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Hidden in plain sight: Is there a crucial role for enthesitis assessment in the treatment and monitoring of axial spondyloarthritis?

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ABSTRACT

Objective: To review the evidence surrounding the pathophysiology of enthesitis in axial spondyloarthritis (axSpA), its prevalence and contribution to the overall disease burden, and response to treatment at axial and peripheral sites.
Methods: Literature searches of the Cochrane Library, PubMed, and Embase / Medline using the terms "enthesitis", "enthesopathy", "spondyloarthritis", "axial spondyloarthritis", and "ankylosing spondylitis" were conducted. Publications mentioning enthesitis or enthesopathy in the context of pathophysiology, diagnosis, or treatment were included.
Results: Enthesitis is a common symptom of axSpA, occurring with high prevalence at axial and several peripheral sites. Inflammation at the site of enthesis is an early key manifestation of axSpA. Clinically evaluable enthesitis contributes significantly to the burden of disease, correlating with worse symptomatology and downstream structural damage. Despite its importance in driving axSpA disease processes, enthesitis is somewhat neglected in current approaches to disease assessment and management. Enthesitis is excluded from some commonly used disease activity measures, is not routinely assessed in clinical practice, and many methods of clinical assessment omit key accessible axial sites, such as the spinous processes.
Conclusion: Enthesitis plays a central role in driving the pathophysiology of axSpA. There is a need for a renewed focus on the early detection, measurement and treatment of enthesitis.

Introduction to enthesitis and axial spondyloarthritis

Enthesitis (inflammation of the insertion sites for tendons, ligaments and capsules into bone) is a characteristic clinical manifestation of spondyloarthritis (SpA) and a key early feature [1]. In axial spondyloarthritis (axSpA), multiple entheses in the axial skeleton can become inflamed, including those in the sacroiliac joints, the chest wall and the spine, which, compared with other joints, have many more attachment sites (Fig. 1) [2]. A significant proportion of patients with axSpA also present with peripheral enthesitis [3].

In his seminal work on enthesitis in ankylosing spondylitis (AS), the prototypic radiographic stage of axSpA, Ball noted that the histopathology of peripheral enthesitis, including iliac crest entheses, was virtually identical to the spine, with inflammatory cell infiltration followed by erosion/repair responses [6]. Subsequently, enthesitis became a central focus in axSpA [5]. As time passed, subsequent studies shifted their focus away from enthesitis and towards the sacroiliac joint cavity and synovium, the earliest site where disease manifestation was most consistently reported using X-rays in AS [7]. Fast-suppression magnetic resonance imaging (MRI) techniques brought evidence that the earliest lesion in AS was detected in the sacroiliac joint subchondral bone, where bone oedema, which histologically corresponds to osteitis, was reported [8]. Osteitis was also shown to be common at sites of peripheral enthesitis [9]. Finally, the common biomechanical link to disease localisation at entheses and to the subchondral sacroiliac joint bone was described, crystallising how close

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment in SpondyloArthritis international Society; ASDAS, AS Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; HLA, human leucocyte antigen; IL, interleukin; JAK, Janus kinase; LEI, Leeds Enthesitis Index; MASES, Maastrich Ankylosing Spondylitis Enthesitis Score; MEI, Mander Enthesitis Index; MRI, magnetic resonance imaging; mSASSS, modified Stoke Ankylosing Spondylitis Spinal Score; nr-axSpA, non-radiographic axial spondyloarthritis; PDUS, power Doppler ultrasound; PsA, psoriatic arthritis; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF, tumour necrosis factor

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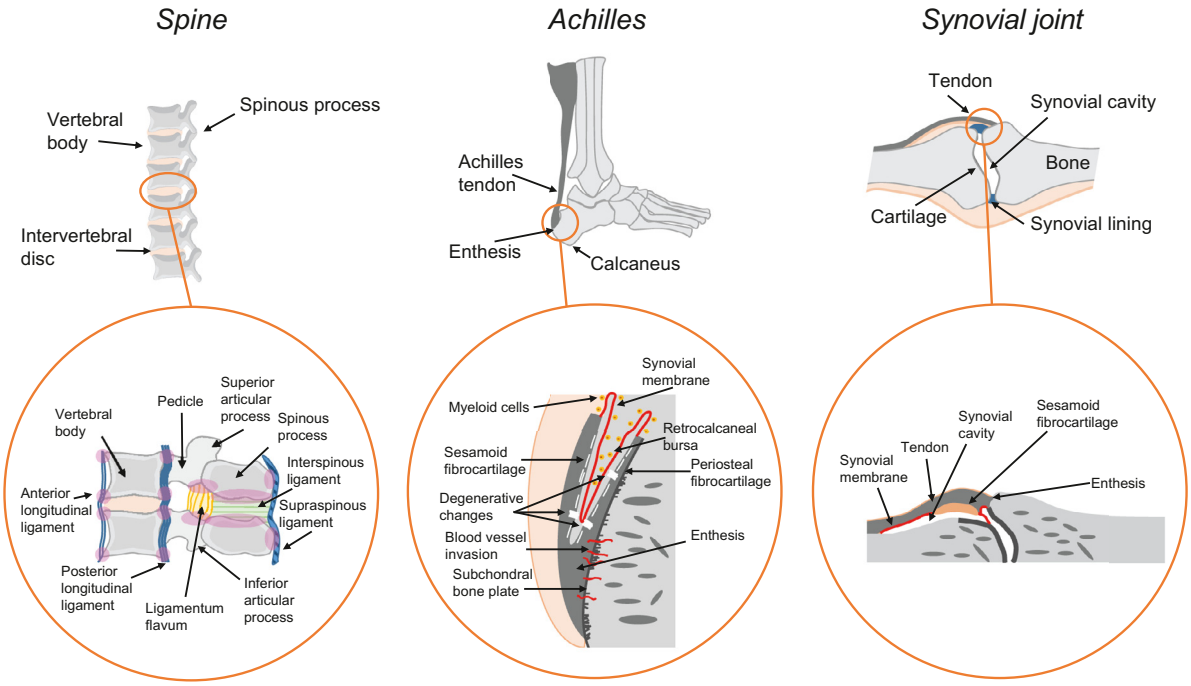

Fig. 1. Anatomy of entheses in the spine, at the Achilles tendon insertion and in synovial joints [4,5]. The numerous entheses in the spine are highlighted in purple.

the pathophysiological process was between the sacroiliac joint and peripheral entheses [4].

The focus on the sacroiliac joint cavity meant that axSpA management gradually shifted away from targeting enthesitis. In clinical practice, the importance of the assessment and treatment of enthesitis in axSpA is sometimes overlooked due to the predominant focus on axial as opposed to peripheral disease, and the clinical inaccessibility of most axial sites. Peripheral enthesitis is, by contrast, routinely assessed in psoriatic arthritis (PsA) research trials and clinical practice. It is also included as a key disease domain in treatment recommendations and as a component of some composite disease activity scores [10,11]. Clearly, there is disparity in the assessment and management of enthesitis between PsA and axSpA, despite the fact that it is equally prevalent across both diseases, significantly adds to the burden of axSpA, and is associated with spinal structural damage [12–15]. While enthesitis is evaluated relatively routinely in axSpA clinical trials [16], albeit using measures that omit key sites in the axial skeleton, it is frequently overlooked in clinical practice. The 2009 Assessment in SpondyloArthritis international Society (ASAS) criteria for axSpA only include enthesitis of the heel, whereas 'enthesitis (of any site)' is a criterion for peripheral SpA[17,18]. This begs the question, are we doing enough to identify and treat enthesitis in axSpA?

Here, we argue for a renewed focus on the early detection, measurement and treatment of enthesitis in axSpA by reviewing its central role in axSpA pathophysiology, its prevalence and contribution to the burden of disease, and the discrepant treatment responses observed at peripheral *versus* axial entheses. A suggested research agenda to guide future investigations into this key topic is highlighted.

Statement of literature search

Articles for this narrative review were identified through searches of the Cochrane Library, PubMed, and Embase / Medline with the search terms "enthesitis", "enthesopathy", "spondyloarthritis", "axial spondyloarthritis", and "ankylosing spondylitis" from 1966 to December 2020. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed. Publications mentioning enthesitis or enthesopathy in the context of axSpA or AS, be it in reference to pathophysiology, manifestation, symptoms, clinical burden, diagnosis, disease progression, or treatment response were included. Irrelevant references were excluded from consideration. The final reference list was generated based on originality and relevance to the broad scope of this review.

Enthesitis is central to axSpA pathophysiology

Enthesitis has a central role in the pathophysiology of axSpA. In otherwise healthy individuals, overuse-related pain at the site of the insertion of tendons into the bone (termed enthesopathy) is considered a normal physiological response to mechanical overload. Increased inflammatory changes within the entheseal soft tissue as well as structural damage in adjacent bony structures in response to age, increased body mass index and physical activity are also often observed [19]. While these changes are usually asymptomatic and not suggestive of a disease, they are exaggerated in SpA and there is a recognised epidemiological association between history of trauma or repeated mechanical stress and development of enthesitis associated with, for example, PsA [20]. In SpA, enthesitis can result from mechanical or other inflammatory stressors (*e.g.*, infection) chronically inflaming entheses in genetically susceptible individuals [1]. Peripheral enthesitis in PsA has been associated with the presence of human leucocyte antigen (HLA)-B*27 [21], suggesting a genetic predisposition for this disease manifestation. It has been hypothesised that patients with SpA have a lower threshold for triggering enthesitis, allowing it to develop with little or no mechanical force [1]. Inflammation at other functional entheses including those in the eye, lung and aortic root are also common in axSpA and explain some of the extra-articular disease manifestations such as uveitis, lung fibrosis and aortic root disease [22].

The pathophysiology of enthesitis in SpA is conceptualised in relation to an abnormal response to biomechanical stress leading to an innate inflammatory response. Animal models and empirical clinical

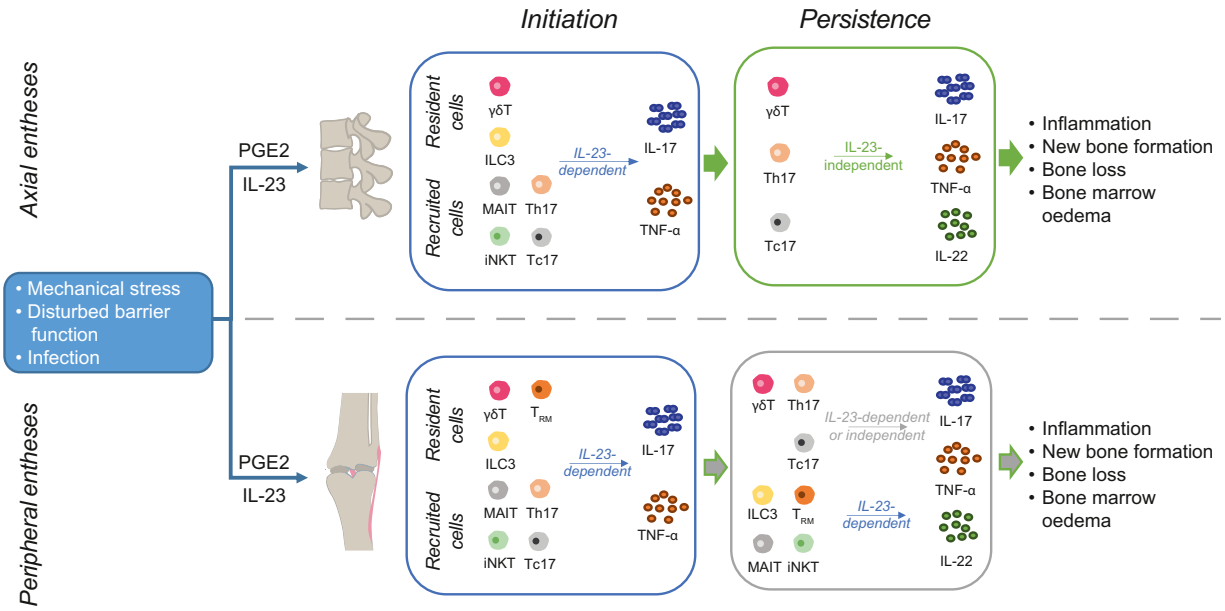

Fig. 2. The differing pathophysiology underlying enthesitis at axial *versus* peripheral sites. Evidence for the emergent roles of various immune cells in the pathophysiology of enthesitis come from a combination of animal studies, ex vivo studies from healthy individuals and studies in patients with spondyloarthritis [1,24–35]. γδT, gamma delta T cell; IL, interleukin.; ILC3, type 3 innate lymphoid cell; MAIT, mucosal-associated invariant T cell; PGE2, prostaglandin E2; Tc17, IL-17-producing CD8+ *T* cell; Th17, T helper 17 cell; TNF, tumour necrosis factor.

observations suggest that prostaglandin E2 and pro-inflammatory cytokines, such as tumour necrosis factor α (TNF-α) and interleukin (IL)−17A, that are produced by resident immune cells, including gamma delta T cells and Type 3 innate lymphoid cells, may be important (Fig. 2) [1,23]. This response may be amplified by the recruitment of additional immune cells such as innate natural killer T cells, mucosal-associated invariant T cells, IL-17-producing CD8+ *T* cells, and T helper 17 cells, that drives the further release of inflammatory cytokines, such as IL-17A, TNF-α, and IL-22 [1,23]. Dysregulation of cytokine cascades may drive the subsequent new bone formation that is characteristic of axSpA through activation and proliferation of mesenchymal stem cells, but this theory remains fairly rudimentary and confirmatory data are needed [1,23,24].

Enthesitis is prevalent in axSpA

Enthesitis is a common manifestation of SpA and is observed with a similar frequency in axSpA and PsA across a range of peripheral and axial sites (Fig. 3a) [3,12]. Although the reported prevalence of enthesitis in axSpA varies greatly between studies depending on factors such as the type of study, the population investigated, and the method of assessment used, data from registries and observational

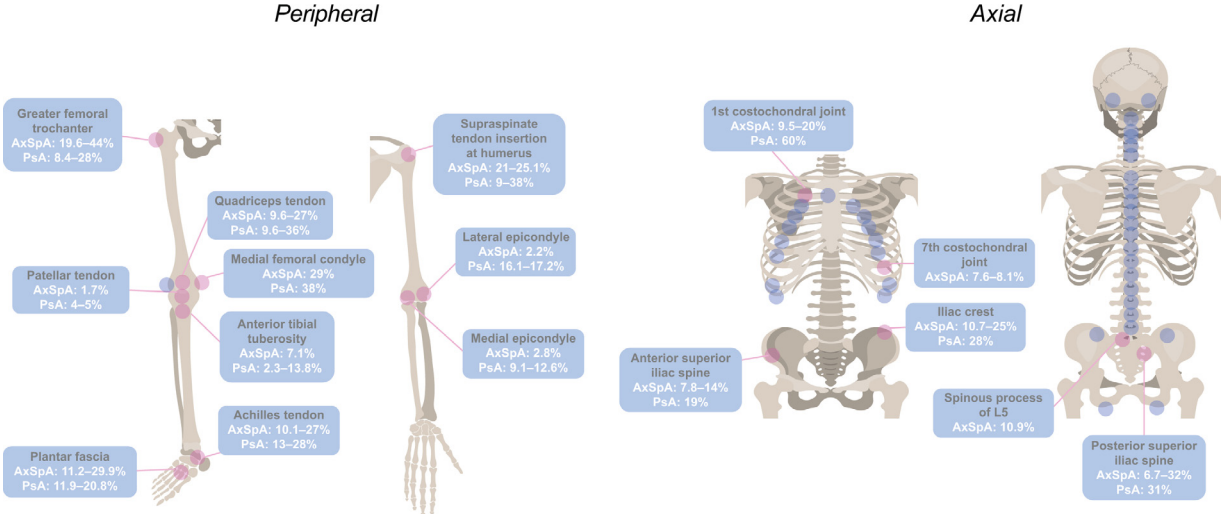

Fig. 3. Evaluation of entheseal sites. Proportion of patients with axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) reporting enthesitis in select sites; data shown are proportion of patients (%) presenting with enthesitis following clinical examination (pink circles); blue circles represent clinically accessible sites that are rarely assessed in practice. B) Enthesitis sites evaluated when using the Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index, Maastricht Ankylosing Spondylitis Enthesitis Score (MASES), and Leeds Enthesitis Index (LEI) [36,44–46].

cohorts suggest that approximately one-third of patients with axSpA present with clinical enthesitis [3,36]. While large axSpA clinical trials often do not report the prevalence of clinical enthesitis at baseline, it may be as high as ~70–80% [37-39]. The higher proportion of patients with enthesitis in clinical trials *versus* registries may reflect the very select patient population enroled in clinical trials or the higher standard of clinical assessment for presence of enthesitis achieved in them. The enthesitis indices used in clinical trials are limited and may not capture the 'true' prevalence of enthesitis in a study population. Indeed, imaging studies indicate that enthesitis may be more prevalent in axSpA than suggested by clinical assessment alone [1]. Entheseal lesions are detectable on ultrasound in more than 95% of patients with AS, although not all ultrasound features suggest an inflammatory enthesitis [40].

There is some evidence that clinical enthesitis might be more common in earlier axSpA [3], despite a 2016 meta-analysis (of mostly longitudinal cohort studies) suggesting no significant difference in the prevalence of clinical enthesitis in non-radiographic (nr)-axSpA and AS [41]. US Corrona registry data show a significantly higher prevalence of clinical enthesitis in nr-axSpA *versus* AS (47·4% *vs* 29·0%, $p<0·001$); [3] mean Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis index scores were also significantly higher (4·9 *vs* 3·1, $p = 0·002$)[3], although channelling bias may be an underlying reason for these differences. In the same registry, clinical enthesitis was more frequently observed in PsA patients with axial involvement than those without (30·7% *vs* 19·2%, $p<0·001$)[42], although an observational study has shown conflicting results [43].

A key point to highlight regarding enthesitis prevalence in axSpA is that a distinction is rarely made between peripheral and axial enthesitis. While details on the precise entheses affected in axSpA has rarely been reported, the available evidence is summarised in Fig. 3a. The most frequently clinically affected peripheral sites in axSpA include the plantar fascia, Achilles tendon, and the supraspinatus tendon insertion, although the latter may be difficult to evaluate due to its close juxtaposition to the shoulder cavity [36,44]. The fact that the plantar fascia and Achilles tendon are commonly affected in axSpA is reflected by the inclusion of heel enthesitis in the ASAS classification criteria [17].

Enthesitis contributes significantly to disease burden

Real-world data indicate that the presence of clinically evaluable enthesitis is associated with worse disease activity, pain and health-related quality of life, reduced spinal mobility, and greater work and activity impairment in patients with axSpA [13,14]. Baseline data from the ACHILLES study, a placebo-controlled trial evaluating the efficacy of secukinumab in patients with axSpA or PsA and Achilles tendon enthesitis, suggest a higher disease burden in axSpA *versus* PsA; despite baseline Leeds Enthesitis Index (LEI) counts being similar, patients with axSpA reported more heel pain and higher disease activity [47]. Perhaps unsurprisingly, the presence of peripheral disease (including peripheral enthesitis, dactylitis and synovitis) in axSpA may result in higher overall disease activity than in patients with purely axial disease [43]. Factors associated with peripheral disease in axSpA included lower prevalence of HLA-B27, older age, later disease onset and lower prevalence of back pain [43]. However, it is not clear whether these differences are a result of the particular demographic of patients included in this cohort or if they highlight true differences between the diseases.

Enthesitis may predict structural damage

Peripheral enthesitis in particular may be predictive of spinal structural damage in axSpA. Although data from the French DESIR cohort showed no association between ultrasound peripheral enthesitis and sacroiliitis, MRI spine inflammatory lesions, or clinical disease activity in patients with early axSpA, the presence of peripheral enthesophytes on ultrasound was strongly associated with presence of axial syndesmophytes in the same patients, suggesting that enthesophytes may be a marker of disease severity in axSpA [15]. A multicentre case-control study found that patients with AS had higher ultrasound Achilles enthesophyte scores than healthy controls (significant in males but not females), and that enthesophyte scores correlated with both the presence of syndesmophytes (modified Stoke Ankylosing Spondylitis Spinal Score [mSASSS] and number of syndesmophytes)[48]. Another cross-sectional study found an association between enthesitis assessed using the MAdrid Sonography Enthesitis Index and peripheral and axial (mSASSS) joint damage in patients with PsA [49]. In a more recent ultrasound study, peripheral enthesitis scores and entheseal damage correlated with radiographic spinal damage (mSASSS); this association was stronger in PsA than AS [50]. Multivariate analysis found that peripheral enthesitis predicted spinal damage in SpA regardless of its subtype, further corroborating similarities in the pathological mechanisms affecting the peripheral enthesis and the enthesis at the junction of the vertebra or annulus fibrosis simultaneously [50].

Could treatment effectiveness differ depending on whether enthesitis is axial or peripheral?

Although there is a lack of consistency in the enthesitis measures used across trials, inhibitors of TNF-α (adalimumab, etanercept, infliximab, certolizumab, and golimumab), IL-17A (secukinumab, ixekizumab, netakimab and bimekizumab [only phase 2 data to date for netakimab and bimekizumab]), and Janus kinase (JAK), (tofacitinib and filgotinib [only phase 2 data to date]) have all shown significant and sustained efficacy in treating enthesitis in AS compared with placebo (Table 1). Additionally, select TNF-α inhibitors have shown significant efficacy in treating enthesitis in patients with nr-axSpA. The IL-17A inhibitors secukinumab and ixekizumab have both met their primary endpoints in phase 3 studies in nr-axSpA [51,52]; while efficacy on peripheral enthesitis has been demonstrated in this population with ixekizumab, data in axial enthesitis with ixekizumab and secondary outcome Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) and SPARCC enthesitis index data are pending for secukinumab. Inhibitors of IL-23 (ustekinumab, risankizumab), IL-6 (tocilizumab), IL-1 (anakinra), and T-cells (abatacept) were not effective for treating enthesitis in AS (Table 1).

It is noteworthy that enthesitis is invariably a lowly ranked secondary or exploratory outcome measure in clinical studies. The exceptions include the HEEL study of etanercept *versus* placebo in refractory heel enthesitis in patients with SpA, where the primary clinical outcome was met but improvement on MRI was not clearly evident [82], and the ACHILLES study of secukinumab *versus* placebo in patients with axSpA or PsA and Achilles tendon enthesitis [47].

Peripheral enthesitis is rarely assessed in axSpA studies. Certain peripheral sites may be included within enthesitis indexes (*e.g.*, the Achilles tendon insertion in MASES) but a distinction between axial and peripheral sites is not routinely reported. Evidence of treatment effectiveness for peripheral enthesitis in axSpA is therefore often extrapolated from PsA. A number of systematic literature reviews and meta-analyses have been published on this topic in PsA [16,102], highlighting the significant efficacy of a range of biological therapies on peripheral enthesitis including inhibitors of IL-17A, IL-23, TNF-α, and JAK.

The discrepant responses to IL-23 inhibition observed in AS *versus* PsA is particularly salient and serves as a call to measure carefully axial and peripheral enthesitis simultaneously. The IL-12/−23 inhibitor ustekinumab and the IL-23 p19 inhibitor risankizumab have both failed to show significant efficacy in axSpA [25,26], while IL-23 inhibition is a relatively well-established and effective approach to the treatment of peripheral disease including enthesitis and IL-12/-23

Table 1
Enthesitis treatment response in axSpA RCTs and observational studies.

Treatment	Population / number of patients	Method of enthesitis assessment	Results	Ref
NET *vs* PBO (NCT02763111) Phase 2 DB RCT	Active AS (n = 89)	MASES	Significant improvement in MASES at week 16 *vs* BL for NET 80 mg (mean ± standard deviation change −3·19±2·40) and 120 mg (−2·05±1·07) (p<0·05 for change from BL but NS *vs* PBO	Erdes S, et al. *Clin Exp Rheumatol* 2020; **38:** 27–34 [53]
SEC *vs* PBO (MEASURE 1–4) Phase 3 DB RCTs	Active AS (n = 693)	MASES (axial and peripheral sites)	**Week 16:** Mean change from BL for all and axial MASES was greater for SEC 150 mg (−2·4 and −2·3) and 300 mg (−2·9 and −2·9) *vs* PBO (−1·9 and −1·8; p<0·05 and p<0·01) Complete enthesitis resolution (MASES=0) of all and axial MASES: SEC 150 mg (40·8% and 42·7%) and 300 mg (36·2% and 42·1%) *vs* PBO (28·9% and 30·1%) AT and peripheral enthesitis changes consistently higher with SEC *vs* PBO **Week 52:** Mean change from BL for all and axial MASES further improved: SEC 150 mg (−3·5 and −3·2) and 300 mg (−3·9 and −3·6) Complete enthesitis resolution (MASES=0) of all and axial MASES further improved: SEC 150 mg (56·4% and 58·6%) and 300 mg (52·9% and 60·0%) *vs* PBO (28·9% and 30·1%) AT and peripheral enthesitis changes continue to improve	Schett G, et al. *Ann Rheum Dis* 2019; **78**: 873–4 [38]
IXE *vs* PBO (NCT02696785, NCT02696798) Phase 3 DB RCTs	Active AS (n = 318)	SPARCC (peripheral sites)	**Week 16:** Complete resolution of peripheral enthesitis (SPARCC=0) in 48.6% and 67.6% of patients with IXE 80 mg Q4W and IXE 80 mg Q2W, respectively, *vs* 22.9% with PBO	Schett G, et al. *Arthritis Rheumatol*. 2020; **72**: [54]
IXE *vs* PBO (NCT02757352) Phase 3 DB RCT	Active nr-axSpA (n = 225)	SPARCC (peripheral sites)	**Week 16:** Complete resolution of peripheral enthesitis (SPARCC=0) in 52.2% and 57.7% of patients with IXE 80 mg Q4W and IXE 80 mg Q2W, respectively, *vs* 31.3% with PBO	Schett G, et al. *Arthritis Rheumatol*. 2020; **72**: [54]
BIM *vs* PBO (NCT02963506.) Phase 2 DB RCT	Active AS (n = 303)	MASES	Mean change from BL in MASES at Week 12 was −2·1 to −2·5 for PBO, −1·2 to −2·0 for BIM 16 mg, −2·4 to −3·6 for BIM 64 mg, −2·0 for BIM 160 mg, and −2·7 for BIM 320 mg; at Week 48 mean change from BL in MASES was −3·3 for BIM 160 mg, and −3·4 for BIM 320 mg	Van der Heijde D, et al. *Ann Rheum Dis*. 2020; **79**: 595–604 [55]
RIZ *vs* PBO (NCT02047110) Phase 2 DB RCT	Active AS (n = 159)	MASES	No significant difference in change in MASES over time for RIZ *vs* PBO	Baeten D, et al. *Ann Rheum Dis* 2018; **77**: 1295–302 [26]
UST (TOPAS) Phase 2 proof-of-concept	Active AS (n = 20)	MASES, SPARCC	No significant change in MASES or SPARCC from BL	Poddubnyy D, et al. *Ann Rheum Dis* 2014; **73**: 817–23 [56]
TOC *vs* PBO (BUILDER-1 & −2) Phase 1/2 RCT; Phase 3 RCT	Active AS (n = 102/204; and n = 113)	MASES	No significant difference in change in MASES over time for TOC *vs* PBO	Sieper J, et al. *Ann Rheum Dis* 2014: **73**: 95–100 [57]
ANR OL study	Active AS	MASES, MRI of axial enthesitis	8 patients had a total of 38 MRI entheseal lesions: 23 (61%) lesions resolved completely. MASES scores also improved	Tan AL, et al. *Ann Rheum Dis* 2004; 63: 1041–5 [58]

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Table 1 (*Continued*)

Treatment	Population / number of patients	Method of enthesitis assessment	Results	Ref
ABT (NCT00558506) Phase 2 OL	Active AS (n = 30)	Not stated but appears to be clinical assessment	No significant changes in peripheral enthesitis with ABT	Song IH, et al. *Ann Rheum Dis* 2011; **70**: 1108–10 [59]
FIL *vs* PBO (TORTUGA) Phase 2 DB RCT	Active AS	MASES, BASDAI item 4	At week 12, the decrease in BASDAI item 4 did not differ significantly between groups. MASES data were collected at week 12 but were not presented	van der Heijde D, et al. *Lancet* 2018; **392**: 2378–87 [60]
TOFA *vs* PBO (NCT01786668) Phase 2, DB RCT	Active AS (n = 207)	MASES	Significant improvements in MASES at week 12 with TOFA 5 mg and 10 mg *vs* PBO	van der Heijde D, et al. *Ann Rheum Dis* 2017; **76**: 1340–7 [61]
GOL (iv) *vs* PBO (GO-ALIVE) Phase 3 DB RCT	Active AS (n = 208)	UCSF Enthesitis Index	Significant improvement in enthesitis resolution with GOL *vs* PBO at week 16 (43·7% *vs* 14·1%, $p<0·0001$). Sustained to week 52 (59·8%) Mean changes from BL were significantly greater with GOL *vs* PBO at weeks 2 (−2·3 *vs* −0·7) and 16 (−3·5 *vs* −1·2; both $p<0·001$). Improvements sustained from week 28 to 52 with GOL	Reveille JD, et al. *J Rheumatol* 2019; **46**: 1277–83 [62] Deodhar A, et al. *J Rheumatol* 2018; **45**: 341–8 [63]
CZP *vs* PBO (C-axSpAnd) Phase 3, DB RCT	Active axSpA without X-ray evidence of AS and objective signs of inflammation	MASES	Numerical improvements with CZP *vs* PBO in MASES at weeks 12 (2·7 *vs* 4·4) and 52 (2·1 *vs* 4·3); not assessed statistically due to hierarchical testing	Deodhar A, et al. *Arthritis Rheumatol* 2019; **71**: 1101–11 [39]
ADA *vs* PBO (NCT01029847) DB RCT	Active axSpA (n = 49)	Whole-body MRI	At week 6, enthesitis inflammation index scores decreased significantly with ADA *vs* PBO (mean change: −0·9 *vs* +0·4)	Krabbe S, et al. *J Rheumatol* 2018; **45**: 621–9 [64]
CZP *vs* PBO (RAPID-axSpA) Phase 3 DB RCT	Active axSpA (n = 218)	MASES	Improvements in MASES observed for both AS and nr-axSpA by week 24 (−3·4 and −3·5, respectively); further improvements to week 204 Total resolution of enthesitis (MASES=0) at week 24: 50·7%; heel enthesitis 61·5%, effect sustained to week 204 (60·8% and 71·2% with resolved enthesitis, respectively)	van der Heijde D, et al. *Rheumatology* 2017; **56**: 1498–509 [65] Landewe R, et al. *Ann Rheum Dis.* 2014; **73**: 39–47 [66]
TNF-α antagonists (individual drugs not named) Prospective observational	Active AS (n = 111)	MASES, US	BL: 85 patients (77%) had MASES ≥1; on US, 202 structural lesions in 74 patients, average 2·7 per patient Month 6: Significant decrease in MASES from 2 to 1 ($p<0·001$) with treatment; decrease according to US was not significant	Wink F, et al. *J Rheumatol* 2017; **44**: 587–93 [67]
ETN (ESTHER)	Early active axSpA (n = 42)	Modified MASES (17 sites), whole-body MRI	MRI showed fewer entheseal sites with ETN *vs* SFZ (11 sites in 11 patients *vs* 26 sites in 14 patients, p = 0·04 at week 48, no difference at week 24) Lower MASES scores at week 24 for ETN *vs* SFZ (1·6 *vs* 2·6, p = 0·01) but no significant difference at week 48 No clear differences observed between AS and nr-axSpA Small but non-significant improvement of enthesitis on MRI in all subgroups treated with ETN at year 2 Proportion of patients with clinical enthesitis decreased from 57% to 19% at year 2 and 14% at year 3 MRI enthesitis decreased from 21% to 13% at year 2 and 14% at year 3	Althoff CE, et al. *J Rheumatol* 2016; **43**: 618–24 [68] Song IH, et al. *J Rheumatol* 2014; **41**: 2034–40 [69] Song IH, et al. *Ann Rheum Dis* 2012; **71**: 1212–5 [70] Song IH, et al. *Ann Rheum Dis* 2011; **70**: 590–6 [71]
GOL *vs* PBO (GO-AHEAD) Phase 2 DB RCT	Active nr-axSpA	MASES	Difference between GOL and PBO at week 16: −0·7 (p = 0·03)	Sieper J, et al. *Arthritis Rheumatol* 2015; **67**: 2702–12 [72]

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Table 1 (*Continued*)

Treatment	Population / number of patients	Method of enthesitis assessment	Results	Ref
ADA Observational	Active AS (n = 41)	CDUS, MRI (SPARCC)	Mean CDUS score of sacroiliac joints and peripheral enthesitis decreased from BL at weeks 12 and 24 (all p<0·05)	Hu Z, et al. *Clin Exp Rheumatol* 2015; **33**: 844–50 [73]
ETN, IFX, & ADA *vs* csDMARDs Observational	Active AS	PE and MASES of AT and/or retrocalcaneal bursa, US of AT (GS, PD, TS)	MASES scores significantly decreased for all treatments at month 3 Decreases in US scores were significant for all biologics but not csDMARDs	Wang CH, et al. *Clin Rheumatol* 2015; **34**: 1073–78 [74]
ADA *vs* PBO (NCT01114880) Phase 3 RCT DB	Active AS (n = 344)	MASES	Mean change from BL to week 12 was significantly higher with ADA *vs* PBO (−1·2 *vs* −0·8; p = 0·030)	Huang F, et al. *Ann Rheum Dis* 2014; **73**: 587–94 [75]
GOL *vs* PBO (GO-RAISE) Phase 3 DB RCT	Active AS (n = 356)	Berlin Index, UCSF, MASES	Significant improvements with GOL *vs* PBO in UCSF, MASES and Berlin Index at week 14, only UCSF at week 2	Van der Heijde D, et al. *Rheumatology* 2013; **52**: 321–5 [76]
ADA *vs* PBO (ABILITY-1) Phase 3 DB RCT	nr-axSpA	MASES	No significant difference in change from baseline in MASES at week 12 with ADA (−0·6) *vs* PBO (−0·8; p = 0·962)	Sieper J, et al. *Ann Rheum Dis* 2013; **72**: 815–22 [77]
ADA (NCT00667355) Phase OL	Active AS	MASES	Improvements from BL in MASES with ADA at weeks 12 (−1·0) and 60 (−1·2)	Kobayashi S, et al. *Mod Rheumatol* 2012; **22**: 589–97 [78]
IFX RCT OL extension	Active AS (n = 33)	Clinical examination	Enthesitis observed in 48·5% at BL, 18·2% after 8 years Mean enthesitic sites decreased from 2·1 at BL to 0·7 at 8 years (p = 0·001)	Baraliakos X, et al. *Rheumatology* 2011; **50**: 1690–9 [79]
ETN *vs* BMZ RCT	AS (n = 12)	CDUS	CDUS signals improved in both treatment groups *vs* BL; NS difference between groups	Huang Z, et al. *Clin Exp Rheumatol* 2011; **29**: 642–9 [80]
IFX, ETN, ADA Observational	Active AS (n = 43)	US (GS, PD, TS [OMERACT]) of AT or retrocalcaneal bursa; PE	BL: 11 (26·2%) patients had Achilles enthesitis or retrocalcaneal bursitis based on PE; 36 (83·7%) based on GS US, 10 (23·3%) had PD signal 2-month follow-up: GS score and TS decreased significantly (3·6 *vs* 2·3, p<0·001 and 4·7 *vs* 2·7, p<0·001, respectively); decrease in PD score was NS	Aydin SZ, et al. *Rheumatology* 2010; **49**: 578–82 [81]
ETN *vs* PBO (HEEL) DB RCT	SpA with heel enthesitis (n = 24)	PGA (AUC), MASES, MRI	AUC for PGA of disease activity significantly reduced with ETN *vs* PBO at week 12 Absolute changes from BL in heel enthesiopathy significantly greater with ETN *vs* PBO from week 8 Numerical differences in favour of ETN observed in MASES and MRI but were NS	Dougados M, et al. *Ann Rheum Dis* 2010; **69**: 1430–5 [82]
ADA (RHAPSODY) OL	Active AS (n = 1250)	MASES	At week 12, median MASES reduced from 5 to 1; inflammation of plantar fascia resolved in 122/173 patients	Rudwaleit M, et al. *Arthritis Res Ther* 2010; **12**: R43 [83]
ETN OL	Active AS	Number of painful entheses, MASES	Enthesitis/dactylitis observed in 8 (35%) patients at BL, 1 (4%) at weeks 24 and 54 (p<0·001)	Cantini F, et al. *Arthritis Rheum* 2006; **55**: 812–6 [84]
ADA *vs* PBO (ATLAS) Phase 3 BD RCT	Active AS (n = 315)	MASES, BASDAI item 4	Statistically significant reductions in MASES from BL at weeks 12 and 24 for ADA *vs* PBO (−2·7 *vs* −1·3, p = 0·018 and −3·2 *vs* −1·6, p = 0·005, respectively). Enthesis pain was also reduced, based on MASES and BASDAI Continued improvements during 2 years of ADA treatment: Observed mean change in MASES 3·8 after 2 years	Van der Heijde D, et al. *Arthritis Rheum* 2006; **54**: 2136–46 [85] Van der Heijde D, et al. *Ann Rheum Dis* 2009; **68**: 922–9 [86]

(*continued on next page*)

Table 1 (*Continued*)

Treatment	Population / number of patients	Method of enthesitis assessment	Results	Ref
IFX *vs* PBO DB RCT	Active AS	BASDAI item 4, MRI of axial enthesitis	A greater decrease in median VAS enthesopathy was observed with IFX *vs* PBO at week 30 (29·5 *vs* 51; $p = 0·001$) Most MRI lesions improved with IFX by week 30 ($p = 0·016$ *vs* PBO)	Marzo Ortega H, et al. *Ann Rheum Dis* 2005; **64**: 1568–75 [87]
IFX *vs* PBO (ASSERT) Phase 3 DB RCT and OL extension (EASIC)	Active AS, $n = 279$	MEI, BASDAI item 4	No significant change in MEI scores but a significant improvement in the enthesitis component of BASDAI with IFX *vs* PBO Enthesitis index scores remained numerically lower with IFX at week 96 *vs* BL At week 192, 81% of patients had no enthesitis	Van der Heijde D, et al. *Arthritis Rheum* 2005; **52**: 582–91 [88] Heldman F, et al. *Clin Exp Rheumatol* 2011; **29**: 672–80 [89] Heldmann F, et al. *Clin Exp Rheumatol* 2016; **34**: 184–90 [90]
ETN *vs* PBO Phase 2 RCT	Active AS ($n = 30$)	BASDAI item 4	Improvement from BL in entheseal pain with ETN at week 6	Brandt J, et al. *Arthritis Rheum* 2003; **48**: 1667–75 [91]
IFX *vs* PBO Phase 3 DB RCT	Severe active AS	BASDAI item 4	Significant decrease in entheseal pain with IFX *vs* PBO at week 12 At week 12, 76·3% of patients had no enthesitis; 48·3% had no enthesitis at all time points, 86·2% had no enthesitis at 90% of time points Enthesitis observed in 18·4% of patients and years 3 and 5, *vs* 50% at BL Enthesitis prevalence and entheseal pain decreased significantly from BL to week 156 ($p<0·0001$)	Braun J, et al. *Arthritis Rheum* 2008; **59**: 1270–8 [92] Braun J, et al. *Rheumatology* 2005; **44**: 670–6 [93] Braun J, et al. *Lancet* 2002; **359**: 1187–93 [94] Braun J, et al. *Arthritis Rheum* 2003; **48**: 2224–33 [95] Braun J, et al. *Ann Rheum Dis* 2005; **64**: 229–34 [96]
ETN *vs* PBO Phase 3 DB RCT	Active AS	Modified Newcastle Enthesitis Index	At month 4, enthesitis scores lower with ETN *vs* PBO (0·0 *vs* 1·5; $p = 0·001$)	Gorman JD, et al. *N Engl J Med* 2002; **346**: 1349–56 [97]
ETN Single-centre OL	SpA ($n = 10$; of whom, 8 fulfilled modified New York criteria for AS)	Entheseal count, VAS scores for entheseal pain; MRI; BASDAI item 4	VAS enthesopathy (0–100 mm scale) reduced from 62 at BL to 3 at week 24 ($p = 0·008$) Nine patients had MRI enthesitis; 38/44 (86%) lesions resolved	Marzo-Ortega H, et al. *Arthritis Rheum* 2001; **44**: 2112–7 [98]
ETO Single-centre OL	AS ($n = 22$)	MASES	Statistically significant reduction in median MASES score from BL to week 6	Jarret S, et al. *Ann Rheum Dis* 2009; **68**: 1466–9 [99]
NAP or ETO *vs* PBO DB RCT	AS	BASDAI item 4	Significant reductions in enthesopathy *vs* PBO for active treatment (−14·9 and −20·3, both $p<0·05$)	Gossec L, et al. *Ann Rheum Dis* 2005; **64**: 1563–7 [100]
MTX + NAP *vs* NAP	AS ($n = 51$)	MEI	Enthesitis decreased after treatment but there were no differences between the treatment groups	Altan L, et al. *Scan J Rheumatol* 2001; **30**: 255–9 [101]

ABT, abatacept; ADA, adalimumab; ANR, anakinra; AS, ankylosing spondyloarthritis; AT, Achilles tendon; ATLAS, Adalimumab Trial Evaluating Long-term Efficacy and Safety for Ankylosing Spondylitis; AUC, area under the curve; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMZ, betamethasone; BIM, bimekizumab; BL, baseline; CDUS, colour Doppler ultrasound; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; DB, double-blind; DMARD, disease-modifying anti-rheumatic drug; EASIC, European Ankylosing Spondylitis Infliximab Cohort; ESTHER, Enbrel Sulfasalazine Early Axial Spondyloarthritis; ETN, etanercept; ETO, etoricoxib; FIL, filgotinib; GOL, golimumab; GS, grey-scale; IFX, infliximab; IL, interleukin; iv, intravenous; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; MEI, Mander Enthesitis Index; MRI, magnetic resonance imaging; MTX, methotrexate; NAP, naproxen; NET, netakimab; nr-axSpA, non-radiographic axial spondyloarthritis; NS, not significant; OL, open label; OMERACT, Outcome Measures in Rheumatology; PBO, placebo; PD, power Doppler; PE, physical examination; PGA, patient's global assessment; RCT, randomised controlled trial; RHAPSODY, Review of Safety and Effectiveness with Adalimumab in Patients with Active Ankylosing Spondylitis; RIZ, risankizumab; SEC, secukinumab; SFZ, sulfasalazine; SpA, spondyloarthritis; SPARCC, Spondyloarthritis Research Consortium of Canada; TNF, tumour necrosis factor; TOC, tocilizumab; TOFA, tofacitinib; TOPAS, Ustekinumab for the treatment Of Patients with active Ankylosing Spondylitis; TS, total score; UCSF, University of California, San Francisco; US, ultrasound; UST, ustekinumab; VAS, visual analogue scale.

has shown superiority in clearing peripheral enthesitis associated with PsA compared to anti-TNF agents [111]. A possible explanation could be the anatomical differences between spinal and peripheral entheses (Fig. 1) [23]. For instance, peripheral entheses are often linked to synovio-entheseal complex structures but these are rare in axial entheses. Further research is also required to understand the contribution of the different types of immune cells at spinal and peripheral entheses, as well as any differences in resident immune cell populations (Fig. 2). Viewing these results in the context of the significant efficacy shown with inhibitors of IL-17A in both axSpA and PsA may shed some further light on this topic. Is IL-17A production IL-23-dependant at peripheral sites and largely IL-23-independent at axial sites? Although further research is required in this area, a recent study showed that human spinal entheseal Vδ1 and Vδ2 subsets of $\gamma\delta$T-cells are tissue resident, with the inducible Vδ1 subset able to produce IL-17A independently of IL-23R expression [27]. Furthermore, data from a mouse model of axSpA suggest that IL-23 is involved in the initiation but not the persistence of axial enthesitis [28].

Further research is also required to understand if the pathogenic mechanisms driving peripheral enthesitis in axSpA are similar to those in PsA. A recent study identified potential genetic differences between peripheral enthesitis in AS *versus* PsA [102]. HLA-B associations with peripheral joint and entheseal involvement previously reported in PsA were not confirmed in AS [103], suggesting that different mechanisms may be driving the pathogenesis of peripheral joint and entheseal involvement in AS and PsA.

Considering the dichotomous therapy findings in axial *versus* peripheral disease, careful assessment of enthesitis in axSpA, and indeed PsA with axial involvement, is warranted. In particular, the rheumatology community needs to know how spinous process, iliac crest and costochondral enthesitis fares in comparison to the peripheral sites.

More rigorous clinical assessment of enthesitis is required

The usual method of clinical enthesitis assessment in practice is via palpation of the affected site to assess pain and tenderness [1]. Clinical assessment of enthesitis in SpA aims to provide as accurate an assessment as possible within an acceptable timeframe during routine consultation while causing the least possible distress to patients. A limitation of this method is the lack of specificity in eliciting tenderness in the area being investigated, as many of the entheseal points are relatively near to joints and/or tender points for fibromyalgia, raising the possibility of misclassification. Physician training can help improve the reliability of clinical assessment and minimise intra-observer variability [104]. It has also recently emerged that clinical and ultrasound assessment correlates well for Achilles and patellar tendon origin enthesitis but not for other large entheses [105]. Further studies are needed with imaging assessment of sites of accessible axial enthesitis.

Numerous clinical scoring systems have been developed, each assessing a range of different sites and each with associated advantages and limitations (Table 2). The most commonly utilised indices in clinical trials are: MASES, which assesses 13 entheses at predominantly axial sites plus both Achilles tendons; SPARCC Enthesitis Index, evaluating nine bilateral sites at predominantly peripheral locations; and LEI, which includes six bilateral peripheral sites (Fig. 3b) [106–108]. Although these methods focus on the entheses suggested to be most frequently affected in patients with SpA [106], many peripheral sites, particularly in the MASES assessment, are omitted, as are many commonly affected accessible axial sites, such as costochondral joints and spinous processes. The spinous processes, in particular, are axial entheses that are prominent targets of SpA and are easily evaluated both clinically and on imaging. A more widespread enthesitis count may therefore be required to provide an accurate assessment of enthesitis in axSpA. With this in mind, the Mander Enthesitis Index (MEI) may be the most appropriate current measure for enthesitis assessment in axSpA. Although more time-consuming for both patient and the physician, MEI has been validated in AS and assesses inflammation at 66 entheses at both axial and peripheral sites, including spinous processes [106]. Given the differences in therapeutic response observed between axial and peripheral disease, a more extensive assessment may also help clinicians to select the most appropriate treatment for patients with SpA.

The large number of different scores available, and in some cases their perceived complexity, may contribute to the low priority given to the clinical assessment of enthesitis in axSpA. Evidence on the relative performance of the various measures is also scant. In a recent Brazilian study in 204 patients with axial and peripheral SpA, MASES performed better than LEI and equal to SPARCC in correlating with disease activity in axSpA; MASES was better than both LEI and SPARCC in correlating with disease activity in peripheral SpA [112]. However, the MEI was not evaluated. Consequently, there is currently no consensus regarding which method of assessment should be used under which circumstances. Although MASES is recommended by ASAS for the assessment of enthesitis in axSpA [113], an independent assessment of enthesitis is not mandatory according to the recommendations of the British Society of Rheumatology [114], European League Against Rheumatism (EULAR) [115], or American College of Rheumatology [116]. Further work is therefore required to agree on the most appropriate method of enthesitis assessment in the axSpA trial and research setting, and potentially also in clinical practice. We argue that a more thorough assessment using an index such as MEI should be part of any future recommendations and other secondary outcomes could be demoted in importance in secondary disease outcome measure evaluation.

Current strategies for the management of axSpA do not adequately consider enthesitis

Incorporation of enthesitis assessment into overall disease activity measures is another important unmet need in axSpA management. There has been a recent shift in the rheumatology field towards evaluating a treat-to-target approach to axSpA management, following recommendations by an international task force [117]. AS Disease Activity Score (ASDAS) inactive disease was suggested as a potential treatment target, as attainment of this status has been associated with slower progression of radiographic damage in several studies [116–118]. However, data from a prospective randomised study proving the efficacy of a treat-to-target strategy compared with routine care are still lacking and further research is required to assess the cost-effectiveness of such an approach and its feasibility in both clinical practice and trials [117,118]. Furthermore, ASDAS only offers measurement of a relatively narrow spectrum of the overall symptoms associated with SpA, omitting enthesitis (both axial and peripheral) as well as peripheral disease and extra-articular manifestations such as psoriasis, uveitis and inflammatory bowel disease. Other commonly used disease activity indices in axSpA, such as Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), also do not include a direct assessment of enthesitis. While it is measured indirectly in BASDAI item 4 (“How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?”) [119], this question is not a reliable assessment of enthesitis [120], and it is not specific enough to distinguish symptoms related to enthesitis from fibromyalgia or osteoarthritis. In contrast, composite measures of disease activity in PsA, such as Minimal Disease Activity and Psoriatic Arthritis Disease Activity Score, both include enthesitis and offer a wider overall measure of disease activity. A more thorough assessment of a wider spectrum of disease manifestations, akin to treatment recommendations in PsA [10] and including

Table 2
Overview of indices used to assess enthesitis in spondyloarthritis.

Index	Sites assessed	Scoring	Pros	Cons	Ref
Leeds Enthesitis Index	6 in total: bilateral lateral epi-condyles, medial femoral condyles, and Achilles tendon insertions	Presence or absence of tenderness; max score=6	Fast Simple Widely used in clinical trials	Includes peripheral sites only	Healy PJ, Helliwell PS, *Arthritis Rheum* 2008; **59**: 686–91 [108]
SPARCC Enthesitis Index	16 in total: the greater trochanter, quadriceps tendon insertion into the patella, patellar ligament insertion into the patella and tibial tuberosity, Achilles tendon insertion, plantar fascia insertion, medial and lateral epicondyles and the supraspinatus insertion	Presence or absence of tenderness; max score=16	Fast Simple Widely used in clinical trials	Includes peripheral sites only	Maksymowych WP, et al. *Ann Rheum Dis* 2009; **68**: 948–53 [107]
Mander Enthesitis Index /Newcastle index	66 in total: nuchal crests, manubriosternal joint, costochondral joints, greater tuberosity and medial and lateral epicondyles of the humerus, iliac crests, anterior superior iliac spines, greater trochanter of the femur, medial and lateral condyles of the femur, insertion of the Achilles tendons and plantar fascia to the calcaneus, cervical, thoracic, and lumbar spinous processes, ischial tuberosities, and posterior superior iliac spines	Each site rated from 0 to 3 (where 0=no pain, 1=mild tenderness, 2=moderate tenderness, and 3=wince or withdraw). Some of the sites are scored individually whereas others are scored as a group; max total score=90	Comprehensive Captures wide range of axial and peripheral sites Validated in ankylosing spondylitis	Time consuming Potential overlap with fibromyalgia tender points 0–3 scoring system could contribute to greater inter- and intra-rater inconsistency	Mander M, et al. *Ann Rheum Dis* 1987; **46**: 197–202 [106]
Maastricht Ankylosing Spondylitis Enthesitis Score	13 in total: 1st costochondral joint, 7th costochondral joint, posterior superior iliac spine, anterior superior iliac spine, iliac crest, 5th lumbar spinous process, proximal insertion of Achilles tendon	Presence or absence of tenderness; max score=13	Recommended by ASAS Fast Simple Widely used in clinical trials	Omits commonly affected yet accessible axial sites Omits commonly affected peripheral sites, except the Achilles tendon	Heuft-Dorenbosch L, et al. *Ann Rheum Dis* 2003; **62:** 127–32 [109]
Gladman Index	6 in total: bilateral tibial tuberosity, plantar fascia and Achilles tendon insertion)	Presence or absence of tenderness; max score=6	Fast Simple	Seldom used Omits commonly affected yet accessible axial sites	Healy PJ, Helliwell PS, *Arthritis Rheum* 2008; **59**: 686–91 [108]
Berlin/Major Index	12 in total: iliac crest, proximal Achilles, greater trochanter, medial condyle femur, lateral condyle femur, insertion plantar fascia	Presence or absence of tenderness; max score=12	Fast Simple	Seldom used Omits commonly affected yet accessible axial sites	Polachek A, et al. *Arthritis Care Res* 2017; **69**: 1685–91 [46]
University of California San Francisco Enthesitis Index	17 in total: vertebral processes of Cl-C2, C7-T1, T12-L1, L5-S1, symphysis pubis, both greater trochanters, pelvic abductor origin, anterior superior border of the iliac crests, ischial tuberosities, insertions of Achilles tendons, and plantar fascia	Each site rated from 0 to 3 (where 0=no pain, 1=mild tenderness, 2=moderate tenderness, and 3=wince or withdraw). Some of the sites are scored individually whereas others are scored as a group; max total score=51	Includes spinous processes	Seldom used 0–3 scoring system could contribute to greater inter- and intra-rater inconsistency Omits key peripheral sites	Clegg D, et al. *Arthritis Rheum* 1996; **39**: 2004–12 [110]

ASAS, Assessment of SpondyloArthritis international Society; max, maximum; SPARCC, Spondyloarthritis Research Consortium of Canada. The term 'Gladman Index' is adopted from a proposal in Araujo EG, et al. *Semin Arthritis Rheum* 2019; 48: 632–7. [110]

comprehensive assessment of enthesitis, would offer a more holistic approach to axSpA management.

What is the role of imaging for a more accurate diagnosis of enthesitis?

Enthesitis is postulated to be the primary pathological lesion driving subsequent manifestations of SpA; [1] early detection may therefore improve opportunities for earlier initiation of appropriate treatment and improved long-term outcomes. Imaging offers the option of longitudinal assessment, examining the degree of inflammation and damage over time, and also allowing detection of subclinical enthesitis (*i.e.*, where no clinical manifestations such as pain or inflammation are apparent); full body imaging could be employed for a more extensive entheseal assessment. However, data to support the hypothesis that identifying and treating subclinical disease may offer better long-term outcomes are currently lacking. It also remains to be seen if assessing and treating asymptomatic enthesitis is feasible in routine clinical practice. Nevertheless, enthesitis is likely to be underdiagnosed based on clinical assessment alone, and the introduction of more sensitive imaging methods may allow the monitoring of both inflammatory and chronic changes in enthesitis at both early and late stages of disease [121].

Current EULAR imaging recommendations suggest that when peripheral SpA is suspected, ultrasound or MRI may be used to detect peripheral enthesitis, which may support the diagnosis [122]. Ultrasound tends to be the preferred method of detecting peripheral enthesitis as it allows accurate assessment of the soft tissue components of the entheses and new bone formation, as well as functional evaluation of vascularisation using Doppler technology [123–125]. Power Doppler ultrasound (PDUS) of ≥1 vascularised enthesis has shown good predictive value for diagnosing SpA [126]. PDUS offers early detection of subclinical peripheral enthesitis, although further work is required to determine if the Glasgow Ultrasound Enthesitis Scoring System score may predict the development of SpA [127]. PDUS of the entheses (8 sites) of people with inflammatory back pain suggestive of axSpA in the DESIR cohort showed that, although enthesitis prevalence was low (14·4%), its specificity for classifying patients as having axSpA according to ASAS criteria was high (83·5%) [128]. Positive predictive value for meeting ASAS criteria for axSpA was 69% [128]. PDUS of the entheses may therefore aid the early diagnosis of patients who do not fulfil ASAS classification criteria. These ultrasound findings in early axSpA resonate well with the pathophysiological importance of the entheseal lesion as a priority clinical and imaging marker for diagnosis, monitoring and prognosis.

MRI can detect both soft tissue and intraosseus abnormalities in active enthesitis, and may therefore be a useful tool in the diagnosis and monitoring of SpA, particularly axial disease [129]. Conventional MRI, like ultrasound and clinical assessment, assesses one anatomical area at a time, whereas whole-body MRI can give a 'head to toe' examination of axial and peripheral enthesitis [45]. Several studies have now looked at the application of whole-body MRI for diagnosing early entheseal abnormalities at axial and peripheral sites [45,130]. While these studies indicate that whole-body MRI is a promising new imaging modality for the evaluation of enthesitis in patients with PsA and axSpA, further investigation is required before it can be used in clinical practice since there is a fairly high frequency of entheseal abnormalities identified at the gluteus medius and supraspinatus tendon insertion locations, potentially suggesting a lack of specificity [45]. The first steps have been taken in developing a scoring system to allow further testing and refinement of this technique [131]. Lack of sensitivity has been raised as an issue for the diagnostic use of MRI in axSpA [132], and high-quality data are lacking. However, the ability of MRI to detect very early-phase disease, where patients have axial symptoms, but no structural changes, may aid in the earlier diagnosis of axSpA.

Discrepancies have been reported between clinical and imaging findings of enthesitis. For instance, in patients with axSpA or PsA, some entheseal sites showed a higher frequency of enthesitis based on clinical assessment *versus* MRI although this difference was not observed in healthy subjects [45]. Clinical examination based on tenderness alone has also reported higher percentages of enthesitis than grey-scale ultrasound combined with PDUS examination, suggesting that tenderness does not always indicate the presence of enthesitis [105,133]. The relationship between clinical and sonographic findings for large entheses may be dependant on the anatomical site and has been shown to be best for the Achilles tendon and patellar tendon origin [105]. It is also worth remembering that ultrasound and MRI changes can occur in people without SpA. Greater understanding of the imaging features (*e.g.*, grey-scale ultrasound *vs* PDUS findings, number of sites involved and location of enthesitis, presence of peri-entheseal tissues inflammation detected by MRI) and interpretation of data is therefore required to ensure differentiation between people with SpA *versus* healthy subjects [45,134,135]. In addition, factors such as age, weight and physical activity need to be considered when interpreting images [19,45].

Consensus is still required regarding the role of both ultrasound and MRI in clinical practice. Furthermore, the specific entheses to be assessed and the methods of assessment require further study and agreement. For example, assessment of the medial femoral condyles using the LEI does not correspond to any particular enthesis on

Table 3
The following research agenda is proposed in order to understand.

- The pathophysiology underlying enthesitis at axial *versus* peripheral sites, including the specific populations of immune cells and cytokines involved
- Potential differences between peripheral enthesitis in axSpA compared with peripheral SpA
- The efficacy of IL-23 inhibitors in peripheral enthesitis in patients with axSpA
- Further data from randomised controlled trials with new molecules in development for nr-axSpA and AS, including secukinumab, ixekizumab, and tofacitinib
- The relevance of subclinical enthesitis to the subsequent development of clinical enthesitis and other disease manifestations
- Imaging approaches for the diagnosis and monitoring of enthesitis, including validated recommendations for the implementation and scoring of power Doppler ultrasound and magnetic resonance imaging in axSpA
- Role of enthesitis in a treat to target strategy for axSpA and the distinction between axial and peripheral enthesitis
- Factors most informative in terms of diagnostic potential, discrimination between SpA types, prognostic use (*e.g.*, prediction of progression from nr-axSpA to AS), sensitivity to change over time, or in response to treatment
- Consensus regarding enthesitis measurement, *e.g.*, sites assessed, number of sites assessed, measurements, and techniques/indices used
- Longitudinal data are required to assess whether enthesitis is predictive of progression from nr-axSpA to AS
- Gender differences in axSpA, peripheral disease and enthesitis specifically
- Distinguishing enthesitis from fibromyalgia and osteoarthritis
- Potential differences related to age at disease onset (enthesitis-related arthritis *vs* adult-onset SpA)
- Impact on enthesitis on patient-reported outcomes, productivity and quality of life

AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; IL, interleukin; nr-axSpA, non-radiographic axial spondyloarthritis; SpA, spondyloarthritis.

ultrasound. While it seems unlikely that these imaging modalities will completely replace clinical assessment of enthesitis, they offer a valuable tool to aid the early detection and treatment of enthesitis in axSpA.

Conclusions / future directions

Enthesitis is a common manifestation of axSpA that plays a central role in driving the pathophysiology of the disease, correlating with downstream structural damage and adding to the burden of disease. Axial and peripheral enthesitis have important anatomical differences and inflammation at these sites is driven by different pathophysiological processes and may respond differently to treatment.

Commonly used clinical enthesitis measures may not be fit for purpose in axSpA and an extensive assessment such as that offered by MEI may be more appropriate. For a briefer but still comprehensive appraisal, a combination of MASES and SPARCC may be considered, enabling assessment of 28 sites with balanced emphasis on both axial and peripheral entheses. Ultrasound and MRI imaging may offer an opportunity for earlier detection and thus earlier treatment of enthesitis in axSpA. In an age when a treat-to-target approach for axSpA is being evaluated, consideration should be given to a wider range of symptoms, including axial and peripheral enthesitis, to ensure holistic disease management. Enthesitis is an important topic of ongoing research (Table 3) as the medical community strives to better understand this key early symptom, its pathophysiology and its role in the clinical management of axSpA.

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Author contributions

DMG was responsible for the conception of the work. All authors contributed to the interpretation of data for the work, were responsible for revising the manuscript for important intellectual content, approve the final version of the manuscript to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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