Enthesitis In Spondyloarthritis: Role Of Musculoskeletal Ultrasound

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Eiman Soliman[1]

[1]Internal Medicine, Rheumatology and Clinical Immunology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
solimaneiman@yahoo.com

Rizwan Rajak[2]

[2]Rheumatology Department, Croydon University Hospital, London, UK.

***Abstract*— Aim:**

The aim of this work is to study and research literature over the last 20 years on the relation between enthesitis and SpA, assessment methods of enthesitis, focusing on the role of MSUS and its available scores. The study will highlight the implication of detection of enthesitis on the diagnosis and follow up of SpA and the effect of its presence on the choice of therapy.

Methods:

Research aims were met through extensive review of relevant literature on enthesitis and musculoskeletal ultrasound.

Results:

The advances in the imaging modalities especially musculoskeletal ultrasound has much improved the assessment of enthesitis. The accuracy of the ultrasound machines and the increased experiences in their application has resulted in better performance of MSUS than clinical examination with discrepancy between their results. MSUS assessment scores still an area of unmet need. The lack of consensus in MSUS definition of the basic pathologic lesions including enthesitis was a drawback against homogeneity between studies. The OMERACT final standardization of the definition of MSUS elementary lesions is an important step towards achieving this.

Conclusion:

From the current search of literature, MSUS detected enthesitis can be a holistic tool for the management of SpA, from enabling early accurate diagnosis, to aiding the choice of therapy and assessment of disease progression and response to therapy.

Keywords*— *Enhesis- Enthesitis- Spondyloarthritis- Ultrasound- Imaging

Introduction (Heading 1) Although it is well known that enthesitis is the hallmark of SpA, the exact mechanisms for its pathogenesis and its relation particularly to SpA were not clearly revealed. Over the past few years and with the start of the era of biologics great interest was focused on disease pathogenesis, consequently on enthesitis. With that better understanding, enthesitis was still attaining this central role.

Several definitions have been proposed to define enthesis and enthesitis. Initially enthesis referred to the site of attachment of the tendon, ligament or joint capsule into the bone. Later, more precise definitions including the histologic features and boundaries of the enthesis were identified. More recently, enthesis is recognized as a part of a larger anatomical organ 'the enthesis organ concept' [1]. The enthesis organ constitute the fibrocartilage, bursa, fat pad and the enthesis itself. The synovio-entheseal complex (SEC) and the 'functional enthesis' concepts are complimentary to the enthesis organ concept and have important implications for the understanding of SpA pathogenesis [1].

Mechanisms and pathogenesis of enthesitis:

Over the past years, several mechanisms of enthesitis development have been postulated. These included the mechanical stress theory, the autoimmune theory, the infectious theory, inflammatory and molecular theories. Each of these different theories or mechanisms does not exclude the others, but all were suggested to be acting together to end by triggering enthesitis [2].

Schett, G., and colleagues [3] have recently proposed a mechanistic enthesitis disease concept that highlighted the key pathways for enthesitis and the interplay between the different proposed pathogenic mechanisms.

Assessment of enthesitis:

Enthesitis is proved to be an early feature and sometimes maybe the only feature of SpA especially PsA. Despite this, enthesitis is underestimated and frequently overlooked by doctors and even patients themselves, or misinterpreted [4].

Clinically enthesitis is diagnosed by eliciting tenderness on applying pressure over the enthesis with the thumb until the nail bed blanches. Sometimes, it may be associated with swelling caused by soft tissue proliferation and/or new bone formation (enthesophyte). Clinically detected enthesitis is non-specific, as it may be the result of mechanical microdamage, fibromyalgia or hyperalgesia [5]. Furthermore, some enthesis cannot be accessible to clinical examination as those of the cruciate ligaments. Nevertheless, several clinical indices for enthesitis assessment have been developed. Three tools were developed for AS, Mander enthesitis

index (MEI) [6], Major enthesitis index [7] and Maastricht ankylosing spondylitis enthesitis score (MASES) [8].

What makes things more complicated, is that the absence of local tenderness does not exclude the presence of enthesitis. It was estimated that the prevalence of clinical enthesitis in PsA is 30-50%, while the actual burden of enthesitis is more than what is reported. Consequently, the role of imaging has gained increasing interest as it may reflect exactly what the fingers can't see.

Imaging Assessment of Enthesitis:

Conventional Radiography

The application of imaging in the assessment of enthesitis revealed an underestimated prevalence of enthesitis. Until 1990, plain radiography was the only used modality for assessing enthesitis. Changes detected by radiography were in the form of periarticular osteopenia caused by inflammation of the bone marrow, calcification, new bone formation at the enthesis, cortical bone irregularities and erosions.

High-resolution Peripheral Quantitative CT

High-resolution peripheral quantitative CT (HR-pQCT) was recently used as an imaging tool allowing high-quality analysis of the bone structural lesions in enthesitis, in particularly the quantification of new bone formation in PsA. HR-pQCT use revealed new bone formation in psoriasis patients as an early sign of musculoskeletal involvement [9].

Magnetic Resonance Imaging (MRI)

McGonagle, D., [10]was the first to use MRI to study SpA and to confirm that enthesitis is a hallmark of SpA. The use of MRI enabled the detection of osteitis as a hallmark of inflammation in SpA. This was demonstrated in the axial fibrocartilaginous joints [11]. Furthermore, MRI on peripheral enthesis revealed the presence of extensive peri-entheseal osteitis in SpA and less extensive lesions in mechanical enthesitis [12].

The use of MRI was increasingly utilized especially in ankylosing spondylitis to reflect edema of the bone marrow and soft tissues of the enthesis. Although MRI is the imaging modality of choice for bone marrow edema, this finding is not specific for SpA, as it was reported in several diseases [13]. Furthermore, studies have reported its presence in healthy individuals and thus questioned its pathologic indication [14, 15]. It was also found that MRI presence of synovitis may mask the MRI features of enthesitis in the adjacent enthesis [16].

More recently, studies have examined the utility of whole-body MRI, by which thirty-five enthesis were examined based on seven clinical enthesis and scored accordingly. This modality has shown promise in the detection of subclinical axial and peripheral enthesitis in axial SpA and PsA patients [17].

Positron-Emission Tomography (PET)

Novel imaging using nuclear medicine, as conventional positron-emission tomography (PET) and PET/CT scan, is a recently researched tool for enthesitis. Results showed that PET/CT scans can detect accumulation of fluorodeoxyglucose at the entheses in SpA. Compared to MRI evaluation, PET/CT scanning may have sensitivity and specificity that are, at least, equivalent or superior to MRI in the SpA group [18].

Role of MSUS

US has the ability to detect all musculoskeletal changes of SpA, including enthesitis, synovitis, bursitis, tenosynovitis and cortical erosions. Thus, this imaging modality can help to differentiate between causes of local tenderness, whether due to underlying enthesitis or synovitis of the adjacent joint or absence of detectable pathology in hyperalgesia or fibromyalgia [19].

MSUS is sensitive to visualize early inflammatory changes as well as later structural ones.

In inflammatory arthritis, US features of synovitis, tenosynovitis and cortical erosions are similar, Whereas, US features of enthesitis differ in SpA than other inflammatory arthritis and non-inflammatory causes.

Appearance of enthesitis by US:

The first description of US features of enthesitis was in 1994 [20]. This was followed in 2002 by Balint et al [21]. Both studies were on the greyscale appearance of lower limb enthesis in SpA. While the first description of the power doppler enthesitis features was in 2003 by D'Agostino et al [22]. This was followed later by an increased interest in the use of US and power doppler to detect enthesitis.

Although the use of MSUS to assess enthesitis in SpA dates more than twenty years ago, there was a lack of consensus on which elementary lesions to assess and how to define their abnormality.

The most commonly elementary greyscale features of enthesitis were hypo-echogenicity, loss of fibrillar pattern, thickening of the tendon or ligament close to the enthesis, focal areas of calcification, enthesophytes, cortical irregularities, and erosions [23].

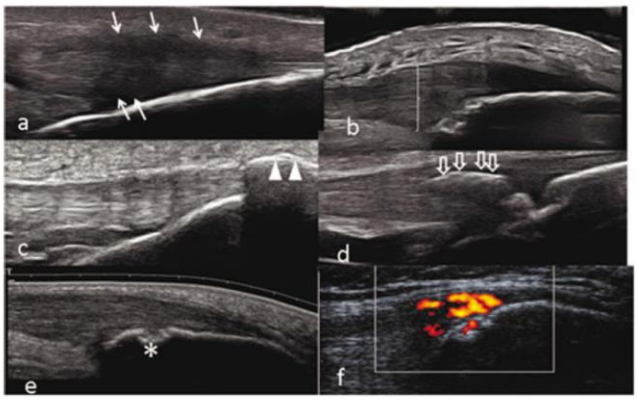
Aiming towards a consensus in defining enthesitis, the Outcome Measures In Rheumatology Clinical Trials (OMERACT) task force produced in 2005 the first consensus definitions of preliminary US pathologies [24]. The group defined enthesopathy instead of enthesitis as: "abnormally hypoechoic (loss of normal fibrillar architecture) and/or thickened tendon or ligament at its bony attachment (may occasionally contain hyperechoic foci consistent with calcification), seen in two perpendicular planes that may exhibit a doppler signal and/or bony changes including enthesophytes, erosions or irregularity" [24].

The appearance of enthesis by US reflects the corresponding pathologic changes in that area [2]. Inflammation causes tissue edema of the enthesis which appears as areas of hypo-echogenicity and leads to loss of the normal fibrillar structure of the distal tendon or ligament. Damage of the collagen fibers causing their breaking and unfolding results in the thickening of the enthesis. As a result of the healing process of the micro-damaged tissues, calcification may be detected. The stage of increased bone formation is reflected by the enthesophyte formation. Whereas erosions and cortical bone irregularities of the enthesis are consequences of the fibrocartilage pathology and damage. Finally, the increased power doppler signals result from the increased

vascularization of the enthesis and reflect the active inflammation and repair processes.

The lack of consensus in enthesis definition was highlighted in a systematic review which revealed the persistence of unclear definitions of the elementary features of enthesitis among the different published studies [23].

Consequently, a Delphi exercise was undertaken to define US-detected enthesitis and its core components in 2014 (figure 1) [25].



Figure(1):The elementary components are as follows: a, hypoechogenicity (white arrows indicate increased thickness with blurring of the tendon margins); b, increased thickness of tendon insertion (white line); c, enthesophyte (the step up of the bony prominence at the end of the normal bone contour is marked with white arrowheads); d, calcifications (the hyperechoic focus consistent with calcific deposit is marked by open arrows); e, bone erosion at the enthesis marked with an asterisk; and f, Doppler at enthesis 2 mm from the bone insertion [25].

Recently, in 2018 Balint et al, had evaluated the reliability of consensus-based definitions of US elementary components of enthesitis and the contribution of each lesion to defining and scoring enthesitis [26].

The panel defined six B-mode and two doppler mode elementary lesions and one combined B and doppler modes. All these lesions were checked at a zone of soft tissue 2 mm adjacent to the bone cortex based on the previous US definition of enthesis [27].

The included US lesions were hypo-echogenicity, increased thickness, calcification, enthesophytes, bone erosions, cortical bone irregularity and doppler signals at the enthesis, doppler signals outside the enthesis and the presence of adjacent bursitis (figure 2). There was an agreement on all elementary lesions to be included in the enthesitis definition except for bone irregularity, doppler signals outside the enthesis (which denotes tendinitis) and bursitis. Despite these latter lesions were not included in the enthesis definition, yet they are important to be reported during US scan of SpA, especially when inflammation has been severe and extended beyond the 2mm distance from the bony cortex [26].

The reason is that the involvement of entheseal-related structures is not always specific to SpA. The more proximal tendon or ligament involvement and the involvement of the nearby bursa were found to occur in the absence of enthesitis with non-inflammatory and traumatic conditions [2].

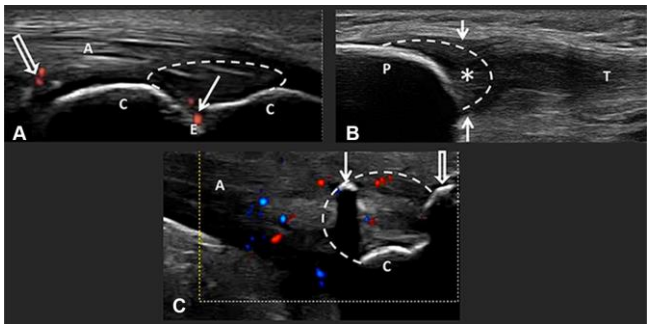


Figure (2): Ultrasound elementary components of enthesitis (A,B,C). Longitudinal scans of Achilles (A and C) and patellar (B) entheseal insertions, in B-mode and power Doppler ultrasound. (A) Achilles enthesis: the arrow points to the Doppler signal at the enthesis, while the open arrow points to the Doppler signal outside of the enthesis at the retrocalcaneal bursa. A, Achilles tendon; C, calcaneal bone surface; E, erosion; the dashed line represents 2 mm distance around the bony surface of the enthesis. (B) Patellar enthesis at the lower pole of the patella: the two arrows show the increased thickness of the enthesis, while the asterisk shows the hypoechogenicity at the enthesis insertion. P, patella bone surface; T, patellar tendon; the dashed line represents 2 mm distance around the bony surface of the enthesis. (C) Achilles enthesis: the arrow points to the calcification, and the open arrow points to the enthesophyte at the enthesis. A, Achilles tendon; C, calcaneal bone surface; colour dots: Doppler signals; the dashed line represents 2 mm distance around the bony surface of the enthesis [26].

Furthermore, the study by Balint et al, [26] had grouped the enthesis US lesions as inflammatory and structural which parallels the proposed pathophysiologic changes of enthesitis. This was an important differentiation between active potentially reversible lesions and permanent structural ones. The application of the proposed consensus US definitions of enthesitis in SpA studies aimed to provide a greater reproducibility and homogeneity. The OMERACT US initiative also grouped the agreed elementary US lesions for scoring enthesitis in SpA and PsA.

MSUS enthesitis scores:

On searching literature there are numerous US enthesitis scores most of them are using only greyscale, [23]. A minority used power doppler in addition and were developed following the first description by [22]. Most of them used a semi-quantitative grading method.

The most widely used MSUS enthesitis scores are: (Table 1)

Glasgow Ultrasound Enthesitis Scoring System GUESS [21]:

In the GUESS five enthesis sites on the lower limbs on each side of the body were examined using greyscale.

Sonographic Enthesitis Index (SEI) [27]:

In this index, the same enthesis sites as GUESS were assessed on each side of the body.

Each site was assessed for the presence of signs of acute inflammation, which included an increase of thickness, hypoechogenicity, and peritendinous edema. In addition, scoring for bursitis whenever applicable. Furthermore, for each enthesis site, the following chronic lesions were assessed: tears, loss of thickness, intratendinous calcification, and bone erosions.

The French scores [22]:

This was the first score based on the power doppler use in the assessment of enthesis in SpA. At each entheses, vascularization was studied at the cortical bone insertion, the junction between tendon and enthesis, the body of tendon, and the bursa. If power doppler signals were detected at these areas within the enthesis it was considered abnormal. According to the detected findings of abnormal grayscale and/or power Doppler features, US enthesitis was classified into 5 distinctive patterns.

MAdrid Sonographic Enthesitis Index (MASEI) [28]:

MASEI included the examination of six enthesis sites bilaterally using power doppler in addition to greyscale [28].

It was found that greyscale lesions are mainly structural rather than inflammatory, thus can occur in SpA and mechanical causes as aging and obesity. As a result, greyscale findings though are important to note, yet they do not differentiate SpA from other inflammatory arthritis or healthy individuals. Thus, the use of scores not including power doppler for SpA detection and quantifications were of doubtful value. Even scores including doppler were subject to debate [29.

Wervers and colleagues suggested a modification to improve the discriminating ability of the MSEI by excluding the thickness of knee entheses from the score. They also suggested that at least one confluent doppler signal is needed to be of value and not just a single spot of doppler [29]. As of D'Agostino M., et al [30], Doppler activity was reported to be of great value in detecting active enthesitis.

In the Delphi process that was a step proceeding the most recent OMERACT definition for enthesitis [25], Doppler activity was detected at the enthesis level in only one-third of images, but when present it showed a high inter- and intraobserver reliability.

Several factors affect the detection of doppler signals, including the agreement on a clear definition. The final OMERACT definition highlighted that signals which are included in the enthesitis must be within 2 mm of the bony cortex, thus excluding those outside the enthesis and within the peri-entheseal structures. Another factor is the need for highly-sensitive Doppler technology, and the training and experience of the performing physician. According to the OMERACT definition, the scoring of each of its elementary components is made binary to facilitate detection. This score is subject to multicenter studies to evaluate its sensitivity to change [31].

Belgrade UltraSound Enthesitis Score (BUSES) [32]:

Recently, Milutinovic, S., et al in 2015 [32] have developed a new score, the Belgrade UltraSound Enthesitis Score (BUSES). It is the first study to be based on the recent OMERACT definition of enthesitis.

BUSES score was developed to differentiate between enthesitis of SpA and enthesitis in non-SpA. It is described as a global US score, as it includes greyscale ultrasound enthesitis signs of increased thickness, hypoechogenicity, loss of normal fibrillar structure, erosions, enthesophytes, as well as power Doppler signals [32].

An excellent agreement between operators [intra-class correlation coefficient (ICC) was 0.990 with 95% CI (0.985, 0.993)] resulted in reliability of BUSES. Also, it has demonstrated good feasibility based on the clear definition and interpretation of its components, its acceptable time for patients and operators, in addition to not requiring additional financial resources.

The same group of researchers demonstrated the construct validity and sensitivity to change of BUSES score over time in a more recent study [33]. This was evidenced by the finding of decreased US signs of active enthesitis in SpA patients after one, three and six months of treatment. They concluded that BUSES could be useful for monitoring the progression and effectiveness of the treatment of enthesitis.

Table 1: The most common US enthesitis scores

[1] *US score*	[2] *Year*	[3] *Author*	[4] *Enthesis Number*	[5] *Grey scale*	[6] *PD*	[7] *Elementary lesions*	[8] *Evaluated enthesis*	[9] *Score*	[10] *LOE* [11] *GOE**
[12] *GUESS*	[13] *2002*	[14] *Balint, P.,*	[15] *five enthesis sites on each side of the body*	[16] *yes*	[17] *no*	[18] *-thickness,* [19] *-erosion,* [20] *-enthesophyte* [21] *-bursitis*	[22] *Quadriceps, Proximal patellar, Achilles, distal patellar, Plantar fascia.*	[23] *Absent = 0 Present =1* [24] *Min–max.: 0–36*	[25] *LOE: 4* [26] *GOE: C*
[27] *The French score* [28]	[29] *2003*	[30] *D'Agostino, M.,*	[31] *nine enthesis sites on each side of the body*	[32] *yes*	[33] *yes*	[34] *Five enthesis types according to grayscale and/or power Doppler features*	[35] *Quadriceps, Proximal patellar, Achilles, Plantar fascia.* [36] *Pubis, greater trochanter,* [37] *anterior tibial, lateral epicondyle, medial epicondyle*	[38] *Staging* [39] *1* [40] *2a* [41] *2b* [42] *3a* [43] *3b*	[44] *LOE:3b* [45] *GOE: B*

[46] ***SEI***	[47] ***2007***	[48] ***Alcade, M.,***	[49] ***five enthesis sites on each side of the body***	[50] ***yes***	[51] ***no***	[52] ***Acute:*** [53] ***↑ thickness,*** [54] ***edema,*** [55] ***bursitis.*** [56] ***Chronic:*** [57] ***↓ thickness,*** [58] ***tears,*** [59] ***calcification,*** [60] ***bone erosions.***	[61] ***As GUESS***	[62] ***Absent = 0 Present =1*** [63] ***SEI-Acute*** [64] ***min–max.: 0–36*** [65] ***SEI-Chronic*** [66] ***min–max.: 0–40*** [67] ***SEI-Total score = 76***	[68] ***LOE:3b*** [69] ***GOE: B***
[70] ***MASEI***	[71] ***2009***	[72] ***de Miguel, E.,***	[73] ***six enthesis sites on each side***	[74] ***yes***	[75] ***yes***	[76] ***-structure,*** [77] ***-thickness,*** [78] ***-bursitis*** [79] ***-erosion*** [80] ***-doppler*** [81] ***-calcification, ossification, cortical bone irregularity***	[82] ***GUESS+*** [83] ***Triceps***	[84] ***Thickness (0,1) Enthesophytes/calcifications (0, 1, 2 or 3)*** [85] ***Erosions (0, 3) Bursitis (0,1)*** [86] ***Structural changes (0, 1) Doppler (0, 3)*** [87] ***Min–max = 0–136***	[88] ***LOE: 3b*** [89] ***GOE: B***
[90] ***BUSES***	[91] ***2015***	[92] ***Milutinovic, S.***	[93] ***six enthesis sites on each side***	[94] ***yes***	[95] ***yes***	[96] ***hypo-echogenicity, increased thickness, calcification, enthesophytes,*** [97] ***bone erosions,*** [98] ***doppler signals***	[99] ***GUESS+*** [100]***Lateral epicondyle***	[101]***Absent=0*** [102]***Present= 1 except for doppler signals and erosions;*** [103]***Absent=0*** [104]***Present= 4***	[105]***LOE:1b*** [106]***GOE: A***

****LOE: level of evidence, GOE: grade of evidence, using the standards of the Oxford Centre for Evidence-Based Medicine (OCEBM, 2011).***

Disparity between clinical and imaging enthesitis/Subclinical Enthesitis

It became well established that there is disparity between the clinical and US findings of inflammation in rheumatic diseases. It was previously reported to find US signs of inflammation, indicated by persistence of power doppler signals, in up to half of rheumatoid arthritis patients in clinical remission [34]. This subclinical synovitis was a poor prognostic sign for future relapse and erosion progression [35].

This inspired the search for power doppler signals in clinically asymptomatic SpA. PsA was in the center of such research owing to the high prevalence of its peripheral joint and entheseal involvement. Imaging assessment in PsA revealed higher sensitivity of US and MRI for the detection of joint inflammation than clinical examination [36]. Furthermore, clinically proven enthesitis in PsA contributed to worse function and poor quality of life.

Polachek and colleagues [37] assessed more than 800 patients with PsA clinically and reported a detailed analysis of the prevalence and clinical presentation of enthesitis in these patients and reported a 35% prevalence of clinically detected enthesitis. The most common sites for clinically detected enthesitis were the Achillis tendon, plantar fascia and the common extensor tendon insertion. Whereas, with the use of imaging the prevalence of enthesitis in PsA was reported to be much higher reaching 70% [38].

Several ultrasound studies revealed a high prevalence of subclinical enthesitis in patients with PsA and psoriasis without arthropathy [39, 40, 41].

Studies on psoriasis patients without arthritis suggested that ultrasound-verified enthesitis might predict onset of PsA [42]. And especially Achilles tendon US detected enthesitis was proposed as a sensitive method for early diagnosis of psoriatic arthropathy in patients with cutaneous psoriasis [43].

The discrepancy between clinical and US detected enthesitis in PsA patients was recently revisited by Michelsen and colleagues [44]. They assessed two hundred and eighty-two Achilles tendons in one hundred and forty-one patients with PsA both clinically and by using US. They reported that none of the clinical disease characteristics were associated with US inflammatory activity. Consequently, the lack of association between clinical and US signs of Achilles enthesitis in PsA. This highlights the value of US evaluation of enthesitis in PsA in addition to the clinical assessment. The same study reported statistically significant association between US structural damage and age, body mass index, regular physical exercise and the use of biological disease-modifying anti-rheumatic drugs. The results of Michelsen et al., study confirms findings from previous ones, and points out to the value of inflammatory changes over the structural findings when considering US enthesitis scores [31].

Thus, the presence of disparity between clinical and US findings of enthesitis [45], together with the lack of a clear consensus definition of the elementary US lesions as well as the need for high performance of the ultrasonographer, all posed obstacles against the solid use of US as a tool to confirm the presence of enthesitis and to differentiate its cause if related to SpA or not. The recent OMERACT enthesitis US definition has finalized the process of development of a consensus definition to provide homogeneity among studies. Despite these obstacles, imaging of enthesitis, especially through the use of MSUS played a very important role in helping to reveal the underlying disease pathogenic mechanisms by reflecting the

changes which escape detection by clinical examination.

The impact of MSUS detected enthesitis on the early diagnosis of SpA

Enthesitis has long been perceived as the hallmark of axial and peripheral SpA. Consequently, it was included in most classification criteria of the disease. The European SpA study group criteria (ESSG) included the presence of heel pain as one of its items which would confirm the clinical diagnosis of SpA in those meeting the entry criterion of inflammatory back pain and or peripheral arthritis [46]. The Assessment of SpondyloArthritis International Society (ASAS) published two separate sets of classification criteria for SpA. The ASAS criteria for axial SpA, included enthesitis as one of eleven disease features [47,48]. In addition, ASAS criteria for peripheral SpA again included enthesitis as a possible entry criterion as well as being included as one of five disease characteristic features for the diagnosis [48]. Furthermore, ClASsification criteria for Psoriatic Arthritis (CASPAR) included the presence of inflammatory articular disease of the joint, spine, or entheseal as a prerequisite entry for the criteria in addition to three or more points to be classified as PsA [49].

MSUS can aid in the fulfillment of these criteria by detecting subclinical enthesitis or by confirming clinically detected enthesitis and thus help in the early diagnosis of SpA.

In 2015 the EULAR has produced the first evidence-based recommendations on the use of imaging in the clinical management of both axial and peripheral SpA [50]. In these recommendations the role of MSUS in the management of SpA was highlighted. It was recommended by the EULAR to use US or MRI to detect peripheral enthesitis, which may support the diagnosis of SpA when clinically suspected (level of evidence III). Furthermore, US or MRI might be used to detect peripheral arthritis, tenosynovitis and bursitis [50].

Relevance of MSUS detected enthesitis to monitoring disease activity and reflecting therapeutic response

The EULAR recommendations had shed light also on the role of MSUS in monitoring SpA disease activity. It has recommended the use of MSUS for assessing synovitis and enthesitis in peripheral SpA, stating that it can provide additional information on top of clinical and biochemical assessments. And that US with high frequency colour or power Doppler is sufficient to detect inflammation (level of evidence Ib) [50]. It was also recommended (with a level III of evidence) to use MSUS to provide additional information in peripheral SpA for monitoring of structural damage [50].

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has recommended enthesitis as one of the outcome domains for assessing disease activity and response in PsA [51].

Relevance of enthesitis to the choice of therapy

Until very recently, therapeutic options for enthesitis were limited. These included NSAIDs, local injections and physiotherapy. More recently, biologic drugs as tumor necrosis factor (TNF) alpha antagonist drugs have shown efficacy as measured by clinical examination, MRI and US.

NSAIDs are the initial treatment of enthesitis and this is related to their pathophysiologic effects. As PGE2 has an important role in initiating inflammation at the enthesis, thus, NSAIDs can improve the pain at enthesis and MSUS can show improvement by detecting the decrease in power Doppler signals. Another line of treatment is physiotherapy, which is often prescribed with varying results.

DMARDs as methotrexate, sulphasalazine and leflunomide do not show effectiveness in enthesitis.

Apremilast is a phosphodiesterase 4 inhibitor, it has been recently approved for the treatment of PsA. It is currently the only orally available DMARD that has proved efficacy in the treatment of enthesitis. Apremilast acts by inhibiting the production of multiple cytokines that are involved in entheseal inflammation, such as IL-17A, IL-23 and TNF. Apremilast was also found to inhibit the migration of neutrophils to the sites of inflammation, thereby interfering with the key cytokines involved in the initiation of enthesitis [52]. Apremilast has shown encouraging results in enthesitis, with complete resolution of enthesitis as measured by MASES in about half of the patients with PsA after one year of treatment [53]. These results need to be confirmed using indices that assess the peripheral enthesis as MASES focuses largely on axial rather than peripheral enthesitis [54].

TNF inhibitors have a well-documented role in controlling enthesitis, this is reflected by their efficacy in improving spinal pain in axial SpA and AS. In addition, TNF inhibitors also improve the signs and symptoms of peripheral enthesitis, such as in the heels of patients with axial SpA and peripheral entheseal involvement [55]. Several studies in PsA provided substantial evidence of the effectiveness of TNF inhibitors in controlling peripheral enthesitis. [56, 57].

Following the proposed role of the IL-23 and IL-17 axis in the pathogenesis of SpA and entheseal inflammation, search for the effect of their inhibition provided supporting data on their central role. IL-17 inhibitors secukinumab and ixekizumab have shown effectiveness in improvements in enthesitis. Ixekizumab, a recombinant, humanised, monoclonal antibody which selectively binds and neutralises IL-17A. It resulted in a complete resolution of enthesitis symptoms at twenty-four weeks of treatment in 39-43% of biologic naive active PsA patients [58]. Secukinumab, a human monoclonal antibody that inhibits the effector function of interleukin 17A, was shown in phase 3 study to resolve enthesitis in about 50% of active PsA patients [59].

Ustekinumab, an antibody against the p40 subunit common to IL-12 and IL-23, was also shown to effectively treat enthesitis. In phase 3 trial, slightly more than 50% of patients with PsA had complete improvement of their enthesitis after 6 months of treatment [60].

Looking at the place of enthesitis in the available treatment recommendations, the GRAPPA presented recommendations on the management of psoriasis and PsA in 2009. These were based on the presenting domain of the disease, peripheral arthritis, spinal disease, skin and nail disease, enthesitis and dactylitis in the setting of PsA. Enthesitis was classified as mild,

moderate or severe according to the involvement of one to two enthesis sites or more than two and according to loss of function. Those with severe enthesitis were recommended to receive biologic anti-TNF treatment [61]. In their 2015 updated recommendations, the GRAPPA maintained enthesitis as one of the main PsA disease domains, though the severity grading was removed being thought of as lacking enough evidence [51]. The EULAR 2015 update on PsA treatment has also considered the presence of enthesitis. It was recommended in PsA patients with active enthesitis and insufficient response to NSAIDs or local glucocorticoid injections, to consider therapy with a biologic DMARD, which according to current practice is a TNF inhibitor (level of evidence Ib) [62].

Conclusion

Over the past twenty-five years, ultrasound has been used to detect enthesitis in SpA, and has been incorporated into its management. Several US enthesitis scores were developed, which included different enthesis sites and variable elementary lesions. For the time being, and from the current search, MSUS detection of enthesitis is of value in enhancing the diagnostic accuracy and aiding the early diagnosis of SpA especially those with incomplete criteria or ASAS negative patients.

The newly revealed SpA disease pathogenetic pathways, created disease targets as the blockade of IL-17 and IL-23 pathways. These targeted therapies were found to be of value in treating enthesitis. Consequently, MSUS detected enthesitis is of value in the choice of therapy. Owing to the ability of MSUS to accurately assess acute and chronic signs of entheseal inflammation it is recommended for follow up of disease progression.

From the current search of literature, MSUS detected enthesitis can be a holistic tool for the management of SpA, from enabling early accurate diagnosis, to aiding the choice of therapy and assessment of disease progression and response to therapy.

Limitations

The topic of enthesitis and SpA is one of the most heavily searched in the current time. Nevertheless, there are still several unmet needs related to the lack of homogeneity among studies and the fact that US is operator dependent. There needs to be a wider spread of awareness of the increasing use and value of MSUS in SpA and particularly for enthesitis. There is an endless need for improving machine settings and Doppler sensitivity for accurate enthesis assessments. The future holds a place for MSUS holistic role in the assessment of SpA.

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