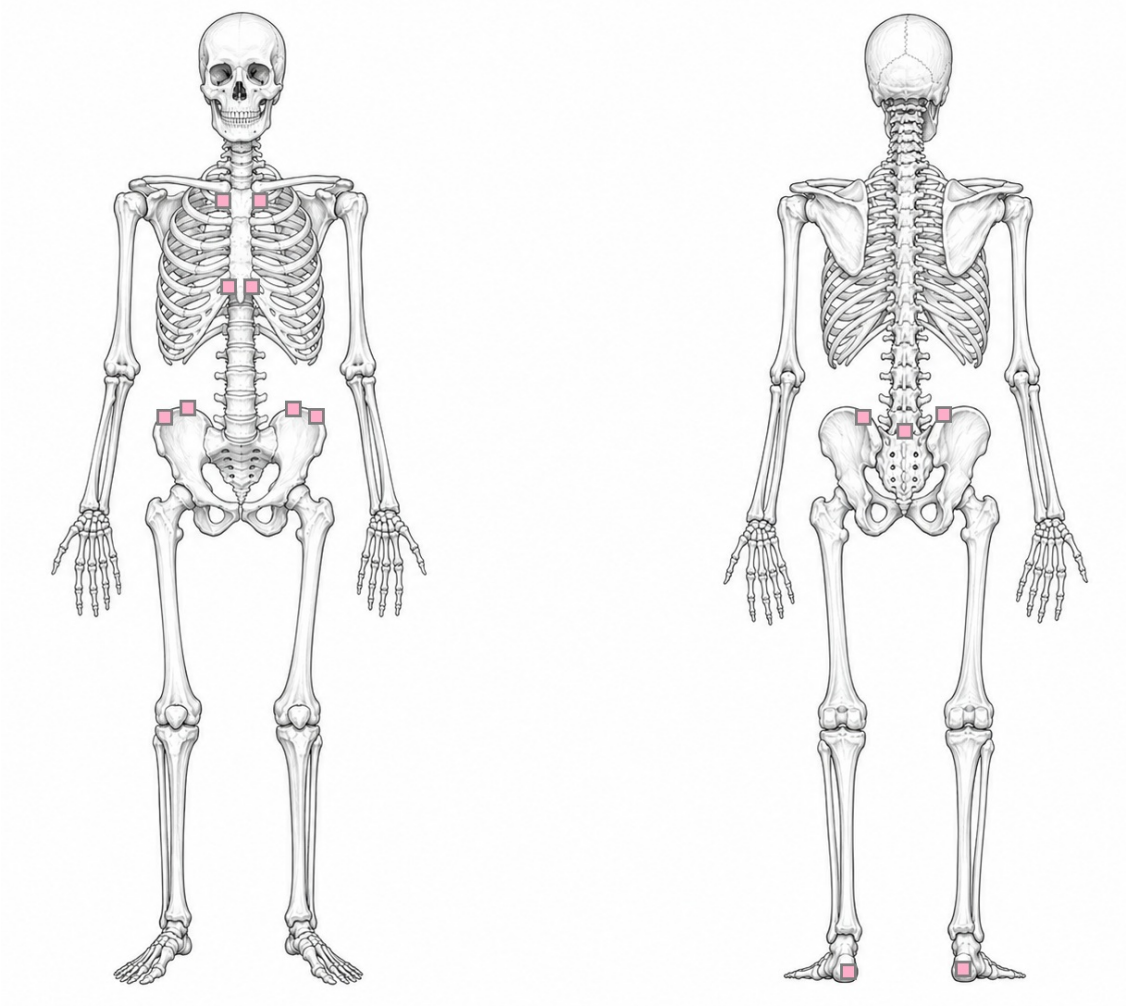
Their new index was deemed to consist of six entheseal sites, these being, the right and left Achilles insertion sites, medial femoral condyles and lateral epicondyles of humeri. During this construction of their individual scoring system, they found out that, MEI, LEI and Major index were most effective in differentiating patients with active disease, and out of those the LEI was the most likely to identify the majority of patients with active enthesitis [32]

Their results from comparing the multitude of indexes showed that LEI was at least in par with the other indexes, and most likely superior in some aspects. One of its superiorities being the ease of use, with only six sites for the physician to evaluate, when compared for example with the sixteen of SPARCC index, and the sites being anatomically easy to identify, making the training of competent physicians fairly easy. [32]

3.3.2C MASES

The MASES index was developed by L. Heuf-Dorenbosch and his colleagues in their 2003 paper. In their study, they assessed the MEI index and decided that reducing the number of assessed entheses from 66 (MEI) to 13 and removing pain-intensity grading (MEI) led to the development of a more practical index, MASES. Underneath a picture of the entheseal sites in question is applied from their paper on the subject. [33]

Figure 6. The 13 assessment sites of MASES index



3.3.2.D Comparison of indexes (and other scales)

As already discussed multiple times above, why enthesitis is such a crucial part of the diagnosis of Spondyloarthropathies, is the fact that it is associated with harsher outcomes later, for example with higher disease activity, increased disability and in general a poorer quality of life within the sphere of spondyloarthropathy influenced patients. [34]

In a paper published in 2019, Penelope Esther Palominos and her colleagues, set out to compare the three most commonly used scoring systems (MASES, SPARCC, LEI). 204 patients were included in their study, 71.1% fulfilling the ASAS criteria for axial SpA, and 28.9% fulfilling the criteria for peripheral SpA [34].

They found out that, in their sample, MASES performed slightly better than the other two indexes, when considering the disease activity and function in daily life, in other words, the MASES index seemed to reflect patients' condition slightly more accurately compared to SPARCC and LEI. [34]

They also noticed in their study the absence of correlation between enthesitis and inflammatory blood markers (e.g., CRP/ESR) reduces the correlation between the enthesitis indices and ASDAS, or Ankylosing Spondylitis Disease Activity Score, because ASDAS includes inflammatory markers. This lack of correlation has also been noted in earlier studies. And due to this, the team hypothesized that the clinical entheseal scores are measuring more pain than inflammation itself. As an answer to this problem they suggested that, a study could be conducted on the correlation between inflammatory markers (such as CRP, ESR, thrombocytes and leukocytes) and more objective findings of inflammation on imaging modalities (such as, ultrasound or MRI). [34]

They also hypothesized on this slight superiority of MASES index, by the fact that the index in question evaluates enthesis with more axial distribution, when compared with LEI and SPARCC indexes. [34]

Now that the individual indices have been outlined, the following discussion will draw on the study by Raquel Ena Maria Granados and colleagues as the basis for comparing the different enthesitis indices. [35]

The aim of the study was to determine whether the number of patients with at least one enthesitis differs between the three common Spondyloarthritis subtypes (Axial SpA, peripheral SpA and psoriatic arthritis) depending on the index used, and to assess how well the indices (SPARCC, LEI, MASES and MEI) agree in identifying patients with enthesitis. [35]

A total of 4185 patients (2719 Axial SpA, 433 peripheral SpA and 1033 Psoriatic Arthritis) were included in the study.[35]

They found out that MEI and MASES indexes seemed to excel in assessing enthesitis in axial spondyloarthropathies, whereas MEI and SPARCC appeared best in the enthesitis of psoriatic arthritis and peripheral spondyloarthropathies. [35]

They also found out that, in their whole study population, and especially in axial SpA, the most frequent enthesitis sites were the lumbar and thoracic spinous processes, followed by the Achilles tendon insertion. They also noted, that a previous study by AJ Mathew had dissimilar results (the most prevalent location being the Achilles tendon, and no mention of lumbar enthesitis) and hypothesized that this might be due to the use of SPARCC index, it lacking the axial locations completely. [35]

Among the Psoriatic Arthritis population of the study, the most common enthesitis site in this study was the Achilles tendon, similar to previous studies, conducted using the SPARCC index. However,

this study also found frequent involvement of the lumbar spinous processes and medial femoral condyle because due to the fact that, MEI evaluates more enthesis locations than SPARCC. [35]

In their findings, they noted, that while LEI, was the easiest and most usable in clinical practise, it also detected fewer patients with at least one enthesitis, as it assesses only six sites. While LEI is easier to use in clinical practice, MEI, MASES, and SPARCC are generally preferred.[35]

Their findings might not have uses in clinical practice, but they proposed that, their results could be helpful in clinical trials or observational studies concerning enthesitis and its treatment regimen and recommended that MASES or SPARCC indexes would be used in accordance with the evaluated disease as noted above. However, it is also worth noting that MEI, with its 66 entheseal locations also fared well in the study, but due to the long time its evaluation takes, it is not recommendable to use in trials or future studies. [35]

They also noted some of the limitations of their study, those being in accordance with the used perSpA database, the large number of axSpA patients when compared with the other two categories, the lack of objective clarification of the disease, such as ultrasound or MRI and the overlapping of FM tender points and those of the MASES index. [35]

Table 5. Comparison of enthesitis indices

Index	Number of inspected points	Advantages	Disadvantages
SPARCC	16 sites	Practical to use; consistent and reproducible results; wide enthesis coverage including axial sites	More extensive than simpler indices; takes longer than LEI
LEI	6 sites	Very easy and quick to use; anatomically easy to identify sites; effective at identifying active enthesitis	Limited number of sites leads to fewer detected cases; narrower coverage

MASES	13 sites	More practical than MEI (reduced from 66 to 13 sites); improved usability; good axial assessment	Possible overlap with fibromyalgia tender points; lacks pain-intensity grading; limited full-body coverage

Another elaborate paper was submitted by Styliani Tsiami and her team, in which they set out to study the effectiveness of patient-reported outcomes (PROs) that have been developed for SpA patients (BASDAI, ASDAS-CRP, DAPSA) [36]

These PROs were evaluated between three groups of patients:

1) Patients with primary FM without chronic inflammatory rheumatic disease
2) Patients with SpA without concomitant FM
3) Patients with SpA with concomitant FM

They found out that, patients with primary FM had significantly higher scores in nearly all assessments compared with the patients with either axSpA or PsA (except for ASDAS-CRP, the difference of which was not statistically significant). [36]

Their results confirmed FM to be an important comorbidity in axSpA and PsA, and showed that current PROs should be interpreted differently (in case of axSpA and PsA) depending on whether concomitant FM is present or not. [36]

Patients having SpA with concomitant FM had high scores on fibromyalgia specific questionnaires, but patients without concomitant FM did not. [36]

Because FM-related widespread pain usually does not respond to anti-inflammatory treatment, this comorbidity should be identified before starting therapy in patients with diffuse pain but no clear inflammation. [36]

Their ultrasound studies showed that PsA patients had more and different enthesis involvement than those with FM, but it is still unclear whether ultrasound can distinguish polyenthesitis from FM when both occur in the same patient. [36]

Their study was very intriguing to say the least, but alas, with insurmountable limitations, as the authors themselves noted; the sample size of axSpA and PsA combined, only presenting thirty individuals in total, which is clearly a hindrance for drawing any definite conclusions from the paper's findings. Nevertheless, there is yet hope, as only a tolerable sample size is needed for the affirmation of their findings. [36]

In a study done by Philip J. Mease and his team, they tested the performance of different indices in context of treatment of pSpA. [37]

They concluded that The LEI and SPARCC enthesitis indices showed better ability to distinguish disease and detect treatment response in peripheral SpA (compared to MASES), likely because they assess more peripheral sites.[37]

As in so many studies earlier, their shortcoming, alas, seemed to be the absence of objective confirmation of enthesitis, such as an mri or ultrasound. [37]

3.3.3 Imaging studies

3.3.3A X-Ray

As discussed earlier, the most affected site in patients with axSpA being the pelvic region, it is no wonder the sacroiliac joint is ofttimes imaged at the beginning of symptoms with the help of x-ray, it being widely accessible and practical to use. However, a key challenge in early disease is that, in most cases, it has not yet produced sufficient articular changes to be detected on plain radiographs alone. [38]

Typical findings of axSpA include among others, sclerosis, erosions and loss of joint space; that are later addressed to a more quantified form through contemporary software applications. The problem with this method however being that, in addition to the radiation exposure, the damage of the sacroiliac joint can be only seen on radiographs of sacroiliac joint multiple years after the start of symptoms. [38]

Enthesitis cannot be reliably diagnosed using conventional radiography, as X-rays are unable to visualize active inflammatory changes at the entheses. At most, radiographs may demonstrate late structural changes such as enthesophytes or calcifications, which are suggestive of chronic enthesopathy rather than active inflammation. Consequently, modern assessment of enthesitis relies primarily on clinical examination supported by ultrasound or magnetic resonance imaging. [39]

3.3.3B CT

Low-dose spinal CT is more sensitive than X-rays for detecting structural changes in axSpA patients, but its role in diagnosing axSpA is not yet fully understood or defined. [38]

At the moment, CT scans are mostly used for the assessment of structural lesions such as joint erosions and ankylosis, which are integral for the differential diagnosis of axSpA. However, in the assessment of enthesitis, CT is of little use, as it can mostly visualize changes in bony structures but not in soft tissues such as entheses. [38]

3.3.3C Ultrasound

Of all common imaging modalities, ultrasound is one of the most valuable tools for detecting enthesitis, even being comparable to MRI. These claims are supported by several studies, as will be shown below.

Ultrasound studies show that PsA patients have more and different enthesis involvement than those with FM, but it is still unclear whether ultrasound can distinguish polyenthesitis from FM when both occur in the same patient.[35]

In a 2021 study by Antonio Marchesoni and his team they set out to assess whether ultrasound of entheses could differentiate between pain caused by PsA enthesitis and pain in the area of entheses caused by FM. The patients (PsA n=140 & FM n=51) included in their study underwent clinical assessment, gray-scale (B-mode) and power Doppler ultrasound examination of the affected sites. [40]

They found out that, ultrasound abnormalities were more common in PsA than in FM in both gray-scale and power Doppler modes. However, many FM patients also showed changes (≈75% on US and ≈35% with Doppler signal). [40]

They figured that, the presence of some ultrasound entheseal lesions alone does not clearly distinguish PsA from FM. However, evaluating the number, location, and type of lesions helps better identify PsA. More gray scale ultrasound abnormalities increased the likelihood of PsA (best cut-off ≈3.5). Achilles and proximal patellar tendon involvement and ≥2 gray scale lesions at these sites leaned more towards the diagnosis of PsA. By limiting the analysis to three more common sites (Achilles, quadriceps and patellar tendon) and including only the three most common lesions on ultrasound (hypoechogenicity, thickening and enthesophyte), they found out that evaluating these sites was the most helpful in distinguishing between PsA and FM. [40]

The aforementioned three common sites and three common regions they termed clusters, and at least to the authors' knowledge it was the first study done concerning the division in clusters and taking into account that only minority of their sample was includable in this category more study on the subject is still needed. [40]

They concluded that, ultrasound of entheses can be helpful in distinguishing PsA enthesitis from that of widespread pain in FM. A higher number, location, and type of lesions increase diagnostic accuracy, but ultrasound should always be interpreted together with clinical evaluation. They also prefaced that FM may coexist with PsA, making the studying of the subject troubled at best. [39]

Andrea Di Matteo and his team also conducted a multicentre study with ultrasound and clinical examinations of the entheses of lower limbs with 413 axial PsA and psoriatic arthritis patients and 282 osteoarthritis and FM patients. [41]

They found out that among the lower limb entheses, only significant association with said conditions, was with the Achilles tendon. The other important key finding was that, ultrasound could help distinguish SpA-related enthesitis from other causes of entheseal damage, such as mechanical enthesitis. [41]

In their paper, Diogo E. Almeida and Richard J. Wakefield raise some concerns regarding the OMERACT group developed standardized definitions and scoring of ultrasound of entheses. These standardized definitions being already discussed earlier (like tendon thickening, hypoechogenicity, bone erosion, and power Doppler signal). [42]

They also commented on a recent study by Di Matteo and his team, concerning how reliably sonographers could apply these definitions to pre-captured US images and videos. They discovered that, Power doppler and bone erosions were rated reliably but tendon thickening and hypoechogenicity were less consistent, especially in mild cases. They noted that the variability could be due to a multitude of factors e.g., differences in the reviewer's experience, how images were captured, patient's age, sex or BMI. [42]

Some issues also noted were the unclear definitions on the thickening of entheses and also the non-consideration of context, as ultrasound findings can occur so in chronic as in non-inflammatory conditions. In their opinion ultrasound was a great tool for enthesis examination but the definitions need some revision as they stand currently. [42]

Concerning a more condensed from of information, I found a great review by Maria-Antonietta D'Agostino from 2018, and underneath I'm going to put a few bullet points concerning the subject from it (some points have been omitted as of newer studies undermining some of the findings): [43]

- Enthesitis is an important feature for diagnosis and monitoring SpA and PsA
- Tenderness alone isn't a reliable indicator of inflammation (as has been pointed out frequently before)
- Enthesitis, even when asymptomatic can be detected via ultrasound
- Ultrasound can aid with the diagnosis and differential diagnosis of SpA/PsA/FM
- Ultrasound findings do not always correlate with pain, physical exam or imflammatory markers [40]

And lastly, to sum up our part in ultrasound and enthesitis (and as a small reminder), I'm turning towards a study conducted by Ari Polachek and his team. [44]

In their study of 156 PsA patients from 2021, they set out to investigate whether ultrasound could be used to evaluate disease activity in PsA patients with concomitant FM. They discovered that among their group of patients with PsA and concomitant FM (n=42), the patients in question had higher disease severity index scores but the total ultrasound scores were similar between the two study groups. So, to sum up, FM was linked to higher clinical scores but not to higher ultrasound findings [44]

The ultrasound scores remarkably seemed to correlate with the disease activity indices only in PsA without FM group. [44]

3.3.3D MRI

As already discussed earlier, the inflammation at entheseal sites can be seen even before clinical symptoms by the method of imaging studies such as ultrasound or MRI.

In 2022, Zikang Guo and his team set out to evaluate the distribution and diagnostic significance of peripheral enthesitis detected by whole-body MRI in axial spondyloarthritis and to assess the usefulness of the peripheral enthesitis score in axSpA evaluation. [45]

They studied 110 people, sixty of whom were axSpA patients, and fifty of chronic lower back pain controls. All the participants underwent a whole-body MRI (WBMRI) and 47 peripheral entheses were assessed (scored between 0-188), and it was discovered that WBMRI identified enthesitis in 78.3% of axial SpA patients – the pelvic region being the most affected location (51.6%) and the foot region being the least (18.3%) – and in 32% of controls. [45]

Their findings indicate that mri can be a usable tool in the diagnosis of SpA, but it has its limitations as the diagnostic value varies by location, specificity being highest in the anterior chest

wall, 100%. (the others: foot (98%), knee (92%), pelvis (90%), and shoulder (84%)). Therefore, detecting inflammation for example in the anterior chest wall can greatly increase diagnostic confidence, as this area is rarely affected by mechanical stress in healthy individuals.[45]

Due to the fact that the shoulder was most affected by degeneration and athletic injuries, they deemed it essential to take into account the patient's motor history for the definitive diagnosis, as can also be seen with the lowest specificity of 84% on their findings.[45]

Overall, the study showed that peripheral enthesitis has low sensitivity but high specificity for diagnosing axSpA, and that practicality of WBMRI as a tool for axSpA detection was adequate, but had some flaws, and larger sample-sizes are needed to confirm their results. They also hypothesized that enthesis scoring may provide a more precise evaluation and diagnosis of axSpA than simply counting affected sites.[45]

MRI of the sacroiliac joints is recommended when clinical suspicion is high but X-rays are inconclusive. Standard protocol includes four sequences in two planes to assess inflammation, structural damage, and the bone–cartilage interface: T1-weighted, STIR/T2 with fat suppression, cartilage-sensitive, and a second T2 fat-suppressed semi-axial sequence. It is worth noting that, excessive reliance on imaging findings can lead to overdiagnosis of the condition, and also that, the absence of inflammation does not exclude the diagnosis. [38]

It is worth noting that imaging modalities like scintigraphy, ultrasound of the sacroiliac joints or PET scans are not recommended regimen in the diagnosis of axSpA [38]

I also found a literary review of collected articles by Olena Zimba and her team. They found out that, if X-rays do not show sacroiliitis but axSpA is still suspected, MRI of the sacroiliac joints is recommended. Adding spinal MRI usually does not improve diagnosis much. MRI is valuable because it can detect early inflammation, such as bone marrow edema, before structural damage and can also identify structural changes accurately. [46]

If readers question the inclusion of sacroiliac joints in the context of enthesitis, this is justified by their shared structural and biomechanical characteristics with fibrocartilaginous entheses. In particular, the sacroiliac joints exhibit features consistent with those of entheses and are therefore, in certain conceptual frameworks, regarded as a functional or "moving" enthesis within the broader enthesis organ concept.. [47]

They also stated that, MRI use in routine, even though being highly sensitive in detecting inflammation, is not recommended, as its added value over other tools is unclear. MRI scoring systems are mainly used in research to assess treatment effectiveness in clinical trials. [46]

A paper by Raphaelle Meunier, sought to also evaluate MRI performance in SpA. The patients (n=145) in this single-center study were followed for seven years in total, but apart from the earlier studies, they also tested the value of adding gadolinium injection for the diagnostics. [48]

Their key findings were thus, MRI might diagnose SpA more accurately than thought before, even when compared with that of a long-term rheumatologist's diagnosis. Secondly, the gadolinium contrast can in fact improve MRI detection, especially for purely entheseal diseases. They also showed that gadolinium contrast injection does not improve the detection of bone abnormalities, such as edema or osteitis. [48]

They recommended that gadolinium should be considered when SpA suspicion is high, and the initial non-contrast MRI is normal or unclear, as they found out that, the injection increased sensitivity of diagnosis without significantly reducing specificity [48]

It is worth noting though that the study was conducted in "*a department with specialization in musculoskeletal imaging",* which might affect the results somewhat, when compared with the normal setting. [48]

3.3.4 Enthesitis scoring methods

Current enthesitis scoring systems mainly assess pain rather than directly measuring inflammation at entheseal sites, but there is a assessment system that measures both inflammation and structural damage in PsA. This MRI-based scoring system, named PsAMRIS or Psoriatic Arthritis magnetic resonance imaging scoring system, has been developed by OMERACT (Outcome Measures in Rheumatology Clinical Trials), was developed for hands and assesses inflammation and damage in PsA. [49]

In a paper published in 2020, concerning the planning of a clinical trial on Achilles tendon imaging, Xenofon Baraliakos and colleagues proposed the use of modified PsAMRIS method of MRI scoring, in their paper. [49]

In their modified method, they introduced additional parameters that more appropriately represented the heel area and evaluated quantified bone oedema and location of bone erosion. All heel MRIs were assessed for changes at the enthesis, including tendinitis, bone edema, erosions, bursitis, and surrounding inflammation, which were followed up till 52 weeks. [49]

The minds behind the ACHILLES trial saw the limitations of current scoring systems, like LEI, MASES, and SPARCC, highlighting the factors such as, varying specificity, validity and reliability.

They noted, that in each index the locations and numerate of entheseal locations vary but in each one pain and tenderness is still applied in a binary fashion, with either *pain* or *no pain*. [49]

They stressed that, tenderness at entheses may be misleading due to FM or mechanical stress, as many points overlap with FM tender sites. Imaging is generally more sensitive and specific for detecting true enthesitis when compared with the clinical examination. [49]

After they had already conducted their study with modified PsAMRIS score, OMERACT published HEMRIS, a heel enthesitis scoring system. ACHILLES assessed most HEMRIS parameters, except tendon thickening and bone spurs, with also assessing the inflammatory and structural properties. Both of the systems use an evaluation scale ranging from 0 to 3, or none, mild, moderate, severe, the difference being subdivision of category 1 into a and b (based on oedema length ≤/> 0.5 cm) in ACHILLES scoring. [49]

It is worth noting that the ACHILLES study has some limitations, as no contrast agent was used and when considering bone erosions applying PsAMRIS to the calcaneus is limited because its larger size makes high-grade bone erosions rare, reducing the score's sensitivity. Also, as of today the results of this upcoming large scale study is not publicly available. [49]

4. Discussion

4.1 Summary of Findings

The differential diagnosis between FM and widespread enthesitis in SpA represents a substantial clinical challenge due to the overlap in symptoms and the absence of specific laboratory markers or radiological features. Both of these conditions may present with diffuse musculoskeletal pain, tenderness at multiple anatomical locations, fatigue, impaired daily functioning, and reduced quality of life but they differ in their pathogenesis significantly. Fibromyalgia is largely considered a disorder of central sensitization, characterized by altered pain processing within the central nervous system, without clear peripheral inflammatory pathology. In contrast, enthesitis in SpA is driven by peripheral inflammation at tendon and ligament insertion sites, involving immune-mediated mechanisms and creating changes perceivable with imaging methods

It is also worth noting that, inflammatory markers such as CRP and ESR often support the presence of active SpA but they might be normal in cases of isolated enthesitis. In contrast, usually CRP and ESR are not elevated in FM, making them the only currently available applicable biomarker in differentiating SpA from FM.

Another potentially useful approach in separating FM from SpA, is to search for certain distinguishing features of specific SpA, such as psoriatic rash, uveitis, associated IBD symptoms, morning stiffness, past urogenital- or enteric infections etc.

As demonstrated throughout this review, distinguishing (inflammatory) enthesitis from centralized pain syndromes, such as, FM is essential, as delayed recognition of SpA may lead to structural progression, disability, and poorer long-term outcomes for the patient.

The literature reviewed in this thesis supports the concept that enthesitis is a central pathological feature of many SpA subtypes. Modern concepts such as the “enthesis organ” and “synovio-entheseal complex” have broadened understanding of the disease process by emphasizing the interaction between mechanical stress, inflammation, adjacent synovial structures, and genetic susceptibility. Whereas FM appears to arise predominantly from altered central pain processing and sensitization mechanisms.

One of the most important findings emerging from this review is that clinical examination alone is often insufficient for distinguishing widespread enthesitis from FM. Tender entheseal sites may overlap considerably with FM tender points. Another problem with the indices being their subjective nature. Multiple studies reviewed in this thesis suggested that these indices might measure pain sensitivity rather than true inflammatory activity alone. This becomes especially problematic in patients with concomitant FM and SpA, where disease activity scores may become falsely elevated.

Imaging modalities therefore have a particularly important role in the differential diagnostic process. Among the available radiological techniques, ultrasound and MRI demonstrated the greatest utility in detecting inflammatory entheseal changes.

Ultrasound was shown to identify structural and inflammatory abnormalities more effectively than clinical examination alone, particularly when gray-scale findings were combined with Power Doppler assessment. However, ultrasound findings are not entirely specific, as entheseal abnormalities may also occur as a consequence of mechanical strain due to obesity, aging or physical activity, and considerable proportion of fibromyalgia patients may also exhibit ultrasound abnormalities, thereby limiting the diagnostic specificity when used without other available tools.

MRI, especially whole-body MRI demonstrated high sensitivity for detecting early inflammatory lesions and bone marrow edema before the structural changes could be seen with radiographic imaging. But alas, it carries many limitations; cost, accessibility, assessment variability. It has to be

also taken into consideration, that if imaging modalities such as MRI were taken as a screening tool, it might lead to multitude of ‘unnecessary diagnoses’, in addition to the substantial costs.

The reviewed studies also highlighted the complexity of placing a diagnosis, as FM could be presented concomitant to SpA. Several studies showed that patients with both conditions often report higher disease activity and symptom burden despite similar imaging findings compared with patients plagued by SpA alone. This further increases the uncertainty in the application of currently used indices

Another important finding of this review is that there are no universally accepted objective standards for assessment of enthesitis. Although ultrasound and MRI are useful, a comprehensive clinical examination and exclusion of other diagnoses is still needed, thereby unnecessarily prolonging the time required to reach an accurate diagnosis and initiate appropriate treatment. Indices, such as, LEI, MASES and SPARCC are helpful in reducing this time from symptoms to diagnosis, but al of them still have their individual shortcomings.

4.2 Conclusions

The differentiation between FM and widespread enthesitis in SpA remains clinically demanding because both conditions share overlapping symptoms, the most noteworthy being, widespread pain. Reliance solely on clinical examination may lead to diagnostic inaccuracies, especially in patients with concomitant FM and SpA.

Enthesitis represents a key pathological and diagnostic component of SpA, but current clinical enthesitis indices are limited by their subjective nature and overlap with FM tender points.

Among the currently available imaging techniques, ultrasound and MRI appear to be the most valuable tools for identifying inflammatory entheseal changes. Ultrasound is widely available and cost-effective and can detect both structural and inflammatory changes, while MRI was deemed better in the detection of early and axial inflammation. However, neither alone is sufficient for diagnosis.

The reviewed literature also shows that concomitant FM significantly complicates the evaluation of disease activity in SpA patients, as they might often report more severe symptoms despite similar objective findings (compared to patients with SpA alone). This consequently might lead to overtreatment or misinterpretation of the effectiveness of current treatment regimen.

Overall, the evidence suggests that the most reliable diagnostic approach is multidisciplinary and multimodal, integrating clinical examination, patient history, laboratory investigations, imaging modalities, and awareness of centralized pain syndromes. Early and accurate differentiation between FM and inflammatory enthesitis remains essential for selecting appropriate treatment strategies and improving long-term patient outcomes.

4.3 Recommendations and Future Directions

Future studies should focus on developing more objective and standardized methods for evaluating enthesitis.

Larger studies evaluating patients with concomitant SpA and FM are also necessary, as current literature remains limited by relatively small sample.

Further investigation into whole-body MRI and advanced ultrasound techniques may also prove beneficial, particularly regarding early detection of subclinical enthesitis.

Additionally, future research should aim to identify potential laboratory biomarkers capable of objectively distinguishing inflammatory enthesitis from centralized pain disorders such as FM.

From a clinical perspective, physicians should remain cautious when interpreting widespread pain and tenderness in SpA patients, particularly when objective inflammatory findings are limited.

Finally, greater emphasis should be placed on interdisciplinary collaboration between rheumatologists, radiologists, physiotherapists, as management of these complex patient groups often requires a broader biopsychosocial and multimodal diagnostic approach.

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