Review

Enthesitis in IBD Patients

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Posted Date: 29 May 2024

doi: 10.20944/preprints202405.1972.v1

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Enthesitis in IBD Patients

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Abstract: Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and encompasses two main subtypes, Crohn's disease (CD) and ulcerative colitis (UC). IBD is frequently accompanied by extraintestinal manifestations (EIMs), with axial and peripheral spondyloarthritis (SpA) being the most common. Enthesitis, an inflammation of the bone insertions of capsules, ligaments, and tendons, represents an initial lesion in SpA. However, enthesitis remains an underestimated and often obscured EIM. The early detection of subclinical enthesial involvement in IBD patients using ultrasound (US) could provide an opportunity for timely intervention. While previous meta-analyses have reported on the incidence and prevalence of SpA in IBD, specific attention to enthesitis has been lacking. Therefore, this narrative review aims to resume the current knowledge on existing IBD-SpA cohorts, focusing specifically on enthesitis.

Keywords: inflammatory bowel disease; Crohn's disease; ulcerative colitis; extraintestinal manifestations; enthesitis

1. Introduction

Inflammatory bowel diseases (IBD) are a heterogeneous group of chronic and recurrent intestinal diseases made of two main clinical phenotypes: Crohn's disease (CD) and ulcerative colitis (UC) [1]. IBD patients sometimes develop an extraintestinal manifestations (EIMs), inflammatory conditions that can involve different organs and systems with a serious impact on morbidity and quality of life [2]. EIMs occur in 25% to 40% of IBD patients and mainly affect the joints, followed by the skin, eyes, and hepatobiliary tract [3]. Musculoskeletal symptoms are the most common EIM associated with IBD [4]. The Assessment of SpondyloArthritis International Society (ASAS) has developed classification criteria for both axial and peripheral arthropathy, which includes the whole spectrum of spondyloarthritis (SpA), such as IBD related arthropathy [5]. SpA is a joint term applied to a group of rheumatic diseases with particular features in common and others distinct from other inflammatory arthritides. It includes IBD-related arthritis, ankylosing spondylitis, reactive arthritis, psoriatic arthritis and undifferentiated SpA [6].

Both axial and peripheral manifestations can be present in patients with IBD. In peripheral SpA, arthritis, dactylitis and enthesitis are the main symptoms. Enthesitis presenting with Achilles tendinitis, plantar fasciitis, and chest wall pain sometimes leads to structural changes of the underlying bones and causes disability [7]. Ultrasonography (US) or magnetic resonance imaging (MRI) examination of the affected area can help in earlier detection missed by clinical inspection [8]. However, prevalence of peripheral SpA is frequently underestimated or mistakenly related to corticosteroid overuse, due to transitory manifestation of some oligoaricular patterns or the use of chronic corticosteroid treatment [9]. Also, recognition of joint and tendon involvement could be delayed by the fact that gastroenterologists may not specifically inquire about musculoskeletal symptoms in everyday clinical inspection [10]. Enthesitis is often the principal sign of SpA in young adults [11], but only a small percentage of cases are discovered by means of a clinical examination:

 doi:10.20944/preprints202405.1972.v1

for example, in a population-based cohort of 499 Norwegian IBD patients, a clinical assessment identified enthesitis in only 11 patients [12]. The pathology of entheses in IBD and SpA patients is often underdiagnosed or mistaken for overuse tendon pathology [13].

Although patients with IBD and SpA appear to share many clinical, immunologic, and genetic characteristics [14], the exact relationship between these two entities has never been comprehensively defined.

The pathophysiology of enthesitis includes the innate and adaptive immunity with overlap of the interleukin (IL)-17 and IL-23 axis [14]. Accordingly abnormal gut microbiome as seen in IBD patients may be a factor in the development of entheseal pathology [15]. Patients with IBD are usually not examined for enthesitis and additionally there is no standard protocol for such examination. Clinical findings including localized pain, tenderness, and swelling are suggestive of enthesitis [16], yet it is discovered by clinical examination only in a low percentage of patients [17]. The most commonly investigated entheses are those located in the lower limbs (i.e., plantar fascia, patellar, quadriceps, and Achilles tendons) [18,19].

Enthesitis is the prime lesion in SpA, but also an isolated peripheral enthesitis has previously been reported following vedolizumab therapy in IBD patients [20–22]. Previous studies have shown a prevalence of SpA under vedolizumab therapy of around 5% [21,22], but in cohort of 90 cases, it was actually double [23]. This entity, so called vedolizumab-associated enthesitis, is not EIM, but it could overlap with entheseal pathology in SpA.

This review describes the current novelties on existing IBD-SpA cohorts, focusing specifically on enthesitis.

2. Materials and Methods

In this narrative review, we conducted search of a PubMed, Scopus, Web of Science, and Cochrane databases. The following terms were used: IBD, CD, UC, enthesitis.

Articles published from January 2013 - March 2023 were included if they evaluated the prevalence/incidence of enthesitis in cohorts of IBD patients. Articles selected for inclusion were limited to availability of full text, English language articles, clinical studies with adult patients. Meta-analyses, case reports and reviews were excluded. Article titles were first reviewed for inclusion by one study investigator (IAO). Abstracts and the full text were further screened by IAO for final inclusion and confirmed by the co-authors (JV, MR, ZS). Studies were included if they evaluated the prevalence/incidence of enthesitis in a cohort of patients with IBD.

Data was extracted by single investigator (IAO) and reviewed by the co-authors. The following data was observed: study setting and design, number of patients with IBD, type of IBD, method of rheumatologic evaluation, imaging modalities used. The prevalence and incidence of enthesitis in the IBD group, individualized for CD and UC where available, was also collected.

There was no direct patient or public involvement in designing, interpreting, discussing or drawing of conclusions.

3. Results

Literature review

We performed a systematic literature review of studies that evaluated enthesitis in IBD cohorts. The initial database search yielded 71 articles; two were removed because they evaluated vedolizumab-associated enthesitis, and four were removed because they evaluated enthesitis in children. After removing non-English language articles, reviews, meta-analyses, and case reports, only 11 studies remained for abstract/full text assessment.

Study design characteristics

Focusing on study design, one was population-based, and ten were clinic-based. Most studies were conducted at a single center, with only two multicentre studies. Three studies reported data for IBD without distinguishing between CD and UC. Rheumatologists were involved in all of eleven studies. A physical examination was included in all studies. Other methods of evaluation included

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questionnaires in 2/11 studies. US was performed in 7/11 studies. Information stratified based on IBD disease duration was obtained in three studies.

Bertolini et al. [24] found clinical evidence of enthesitis (tenderness and/or swelling) in 33% of IBD patients, and it was significantly more frequent in UC patients compared to CD patients (37.7% versus 25%, p=0.012). This is the one of two studies that observed and distinguished acute and chronic entheseal lesions. Patients with longer disease duration had more frequently entheseal abnormalities at US evaluation (85/98 patients (90%) versus 38/53 (72%), p=0.003) [24]. The following entheses were examined for tenderness and swelling bilaterally: common extensor tendon (CET), insertion on the lateral epicondyle of the humerus, quadriceps tendon (QT), patellar tendon (PT), tibial tuberosity (TT), Achilles tendon (AT) and plantar fascia (PF) insertion on the calcaneus. US was performed in B-mode and power Doppler (PD) mode. Abnormal findings were entheseal thickening, entheseal hypoechogenicity, bony erosions, enthesophytes and enlargement of bursae. Entheseal thickening, entheseal hypoechogenicity, and bursal enlargement were considered acute lesions. Bony erosions, calcifications, and enthesophytes were considered chronic lesions. Vascularization was examined using PD-mode, and studied at the following areas: cortical bone insertion, body of tendon and bursa. The detection of vascularization in any of these areas was considered abnormal. Enthesis US vascularity was classified into four distinctive patterns according to the number of vessels involved: 0 = none; 1 = 1-3 vessels; 2 = 4-5 vessels; 3 = >5 vessels. The presence of PD ≥1 was considered indicative of an acute lesion [24]. Ultrasonographic findings were scored according to the Madrid sonography enthesitis index (MASEI) [25] and Glasgow ultrasound enthesitis scoring system (GUESS) [26]. No statistically significant differences were observed comparing patients with shorter or longer disease duration (≤12 months versus >12 months) regarding rheumatological evaluation (data not shown). As expected, patients with longer disease duration (≤12 months versus >12 months) had more frequently entheseal abnormalities at US evaluation, at least one enthesis with erosions and more entheses with chronic lesions/patient.

In study of Bakirci Ureyen et al., entheseal inflammation scores were higher in patients with IBD than in healthy control group. Also, IBD disease duration was independent of inflammation and damage score. Interestingly, they showed BMI correlation to US scores and inflammation in IBD patients [27].

Cantini et al. [28] showed that enthesitis frequency was significantly higher in IBD-SpA patients with associated psoriasis. Enthesitis occurrence was not different in patients with UC and those with CD.

Husic et al. [29] did not find a significant correlation of disease duration and activity of IBD with MASEI score, but US verified enthesitis was more common in patients with IBD as compared to healthy subjects. No association was found between clinical IBD activity and MASEI, nor between clinical IBD activity and erosion, PD and enthesophyte subscores.

Bandinelli et al. [30] suggested that entheseal involvement may also be present in early IBD disease. The entheseal involvement is related neither to duration nor to disease activity according to their study. In disagreement with Kiris et al [31], who showed that entheseal pain tightly correlated with vascularity shown by PD, 16% of Bandinelli patients were positive at PD signal on entheses without symptoms.

Tavassoli et al [32] found enthesopathy in 6.5% IBD patients without US assessment.

Table 1. Study characteristics.

Study	Setting	Design	IBD	RI	PE	US	PD	A/C	EE	MASEI	GUESS	ASAS	Q	UC	CD
Variola et al. [33]	clinic	cross-sectional	181	yes	yes	no							IBIS	Partial Mayo score	HBI

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Bakici Ureyen et al. [27]	clinic	cross-sectional	43	yes	yes	yes	yes	no	QT, AT, PT, TT	no	no	no	no	no	no
Ossum et al. [34]	population-based	cohort	441	yes	yes	no							yes	no	no
Tavassoli et al. [32]	clinic	cross-sectional	96	yes	yes	no							no	no	no
Bandinelli et al. [30]	clinic	cross-sectional	81	yes	yes	yes	yes	no	QT, AT, PF	no	yes	yes	no	Truelove	CDAI
Bertolini et al. [24]	clinic	cross-sectional	148	yes	yes	yes	yes	yes	CET, QT, PT, TT, AT, PF	yes	yes	yes	no	Mayo	HBI
Husic et al. [29]	clinic	cross-sectional	47	yes	yes	yes	yes	no	QT, PT, AT, PF, TT	yes	no	yes	no	Mayo	CDAI
Cantini et al. [28]	clinic	case-control	88	yes	yes	no							no	no	no
Hsiao et al [35]	clinic	prospective	18	yes	yes	yes	yes	no	PT, AT, PF	no	yes	yes	no	no	no
Roviscio et al.	clinic	case-	76	ye	ye	ye	ye	no	PT, AT,	no	no	yes	no	Mayo	CD

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[36]		control		s	s	s	s		PF, QT						AI
Martinis et al. [37]	clinic	case-control	301	yes	yes	yes	yes	yes	CET, PT, TT, PF, AT	yes	yes	no	no	Mayo	HBI

Abbrevations: IBD: number of patients with IBD; RI: rheumatologist input; PE: physical examination; US: studies with performed ultrasound examination; PD: power Doppler mode; A/C: studies with US made distinguish between acute vs chronic lesions; EE: examined entheses; MASEI: Madrid sonography enthesitis index; GUESS: Glasgow ultrasound enthesitis scoring system; ASAS: PD positive entheseal site in ASAS neg patients; Q: questionnaire; UC: ulcerative colitis; CD: Crohn's disease; HBI: Harvey Bradshaw Index; CDAI: Crohn Disease Activity Index; CET: common extensor tendon; QT: quadriceps; PT: patellar tendon; TT: tibial tuberosity; AT: Achilles tendon; PF: plantar fascia; IBIS: IBd Identification of Spondyloarthritis Questionnaire.

Rovisco et al. conducted a multicenter study using US assessment to explore joint and entheseal involvement in IBD patients with no signs or symptoms of musculoskeletal disease, and their findings indicate that the prevalence of sub-clinical entheseal and joint involvement is high in IBD patients [36].

The study of Martinis et al. found that a positive Doppler signal at entheseal level was more frequently observed in IBD subjects with SpA than in IBD patients with fibromyalgia [37].

The most affected entheseal site in these studies was the patellar tendon, followed by the Achilles tendon, which is often described as being the most affected in patients with SpA [38,39]. The most relevant findings shown by US in the early phase of entheseal pathology were thickness and PD signal at entheses in accordance to previous studies [40,41], probably due to edema, neovascularization, and cell infiltration.

4. Discussion

In this narrative review of eleven studies analyzing enthesitis in patients with IBD, several limitations were identified. The majority of the included studies were clinic-based, single-center, and cross-sectional in design. This limited number of studies is unlikely to provide sufficient evidence to fully describe the involvement of enthesitis and its correlation with IBD activity. Additionally, there were variations in the scoring systems used to assess IBD activity among these studies, further complicating the interpretation of results.

Also, there were variations in US assessment. While the MASEI included retrocalcaneal and infrapatellar bursitis in the score, bursitis is not considered an elementary lesion of enthesitis according to OMERACT. The OMERACT experts were of the opinion, that bursae are not part of the enthesitis complex, and that inflammation affects them only at a later stage of enthesitis when it extends toward the tendon and peri-tendinous structures [42].

Previous reviews attempted to identify relevant studies about EIMs from database inception to August 2016., and found only few estimates available for enthesitis (prevalence range from 1% to 54%) [43].

Systematic review by Sakellariou et al. provided an overview on the clinical applicability of musculoskeletal ultrasonography in patients with IBD without an overt joint involvement, and they included only studies with US assessment. They did not find any correlation between the type of IBD and the disease activity. They have found that only IBD disease duration correlated with a higher

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frequency of US abnormalities; but this result emerged from a single study which enrolled patients with a very short disease duration (<12 months of disease duration) [44].

This review represents an attempt to systematically investigate the study design and characteristics of entheseal involvement in IBD patients. Still, it was limited by incomplete or absent reporting of important variables such as body mass index (BMI), medication usage, and heterogeneity in disease activity classification.

Also, small number of studies performed US assessment, and those who did performed it, did not use the same scoring system.

Based on the available data, it is recommended to assess the frequency of enthesitis using both physical examination and ultrasound as the reference standard. However, it is important to acknowledge that data on such assessments are limited. Future studies with larger and more extensive cohorts are necessary to better evaluate enthesitis in IBD patients.

The relationship between enthesitis and IBD activity index remains unclear, and further research is required to explore this association. It is worth noting that enthesitis may be asymptomatic in majority of patients, and there is currently a lack of standardized protocols for examining enthesitis in IBD patients. Consequently, many IBD patients are not routinely examined for enthesitis.

The researchers express a particular interest in studies investigating the impact of increased BMI on entheseal involvement in IBD patients, as this information could help prevent further complications. Effective treatment is available for both axial and peripheral SpA and early diagnosis and treatment are important to modify disease progression and decrease the disease burden [45]. Every patient with possible SpA should be seen by a rheumatologist for final diagnosis and the coordination of multidisciplinary nonpharmacological and pharmacological treatment [46]. For example, in patients with predominant enthesitis, a biologic may provide efficacy that supersedes conventional disease modifying anti-rheumatic medications [47–49]. US is increasingly being used in the identification of inflammatory arthritis [50], and it has the potential to provide a unique opportunity to assess SpA, particularly in early disease stage, in IBD.

To the best of our knowledge, this is the first study that systematically highlights the limitations of the available studies on enthesitis in IBD patients, emphasizing the need for more extensive research with standardized protocols. The presence of enthesitis should be assessed using both physical examination and ultrasound, and future studies should aim to clarify the relationship between enthesitis and IBD activity. Additionally, efforts should be made to establish a standard protocol for examining enthesitis in IBD patients, and further investigations into the impact of increased BMI on entheseal involvement are warranted to improve patient outcomes and prevent complications.

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

5. Conclusions

The frequency of the enthesitis should be assessed using both physical examination and ultrasound as the reference standard. Data of such assessments are limited. Future studies with more extensive cohorts are needed to evaluate enthesitis. Is enthesitis generally independent of IBD activity index? Enthesitis may be asymptomatic in majority of patients. IBD patients are often not examined for enthesitis and there is a lack of standard protocol. We are looking forward to seeing some studies about impact of increased BMI on entheseal involvement in IBD patients in order to prevent further complications. The use of inexpensive and rapid imaging techniques, such as US, could be routinely represented in daily clinical examination and trials to correctly evaluate occult SpA, thus preventing disability and worsening of quality of life in IBD patients.

This section is not mandatory but can be added to the manuscript if the discussion is unusually long or complex.

Author Contributions: Conceptualization, M.R. and I.A.O.; methodology, J.V.; software, J.V.; validation, M.R., I.A.O. and J.V.; formal analysis, M.R.; investigation, I.A.O.; resources, I.A.O.; data curation, I.A.O.; writing—

 doi:10.20944/preprints202405.1972.v1

original draft preparation, J.V., M.R.; writing—review and editing, M.R.; visualization, M.R.; supervision, M.R., Z.S.; project administration, M.R., Z.S; funding acquisition, Z.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Adolph TE, Meyer M, Schwärzler J, Mayr L, Grabherr F, Tilg H. The metabolic nature of inflammatory bowel diseases. *Nature Reviews Gastroenterology & Hepatology*. **2022** *Jul 29*;19(12):753–67
2. Harbord M, Annese V, Vavricka SR, Allez M, Barreiro-de Acosta M, Boberg KM, et al. The First European Evidence-based Consensus on Extra-intestinal Manifestations in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis* [Internet]. **2015** *Nov 27*;10(3):239–54. Available from: http://www.spgp.pt/media/1069/pdf8.pdf
3. Vavricka SR, Schoepfer A, Scharl M, Lakatos PL, Navarini A, Rogler G. Extraintestinal Manifestations of Inflammatory Bowel Disease. *Inflammatory Bowel Diseases* [Internet]. **2015** *Jul 2*;21(8):1982–92. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4511685
4. Bourikas LA, Papadakis KA. Musculoskeletal manifestations of inflammatory bowel disease. *Inflammatory Bowel Diseases*. **2009** *Dec*;15(12):1915–24
5. Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Annals of the Rheumatic Diseases*. **2010** *Nov 24*;70(1):25–31
6. Lipton S, Deodhar A. The new ASAS classification criteria for axial and peripheral spondyloarthritis: promises and pitfalls. *International Journal of Clinical Rheumatology*. **2012** *Dec*;7(6):675–82
7. Amarnani A, Thakker S, Panush RS. Reflecting on the immunopathology of arthritis associated with inflammatory bowel disease: what do we know and what should we know? *Clinical Rheumatology*. **2022** *Aug*;41(8):2581-2588
8. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. *Nature Reviews Rheumatology* [Internet]. **2017** *Nov 21*;13(12):731–41. Available from: https://www.nature.com/articles/nrrheum.2017.188
9. Arvikar SL, Fisher MC. Inflammatory bowel disease associated arthropathy. *Current Reviews in Musculoskeletal Medicine* [Internet]. **2011** *Jun 28* [cited 2019 Oct 16];4(3):123–31. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3261248
10. Ibn Yacoub Y, Amine B, Laatiris A, Bensabbah R, Hajjaj-Hassouni N. Relationship between diagnosis delay and disease features in Moroccan patients with ankylosing spondylitis. *Rheumatology International*. **2010** *Nov 26*;32(2):357–60
11. Mielants H, Veys EM, Cuvelier C, De Vos M, Goemaere S, De Clercq L, et al. The evolution of spondyloarthropathies in relation to gut histology. III. Relation between gut and joint. *The Journal of Rheumatology* [Internet]. **1995** *Dec 1* [cited 2024 Apr 13];22(12):2279–84. Available from: https://pubmed.ncbi.nlm.nih.gov/8835562/
12. Palm O. The prevalence and incidence of peripheral arthritis in patients with inflammatory bowel disease, a prospective population-based study (the IBSEN study). *Rheumatology*. **2001** *Nov 1*;40(11):1256–61
13. Terslev L, Qvistgaard E, Torp-Pedersen S, Laetgaard J, Danneskiold-Samsøe B, Bliddal H. Ultrasound and Power Doppler findings in jumper's knee — preliminary observations. *European Journal of Ultrasound*. **2001** *Jul*;13(3):183–9
14. Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-γt+ CD3+CD4−CD8− entheseal resident T cells. *Nature Medicine*. **2012** *Jul*;18(7):1069–76
15. Kalinkovich A, Livshits G. A cross talk between dysbiosis and gut-associated immune system governs the development of inflammatory arthropathies. *Seminars in Arthritis and Rheumatism*. **2019** *Dec*;49(3):474–84
16. Rodríguez-Reyna TS, Martínez-Reyes C, Yamamoto-Furusho JK. Rheumatic manifestations of inflammatory bowel disease. *World Journal of Gastroenterology*. **2009**;15(44):5517
17. Bandinelli F, Prignano F, Bonciani D, Bartoli F, Collaku L, Candelieri A, et al. Ultrasound detects occult entheseal involvement in early psoriatic arthritis independently of clinical features and psoriasis severity. *Clinical and Experimental Rheumatology* [Internet]. **2013** [cited 2024 Apr 13];31(2):219–24. Available from: https://pubmed.ncbi.nlm.nih.gov/23190740

 doi:10.20944/preprints202405.1972.v1

18. Maria Antonietta D'Agostino, Aegerter P, Sandrine Jousse-Joulin, Chary-Valckenaere I, Lecoq B, Gaudin P, et al. How to evaluate and improve the reliability of power Doppler ultrasonography for assessing enthesitis in spondylarthritis. *Arthritis & Rheumatism*. **2008** *Dec 30*;61(1):61–9
19. Schett G, Lories RJ, D'Agostino MA, Elewaut D, Kirkham B, Soriano ER, et al. Enthesitis: from pathophysiology to treatment. *Nature Reviews Rheumatology* [Internet]. **2017** *Nov 21*;13(12):731–41. Available from: https://www.nature.com/articles/nrrheum.2017.188
20. Sayam Dubash, Thiraupathy Marianayagam, Ilaria Tinazzi, Tariq Al-Araimi, Pagnoux C, Weizman AV, et al. Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease. *Rheumatology*. **2018** *Sep 10*;58(6):963–8
21. Alivernini S, Pugliese D, Tolusso B, Felice C, Gremese E, Armuzzi A. Comment on: Emergence of severe spondyloarthropathy-related entheseal pathology following successful vedolizumab therapy for inflammatory bowel disease. *Rheumatology* (Oxford, England) [Internet]. **2019** *Jun 1* [cited 2024 Apr 13];58(6):1113–5. Available from: https://pubmed.ncbi.nlm.nih.gov/30847491
22. Dupré A, Collins M, Nocturne G, Carbonnel F, Mariette X, Seror R. Articular manifestations in patients with inflammatory bowel disease treated with vedolizumab. *Rheumatology* (Oxford, England) [Internet]. **2020** *Nov 1* [cited 2024 Apr 13];59(11):3275–83. Available from: https://pubmed.ncbi.nlm.nih.gov/32259251
23. Mirko Di Ruscio, Ilaria Tinazzi, Variola A, Geccherle A, Marchetta A, McGonagle D. Prevalence and real-world management of vedolizumab-associated enthesitis in successfully treated IBD patients. *Rheumatology* (Oxford). **2021** *Dec 1*;60(12):5809-5813.
24. Bertolini E, Macchioni P, Rizzello F, Salice M, Vukatana G, Sandri G, et al. Ultrasonographic and clinical assessment of peripheral enthesitis and arthritis in an Italian cohort of inflammatory bowel disease patients. *Seminars in Arthritis and Rheumatism*. **2020** *Jun*;50(3):436–43
25. de Miguel E, Cobo T, Muñoz-Fernández S, Naredo E, Usón J, Acebes JC, et al. Validity of enthesis ultrasound assessment in spondyloarthropathy. *Annals of the Rheumatic Diseases* [Internet]. **2008** *Apr 7* [cited 2019 Dec 3];68(2):169–74. Available from: https://ard.bmj.com/content/annrheumdis/68/2/169.full.pdf
26. Balint PV, Kane DM, Wilson HR, McInnes IB, Sturrock RD. Ultrasonography of entheseal insertions in the lower limb in spondyloarthropathy. *Annals of the Rheumatic Diseases*. **2002** *Oct 1*;61(10):905–10
27. Sibel Bakirci Ureyen, Cengiz Karacaer, Bilal Toka, Zeynep Erturk, Ahmet Tarik Eminler, Kaya M, et al. Similar subclinical enthesitis in celiac and inflammatory bowel diseases by ultrasound suggests a gut enthesis axis independent of spondyloarthropathy spectrum. *Rheumatology* [Internet]. **2018** *May 8* [cited 2024 Apr 13];57(8):1417–22. Available from: https://pubmed.ncbi.nlm.nih.gov/29741671
28. Cantini F, Niccoli L, Nannini C, Cassarà E, Kaloudi O, Rizzello F, et al. Case-control Study on Dactylitis, Enthesitis, and Anterior Uveitis in Spondyloarthritis Associated with Inflammatory Bowel Diseases: Role of Coexistent Psoriasis. *The Journal of Rheumatology*. **2017** *Apr 15*;44(9):1341–6
29. Husic R, Lackner A, Kump PK, Högenauer C, Graninger W, Dejaco C. High Prevalence of Ultrasound Verified Enthesitis in Patients With Inflammatory Bowel Disease With or Without Spondylarthritis. *Frontiers in Medicine* [Internet]. **2021** [cited 2024 Apr 13];8:637459. Available from: https://pubmed.ncbi.nlm.nih.gov/33644102
30. Bandinelli F, Milla M, Genise S, Giovannini L, Bagnoli S, Candelieri A, et al. Ultrasound discloses entheseal involvement in inactive and low active inflammatory bowel disease without clinical signs and symptoms of spondyloarthropathy. *Rheumatology*. **2011** *Feb 10*;50(7):1275–9
31. Kiris A, Kaya A, Ozgocmen S, Kocakoc E. Assessment of enthesitis in ankylosing spondylitis by power Doppler ultrasonography. *Skeletal Radiology*. **2006** *Feb 10*;35(7):522–8
32. Tavassoli S, Shahabinasab I, Norouzi A, Amiriani T, Abdolahi N, Livani S, et al. From bowel inflammation to the bone and joints: musculoskeletal examination in inflammatory bowel disease (IBD). *BMC Musculoskeletal Disorders*. **2021** *Dec 4*;22(1):1019.
33. Variola A, Zanolin ME, Cipriano G, Macchioni P, Martinis F, Pasetti A, et al. The IBIS-Q [IBd Identification of Spondyloarthritis Questionnaire]: A Novel Tool to Detect Both Axial and Peripheral Arthritis in Inflammatory Bowel Disease Patients. *Journal of Crohn's & Colitis* [Internet]. **2020** *Dec 2* [cited 2024 Apr 13];14(12):1680–6. Available from: https://pubmed.ncbi.nlm.nih.gov/32413102
34. Ossum AM, Palm Ø, Cvancarova M, Solberg IC, Vatn M, Moum B, et al. Peripheral arthritis in patients with long-term inflammatory bowel disease. Results from 20 years of follow-up in the IBSEN study. *Scandinavian Journal of Gastroenterology*. **2018** *Oct 24*;53(10-11):1250–6
35. Hsiao YF, Wei S, Lu C, Wu CH, Hsieh SC, Li KJ. Patients with Inflammatory Bowel Disease have Higher Sonographic Enthesitis Scores than Normal Individuals: Pilot Study in Taiwan. *Journal of Medical Ultrasound*. **2014** *Dec 1*;22(4):194–9
36. Rovisco J, Duarte C, Batticcioto A, Sarzi-Puttini P, Dragresshi A, Portela F, et al. Hidden musculoskeletal involvement in inflammatory bowel disease: a multicenter ultrasound study. *BMC Musculoskeletal Disorders*. **2016** *Feb 16*;17(1)
37. Martinis F, Tinazzi I, Bertolini E, Citriniti G, Variola A, Geccherle A, Marchetta A, McGonagle D, Macchioni P. Clinical and sonographic discrimination between fibromyalgia and spondyloarthopathy in

inflammatory bowel disease with musculoskeletal pain. *Rheumatology* (Oxford). **2020** *Oct 1*;59(10):2857-2863.
38. Olivieri I, Foto M, Ruju GP, Gemignani G, Giustarini S, Pasero G. Low frequency of axial involvement in Caucasian pediatric patients with seronegative enthesopathy and arthropathy syndrome after 5 years of disease. *The Journal of Rheumatology* [Internet]. **1992** *Mar 1* [cited 2024 Apr 13];19(3):469–75. Available from: https://pubmed.ncbi.nlm.nih.gov/1578464
39. Olivieri I, Padula A, Pierro A, Favaro L, Oranges GS, Ferri S. Late onset undifferentiated seronegative spondyloarthropathy. *The Journal of Rheumatology* [Internet]. **1995** *May 1* [cited 2024 Apr 13];22(5):899–903. Available from: https://pubmed.ncbi.nlm.nih.gov/8587079
40. D'Agostino MA, Aegerter P, Bechara K, Salliot C, Judet O, Chimenti MS, et al. How to diagnose spondyloarthritis early? Accuracy of peripheral enthesitis detection by power Doppler ultrasonography. *Annals of the Rheumatic Diseases*. **2011** *May 17*;70(8):1433–40
41. McGonagle D, Marzo-Ortega H, O'Connor P, Gibbon W, Hawkey P, Henshaw K, et al. Histological assessment of the early enthesitis lesion in spondyloarthropathy. *Annals of the rheumatic diseases* [Internet]. **2002** [cited 2019 Dec 5];61(6):534–7. Available from: https://www.ncbi.nlm.nih.gov/pubmed/12006328
42. Balint PV, Terslev L, Aegerter P, Bruyn GAW, Chary-Valckenaere I, Gandjbakhch F, et al. Reliability of a consensus-based ultrasound definition and scoring for enthesitis in spondyloarthritis and psoriatic arthritis: an OMERACT US initiative. *Annals of the Rheumatic Diseases*. **2018** *Aug 3*;77(12):1730–5
43. Karreman MC, Luime JJ, Hazes JMW, Weel AEAM. The Prevalence and Incidence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Journal of Crohn's and Colitis*. **2016** *Nov 4*;jjw199
44. Sakellariou G, Schiepatti A, Scalvini D, Lusetti F, Fazzino E, Biagi F, et al. Musculoskeletal Ultrasound to Identify Subclinical Joint and Periarticular Involvement in Patients With Inflammatory Bowel Disease: A Systematic Literature Review. *Frontiers in Medicine* [Internet]. **2022** [cited 2024 Apr 13];9:919521. Available from: https://pubmed.ncbi.nlm.nih.gov/35652081
45. Sieper J, Rudwaleit M, Khan MA, Braun J. Concepts and epidemiology of spondyloarthritis. *Best Practice & Research Clinical Rheumatology* [Internet]. **2006** *Jun* [cited 2019 May 9];20(3):401–17. Available from: https://www.sciencedirect.com/science/article/pii/S1521694206000246
46. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. *Annals of the Rheumatic Diseases*. **2011** *May 2*;70(6):896–904
47. Coates LC, Kavanaugh A, Mease PJ, Soriano ER, Laura Acosta-Felquer M, Armstrong AW, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis & rheumatology* (Hoboken, NJ) [Internet]. **2016**;68(5):1060–71. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26749174
48. Mease P, Sieper J, Bosch F, Rahman P, Karunaratne PM, Pangan AL. Randomized Controlled Trial of Adalimumab in Patients With Nonpsoriatic Peripheral Spondyloarthritis. *Arthritis & Rheumatology*. **2015** *Mar 27*;67(4):914–23
49. McGonagle D, McInnes IB, Deodhar A, Schett G, Shawi M, Kafka S, et al. Resolution of enthesitis by guselkumab and relationships to disease burden: 1-year results of two phase 3 psoriatic arthritis studies. *Rheumatology*. **2021** *Apr 6*;60(11):5337–50
50. Kaeley GS, Bakewell C, Deodhar A. The importance of ultrasound in identifying and differentiating patients with early inflammatory arthritis: a narrative review. *Arthritis Research & Therapy*. **2020** *Jan 2*;22(1)