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ULTRASONOGRAPHIC AND CLINICAL ASSESSMENT OF
PERIPHERAL ENTHESITIS AND ARTHRITIS IN AN ITALIAN
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High-resolution peripheral quantitative computed tomography (HR-pQCT) scan through the metacarpal head of a patient with rheumatoid arthritis demonstrating erosion and cortical break.

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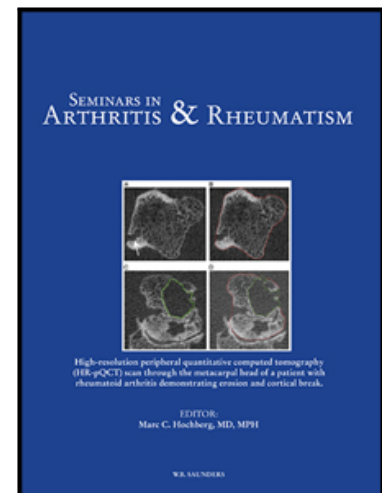
ULTRASONOGRAPHIC AND CLINICAL ASSESSMENT OF PERIPHERAL ENTHESITIS AND ARTHRITIS IN AN ITALIAN COHORT OF INFLAMMATORY BOWEL DISEASE PATIENTS

Elena Bertolini[a], Pierluigi Macchioni[b], Fernando Rizzello[c], Marco Salice[c], Gentiana Vukatana[d] , Gilda Sandri[e], Angela Bertani[f], Giovanni Ciancio[g], Marcello Govoni[g], Angelo Zelante[h], Nazzarena Malavolta[d], Marina Beltrami[a], Carlo Salvarani[b,e]

[a]Medicina Gastroenterologica e [b]Reumatologia, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [c]Dipartimento di Medicina Interna e Gastroenterologia e [d]Reumatologia , Università di Bologna-Policlinico S.Orsola Malpighi, Bologna, Italy; [e]Reumatologia e [f]Gastroenterologia, Azienda Ospedaliero-Unversitaria di Modena e Università di Modena e Reggio Emilia, Modena, Italy; [g]Reumatologia, Azienda Ospedaliero-Universitaria S. Anna di Ferrara (Cona) e Università di Ferrara, Ferrara, Italy; [h]Gastroenterologia, Ospedale Santa Maria della Misericordia, Rovigo, Italy

Short title: spondyloarthritis and enthesitis in IBD

[*]**Corresponding author:** Carlo Salvarani, MD, Azienda USL-IRCCS di Reggio Emilia and Università di Modena e Reggio Emilia, V.le Risorgimento n 80, 42123 Reggio Emilia, Italy.

e mail: carlo.salvarani@ausl.re.it; telephone: +39 0522 296616

Declarations of interest: none

Abstract

Aims. To evaluate the prevalence of clinical and ultrasonographic musculoskeletal involvement in Italian patients with inflammatory bowel disease (IBD).

Methods. In this cross-sectional multicenter study, 148 consecutive patients with IBD were evaluated by a gastroenterologist and a rheumatologist. All patients underwent a B-mode and power Doppler ultrasonographic examination of 6 pairs of entheses and of knee and ankle joints.

Results. A positive history for at least one musculoskeletal manifestation was reported by 40.5% of patients, more frequently in ulcerative colitis (UC) (p = 0.033). Inflammatory back pain was reported by 13.5% of patients, and a past history of peripheral arthritis by 14.9%, entheseal inflammation by 14.2% and dactylitis by 2.7%. At clinical examination, arthritis was observed in 19.6% of patients and enthesitis in 33%. Oligoarthritis and enthesitis at clinical examination were more frequently observed in UC than in Crohn disease (CD). 37.8% of total IBD patients fulfilled ASAS classification criteria for axial and/or peripheral spondyloarthritis, 8.1% ASAS classification criteria for axial spondyloarthritis, and 29.7% ASAS classification criteria for peripheral spondyloarthritis. With ultrasonographic examination, signs of entheseal involvement were observed in 87.8% of patients, while at power Doppler, ≥ 1 abnormality was observed in 27.1%. ASAS+ patients compared to those ASAS- had a significantly higher frequency at ultrasonography of acute entheseal abnormalities, power Doppler entheseal positivity and joint involvement. These abnormalities at ultrasonography were also observed in 34%, 13% and 12% of ASAS- patients.

Conclusions. Musculoskeletal manifestations occur frequently in patients with IBD. Ultrasonographic entheseal and joint involvement were also observed in asymptomatic patients.

Key words: inflammatory bowel disease, spondyloarthritis, ultrasonography, enthesitis, clinical examination

Spondyloarthritis (SpA) is a group of diseases with similar clinical, radiologic, and serologic findings that represent the most common extra-intestinal manifestation of inflammatory bowel disease (IBD) occurring in 17% to 39% of patients with these conditions[1,2]. Entheseal inflammation is a distinctive feature of SpA, and may represent the primary lesion responsible for all skeletal manifestations characteristic of these disorders, including synovitis [3-5].

In a previous clinical study, our group demonstrated a prevalence of SpA-related manifestations in 33% of an inception cohort of 160 new-onset IBD patients [6]. Twenty-three of these patients (14%) developed SpA-related manifestations without fulfilling any of the classification criteria available at that time for SpA and ankylosing spondylitis (AS), including the modified New York criteria and the European Spondyloarthropathy Study Group (ESSG) criteria [7,8]. Recently, a systematic review and meta-analysis calculated the pooled prevalence of SpA manifestations in IBD patients [1]. The pooled prevalence was 10% for sacroiliitis, 3% for AS, and 13% for peripheral arthritis. Few studies have evaluated the presence of enthesitis and dactylitis, reporting with a wide range for the prevalence of enthesitis (from 1% to 54%) and usually a low prevalence for dactylitis (between 0 and 5%)[1, 6, 9-14]. The Assessment of SpA International Society (ASAS) criteria that were developed in 2009[15] to classify the whole spectrum of SpA and to distinguish between patients with axial and peripheral SpA have rarely been applied to IBD patients [16, 17]. In a population-based cohort of IBD patients followed prospectively for 20 years axial SpA classified according to the ASAS classification criteria were observed in 7.7% of patients, while AS in 4.5% [16].

Different studies have demonstrated the higher sensitivity of ultrasonographic (US) examination compared to clinical inspection for the detection of entheseal and joint abnormalities in SpA[18-21]. There is also a growing body of evidence for the presence of subclinical enthesitis in psoriasis[22, 23], Behçet's syndrome[24], and SpA[(19, 20, 25, 26]. These studies observed a low concordance rate between clinical and US examination and a high prevalence of entheseal abnormalities at US, even in the absence of clinically overt enthesitis or arthritis. Only few studies have evaluated the presence of

subclinical enthesitis at US in IBD[27,28], without simultaneously evaluating the US presence of subclinical arthritis.

The primary objective of this study was to evaluate the prevalence of clinical as well as B-mode and power Doppler (PD) US signs of enthesitis and arthritis in a consecutive series of IBD patients followed in gastroenterological out-patient clinics stratified according to IBD type, disease duration (over or under 12 months), and anatomical localization of the inflammation. Furthermore, we evaluated in the same patients the prevalence of peripheral or axial SpA according to ASAS classification criteria [15].

Patients and Methods

Study design

This is a cross-sectional multicenter study conducted in 4 Italian rheumatologic centers in the regione Emilia Romagna (Reggio Emilia, Bologna, Modena, Ferrara). The 4 centers closely liaise with the corresponding gastroenterological (GE) centers and have a specific expertise in SpA and US imaging. The study was approved by the local ethical committees of all participating centers according to Italian current legislation on epidemiological studies.

Study populations

Adult patients (age 18–65 years) were consecutively enrolled by the participant GE centers if they had inflammatory bowel diseases (IBD) [ulcerative colits (UC), Crohn disease (CD), or unclassified IBD (IBDU)] diagnosed by the gastroenterologist according to European Crohn's and Colitis Organization (ECCO) guidelines[29,30]. Written consent, according to the Declaration of Helsinki, was required.

Exclusion criteria were the presence of tendinitis due to overuse, physical stress or recent articular injury. Patients who had received intra-articular or intra-entheseal corticosteroids during the past

four weeks were excluded, as were patients participating in clinical trials or with any medical condition that could have limited their ability to participate in the study.

Collection of clinical data

Demographic, personal and clinical data of 148 consecutive IBD patients were collected by gastroenterologists; they included patient demographics, anthropometry (including body mass index), lifestyle (including alcohol consumption, smoking and physical activity), social profile, date of disease onset and diagnosis, concomitant diseases and ongoing and previous medications. The extent and localization of the disease (in CD patients: esophageal-gastroduodenal, ileal, ileo-colonic or colonic involvement; in UC patients: colonic or isolated rectal involvement), previous surgical interventions and extraintestinal complications/manifestations (perianal disease, fistulating disease, intrabdominal or perianal abscess, uveitis/iritis, arthropathy, cutaneous manifestations, venous thromboembolism and hepatobiliary disease) were recorded for each patient. The IBD activity score was defined by the Harvey-Bradshaw index (HBI) for CD patient [31] and by the Mayo partial score or Mayo complete score (if endoscopic examination was available in the last previous three months) for UC patient [32, 33]. Remission was defined when Mayo partial or complete score was less than 2 or HBI was less than 5, mild disease when Mayo partial score was between 2 and 4, or Mayo complete score between 3 or 5, or HBI between 5 or 7, moderate disease when Mayo partial score was between 5 or 7, or Mayo compete score between 6 and 10, or HBI between 8 and 16, severe disease when Mayo partial score was more than 7, or Mayo complete score more than 10, or HBI more than 16.

After the identification by gastroenterologist, the patients were visited by a rheumatologist in each of these centers. Rheumatological assessment included a structured interview covering family history of uveitis, arthritis, any inflammatory rheumatic conditions, IBD, and past medical history of previous arthritis (pain and swelling in one or more joints), peripheral enthesitis (history of severe pain and limited function lasting at least 2 weeks in an anatomical enthesis, particularly in

the calcaneal areas), and dactylitis (history of a sausage digit); the presence of inflammatory back pain (according to ASAS criteria), buttock pain and its distribution, and anterior chest wall pain were also evaluated. Clinical rheumatological examination consisted of joint count (64 joints were evaluated for swelling and tenderness) and entheses' examination; the number of the sausage digits and the site of dactylitis, and the measures of finger-floor distance and Schober's test were also recorded. 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. Leeds Enthesitis Index (LEI)[34], Maastricht Ankylosing Spondylitis Enthesitis Score (MASES)[35] were calculated. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[36] and Bath Ankylosing Spondylitis Functional Index (BASFI)[37] were also recorded. In addition to clinical data, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin and fecal calprotectin levels were measured.

US and MRI examination

Ultrasound was performed in B-mode and PD-mode. All centers used the same US machine (ESAOTE MyLab70 or MyLabClass, Genoa, Italy) equipped with 18-6 MHz and 13-5 MHz multifrequency linear probe. To standardize the US evaluation of the entheseal, tendon and articular sites, all the sonographers attended a training meeting. In addition, a booklet with standard US imaging instructions was given to all ultrasonographers participating in the study. All the operators were experienced in musculoskeletal ultrasonography and blinded to diagnosis and clinical findings. All the scan images were recorded for digital imaging. The US evaluation was performed within one week of the clinical evaluation. The following entheseal sites were examined bilaterally in transverse and longitudinal planes according to a standard protocol: CET, QT, PT, TT, AT, and PF. In B-mode assessment, all the following abnormal findings were recorded: entheseal thickening measured at 2 mm proximal to the bony contour (abnormality definitions: quadriceps tendon >6.1

mm, proximal and distal patellar ligament >4 mm, Achilles tendon >5.29 mm, plantar aponeurosis >4.4 mm) (19), entheseal hypoechogenicity (defined as loss of normal fibrillar architecture), bony erosions (defined as a cortical break with a step down contour defect, seen in two perpendicular planes, at the insertion of the enthesis to the bone), enthesophytes (defined as bony prominence at the end of the normal bone contour, seen in two perpendicular planes, with or without acoustic shadow), and enlargement of bursae (defined as the presence of enlarged bursae at their anatomic sites as a well-circumscribed localized anechoic or hypoechoic area at the site of an anatomic bursa compressible by the transducer). These lesions were scored as 1 or 0 if present or absent. Entheseal thickening, entheseal hypoechogenicity, and bursal enlargement were considered acute lesions. Bony erosions, calcifications, and enthesophytes were considered chronic lesions. Entheses were scored globally as 1 (presence of ≥1 lesion) and separately as 1 for acute involvement (presence of ≥1 acute lesion), and 1 for chronic involvement (presence of ≥1 chronic lesion). Vascularization was examined using PD-mode, standardized with a pulse repetition frequency of 750 Hz and a PD gain of 50 to 53 dB. Vascularization was 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 to 3 vessels; 2 = 4 to 5 vessels; 3 = >5 vessels. The presence of PD ≥1 was considered indicative of an acute lesion.

Ultrasonographic findings were scored according to the Madrid sonography enthesitis index (MASEI)[38] and Glasgow ultrasound enthesitis scoring system (GUESS)[39].

Knees and ankles were evaluated according to standardized methods: synovial hypertrophy, effusion and articular erosions were recorded as present or absent. The presence of articular PD and synovial hypertrophy were recorded using a 4 grade scale (0 = absent, 1 = low, 2 = medium, 3 = massive). The flexor and extensor tendons of the feet were also evaluated at the ankle and dorsal

foot areas for the presence of tendon sheaths' synovial hypertrophy and fluid distension as well as for the presence of tendon and tendon sheaths PD signal according to EULAR recommendations [40].

MRI of the sacroiliac joints was performed in all 20 patients with evidence at rheumatological visit of inflammatory back pain. Evidence on MRI short tau inversion recovery (STIR) sequences of bone marrow edema in subcondral bone was considered indicative of active sacroiliitis. MRI was read by the same radiologist at Reggio Emilia Hospital with a specific expertise in musculoskeletal diseases.

Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD) or median and interquartile range (IQR), and categorical variables as absolute frequencies and percentages. Continuous variables were compared by using t-test or Mann-Whitney test when the distributions were skewed. Comparison of categorical variables was performed by using chi square or Fischer's exact test as appropriate. The level of significance was set at 0.05. Data were analyzed using the SPSS v.20 (IBM Statistics, Armonk, NY, USA).

Results

The final study population included 148 patients: 68 with CD, 77 with UC, and 3 with IBDU. Demographic, clinical and laboratory findings, comorbidities, and extra-intestinal manifestations of the study population are reported in Tables 1. Between CD and UC groups, statistically significant differences were found for sex (more male patients in CD group; p= 0.006) and dislypidemia (more frequent in UC group; p= 0.03). No differences in the prevalence of the different extraintestinal manifestations were observed. Surgical intervention for IBD complications and previous biological treatment were more frequently reported in CD patients (48.5% versus 5.2%, p < 0.001; and 27.9% versus 7.8%, p = 0.005; respectively), while the frequency of current biological therapy was not statistically different (23.5% versus 13.0%) . Mesalazine and topical steroids were

more frequently used in UC (83.0% versus 39.7%, p < 0.001 and 10.4% versus 0, p = 0.02,

respectively). The distribution of the activity scores of IBD between the two groups of patients was

similar (remission according to HBI in CD and to partial Mayo score in UC: 30.4 % and 28.4%

respectively, moderate/high activity 6.1% in CD group and 11.5% in UC group) (Table 2).

A positive history for at least one musculoskeletal manifestation was reported by 40.5% of the total

population and was more frequently observed in UC patients (50.6% versus 29.4 %, p = 0.033)

(Table 3). Inflammatory back pain (IBP) was reported by 13.5% of the patients, a past history of

peripheral arthritis by 14.9%, entheseal inflammation by 14.2%, and dactylitis by 2.7%. Psoriasis

was present in 6.1% of the total population. There was no statistically significant differences

comparing the individual rheumatological manifestations between UC and CD patients.

Twenty-seven patients were treated with biological agents (TNF blockers). These patients had more

frequently a positive history of peripheral arthritis and enthesitis compared to those not treated with

TNF blockers (29.6% versus 11.6%, p = 0.032 and 29.6% versus 10.7%, p = 0.027, respectively).

The following differences for gastroenterological findings between patients with shorter (≤ 12

months) and longer disease duration (> 12 months) were found: significantly more patients with

longer disease duration were treated with thiopurine or biological therapy (9.5% versus 0%, p =

0.021; and 23.1% versus 9.4%, p = 0.038; respectively), while they were less frequently treated

with systemic glucocorticoids (GCs) (13.0% versus 32.0%%, p = 0.004). UC patients with shorter

disease duration had significantly higher Mayo complete and partial scores (4.9 ± 3.3 vs 2.2 ± 3.0,

p = 0.004; and 3.09 ± 2.3 vs 1.8 ± 2.3, p = 0.023; respectively) and higher fecal calprotectin values

(253 ± 186 mg/Kg vs 137 ± 153 mg/Kg, p = 0.02). In CD patients no differences were observed in

HBI activity score between patients with longer and shorter disease duration.

Clinical rheumatological evaluation

At least one painful joint at examination was observed in 19.6% of the total population and was more frequent in UC patients than in CD patients (23.4% vs 13.2%, p = 0.036) (Table 3). Oligoarthritis was more frequently observed in UC (p = 0.001), while the frequency of polyarthritis was similar in UC and CD. Dactylitis was not observed. Clinical evidence (tenderness and/or swelling) of enthesitis was seen in 33% of the total IBD patients, and it was significantly more frequent in UC patients compared to CD patients (37.7% versus 25.0%, p = 0.012). However, LEI and MASES values and the percentages of patients with a score of at least one in both indexes were similar in UC and CD. Patients with CD and ilio-colonic localization compared to patients with other localizations had a higher percentage of at least one painful joint at clinical examination [16.7% (6/36 patients) versus 9.4% (3/32 patients), p = 0.031) and more frequently fulfilled ASAS classification criteria for axial and/or peripheral disease [41.7% (15/36 patients) versus 18.7% (6/32 patients), p= 0.048). No significant differences in rheumatological manifestations were observed among UC patients comparing isolated rectal disease versus colonic involvement (data not shown).

No statistically significant differences were observed comparing patients with shorter or longer disease duration ($\leq$ 12 months versus > 12 months) regarding rheumatological evaluation (data not shown).

37.8% of total IBD patients fulfilled ASAS classification criteria for axial and/or peripheral disease, 8.1% ASAS classification criteria for axial disease, and 29.7% ASAS classification criteria for peripheral disease. No statistically significant differences were observed comparing the frequencies of patients satisfying ASAS classification criteria between CD and UC (Table 3). No differences were also observed in patients positive for ASAS classification criteria according to disease duration ($\leq$ 12 months versus > 12 months), although more patients ASAS positive were observed in the group with the longer disease duration [39/98 patients (41.1%) versus 17/53 (32.1%), p = NS].

US evaluation

19.7% of patients had at least one US abnormality in the knees and ankles; no significant differences were observed between patients with CD and UC. Most of the patients had at least one abnormality detected by US entheseal evaluation (87.8%) without any statistically significant difference between CD and UC (83.8% versus 90.9%) (Table 4).

At PD-mode evaluation, ≥1 abnormality was observed in 27.1% of the total IBD population, without any statistically significant difference between CD and UC patients (21.5% and 31.6 %). The mean number $\pm$ SD of entheses per patient with positive vascular signal at PDUS examination was 0.63 ± 1.29, without any statistically significant difference between UC and CD population (0.81 ± 1.44 versus 0.44 ± 1.09, p = 0.087). Acute US signs of enthesitis were observed in 43.8% of the patients without differences between the two diseases (CD 42.4% versus UC 45.3%). US chronic entheseal lesions were observed in 83.8% of the total patients without statistically significant differences between CD and UC (79.4% versus 87.0%) (Table 5). Mean values of GUESS and MASEI scores and the frequency of patients with GUESS and MASEI of at least 1 did not differ between CD and UC patients (Table 4). No differences in US evaluations were also observed comparing patients with different IBD localizations (data not shown).

Patients with longer disease duration ($\leq$ 12 months versus > 12 months) had more frequently entheseal abnormalities at US evaluation [85/98 patients (90%) versus 38/53 (72%), p = 0.003], at least one enthesis with erosions [7/98 (7.4 %) vs 0/53 , p = 0.04], more entheses with erosions/patient (0.07 ± 0.2 versus 0, p= 0.007), and more entheses with chronic lesions/patient (4.0 ± 2.5 versus 2.9 ± 2.6, p= 0.023). No differences in mean GUESS and MASEI scores were observed (5.2 ± 3.5 versus 5.0 ± 3.8, p = NS; and 8.8 ± 6.4 versus 8.1 ± 7.0, p = NS, respectively)

Clinical and US evaluations in ASAS classification criteria positive and negative patients

Fifty-six patients (37.8%) satisfied ASAS classification criteria for SpA. Twelve patients were classified as axial SpA (8.1%) [2 patients were HLA-B27 positive, one patient had sacroileitis at pelvis radiological examination and 10 patients had evidence of sacroiliac bone marrow edema at magnetic resonance imaging (MRI)] and 44 patients as peripheral SpA (29.7%) (38 patients had peripheral enthesitis, 23 peripheral arthritis and 4 dactylitis). In ASAS+ patients compared to those ASAS- there was a significantly higher frequency of current smokers (37.5% versus 17.4%, p=0.022) without significant differences for alcohol consumption, regular physical activities, psoriasis and BMI (data not shown). No significant differences were observed for the prevalence of surgical intervention for IBD, intestinal localization of the disease, elevated levels of fecal calprotectin, perianal disease and distribution of Mayo/HBI activity scores (data not shown). A significantly higher percentage of ASAS + patients had extraintestinal manifestations other than articular manifestations (30% versus 11% , p = 0.003), current treatment with thyopurine (77.8% vs 22%, p=0.01) and/or with biologic drugs (18.2% vs 12%, p = 0.01).

Table 5 shows the distribution of rheumatological manifestations between ASAS + and ASAS – patients. Significant differences were observed at US for the prevalence of acute entheseal abnormalities (59.0 vs 34.0%, p = 0.004), presence of PD entheseal positivity (52.0% vs 13.0% p < 0.001) and inflammatory joint involvement (32.7% vs 12.0% p = 0.002). The mean number of PD positive entheses/patient was significantly higher in ASAS positive patients (1.2±1.5 versus 0.3 ± 1.0, p < 0.001). No statistically significant differences in the US scores GUESS and MASEI were observed.

Discussion

This is the first study evaluating the prevalence of self-reported, clinical and subclinical US rheumatological findings in a consecutive series of IBD patients followed in a GE clinic. We have observed both a high prevalence of self-reported rheumatological manifestations and of subclinical US entheseal and joint involvement.

40.5% of IBD patients reported, when interviewed, a positive history for at least one musculoskeletal SpA feature. Similar results were reported by Stolwijk et al.[41] in a consecutive series of Dutch IBD patients (36.9%) and by Salvarani et al.[6] in an inception cohort of European IBD patients (33.1%), but differently from our results, these studies found no significant differences between CD and UC. In our cohort of IBD patients the most frequently reported musculoskeletal manifestation was peripheral arthritis (14.9%), followed by peripheral enthesitis (14.2%), IBP (13.5%) and dactylitis (2.7%). A similar prevalence of IBP (11.5%) and peripheral arthritis (17.0%) was recently reported in a population based-cohort of IBD patients (the IBSEN study) from Norway followed for 20 years[16], while in an inception cohort of European IBD patients IBP and peripheral arthritis were observed in 8.8% and 10.6% of patients, respectively[6]. Our data are in agreement with these observations and also with a recent systematic review and meta-analysis that included 71 studies and reported a pooled prevalence of 13% for peripheral arthritis[1]. We have confirmed the low prevalence of dactylitis (2.7%) reported in 2 IBD population-based studies by Salvarani et al (1.9%)[6] and by Palm et al (4.4%)[11]. Peluso et al reported a higher prevalence of dactylitis (15.3%) in a consecutive series of Italian patients with already defined enteropathic SpA [42]. Differently, we confirmed the data of Cantini et al[43] that dactylitis is uncommon in SpA associated with IBD, however enthesitis in our series was more frequent compared to the study by Cantini et al (68% versus 18.1%). In a previous study Palm et al reported calcaneal enthesitis in 33% of patients with AS associated to IBD[11]. Differences in the number and type of entheseal examination sites and differences in the ethnic background of the population studied can partially explain these differences.

Several factors may explain the large variations in the prevalence of SpA in IBD in different studies. The prevalence depends on the criteria used to classify SpA and on the IBD duration.

Few studies have applied the ASAS classification criteria which were developed in 2009 to classify the whole spectrum of SpA and to distinguish between patients with axial and peripheral SpA[15].

We observed a prevalence of axial SpA of 8.1%, while the prevalence of peripheral SpA was 29.7% and the total prevalence of all forms of SpA applying ASAS classification criteria for peripheral and axial SpA was 37.8%. In the IBSEN study, axial SpA using ASAS classification criteria was classified in 7.7% of Norwegian IBD patients followed for 20 years[16], while in a cohort of Dutch IBD patients who were seen by a rheumatologist for musculoskeletal manifestations, using ASAS classification criteria, axial SpA was classified in 27.3% and peripheral SpA in 30.3%[41]. In a population based cohort of IBD patients in Reggio Emilia, Italy, we previously observed that 13.2% of patients satisfied the European Spondylarthropathy Study Group (ESSG) criteria for SpA, while 3.9% satisfied the modified New York criteria for AS[6]. Using ASAS classification criteria and the resources of Rochester Epidemiology Project (REP), Shivashankar et al observed in a population-based cohort of Olmsted County patients with UC and CD that the cumulative incidence of all forms of SpA increased in CD to 18.6% and in UC to 22.1% by 30 years from the diagnosis [44,45]. Our prevalence of axial SpA is similar to that observed in the IBSEN study[16], while the prevalence of peripheral SpA is similar to that observed in the Dutch study[41], although this latter study is not completely comparable in the design to our study because it evaluated only the patients who were visited by a rheumatologist for musculoskeletal findings. The mean IBD duration in our study was ~ 9 years. As Shivashankar et al demonstrated[44,45], the cumulative probability of SpA increases with longer duration of IBD. In the previous study from Reggio Emilia area, we included IBD patients with shorter disease duration (mean: ~ 4 years) and we did not use ASAS classification criteria for axial and peripheral SpA[6]. Therefore, in the first study we observed a lower prevalence of SpA. In comparison to the Olmsted County study, we observed in this study a higher prevalence of SpA despite the application of the same ASAS classification criteria and a shorter disease duration (9 years versus 30 years). The reason is probably related to the fact that Olmsted County study was based only on medical record review and not all patients were evaluated by a rheumatologist, as we did in our study.

A high prevalence of subclinical US entheseal involvement has been observed in SpA, including psoriatic arthritis (PsA) and in different conditions associated with SpA[19, 20, 22-26, 46,47]. Balint et al in a cohort of 35 patients with SpA, including 7 PsA patients, showed that 22% of entheses assessed were abnormal on clinical examination and 56% on gray scale US[19]. However, these authors did not use PD, therefore the study had limitated sensitivity in the evaluation of active inflammation. D'Agostino et al showed US abnormalities in 38% of entheses examined in a cohort of SpA patients and in 11% of entheses in a control group; interestingly, enthesitis was most commonly distributed in the distal portion of the lower limbs and evidence of vascularization in the entheses was observed only in the SpA group, where it was always detected at the cortical bone insertion and sometimes also in the bursa[20].

Entheseal abnormalities were also documented by US in clinically asymptomatic patients with psoriasis, Behçet's disease, and patients with idiopathic recurrent acute anterior uveitis (AAU) without features of SpA[22-24,46,47].

Naredo et al observed US enthesopathy in 62.5% and entheseal PD signal in 7.4%. of patients with psoriasis without musculoskeletal manifestations[23]. Macchioni et al showed similar results, US enthesopaty was observed in 41.2% and entheseal PD signal in 12.7% of 51 patients with psoriasis alone[47].

We observed the presence of at least one acute or chronic entheseal lesion in 88.2% of our IBD patients (chronic 83.8%, acute 43.8%) and at least one active lesion at PD in 27% of patients, while at least one tender enthesis at clinical examination was observed in 33% of patients. There was also a correlation between IBD duration and the frequency of entheseal lesions, in particular at least one enthesis with erosions was more frequently observed in patients with disease duration longer than 12 months. No differences were observed between CD and UC. Acute entheseal lesions and PD enthesitis were more frequently observed in the patients satisfying ASAS classification criteria for SpA (59% and 52%, respectively), however these lesions were also observed in 34% and 13% of patients without SpA. Very few studies have evaluated the presence of subclinical enthesitis in

patients with IBD without clinical signs and symptoms of SpA. Similarly to our study, Bandinelli et al observed at PD subclinical entheseal involvement in 16% of 81 IBD without signs or symptoms of SpA and also the mean GUESS and the percentage of patients with GUESS > 1 were similar in the two studies (5.1±3.5 for both studies and 93% versus 92%, respectively)[27]. Similar results were also reported by Rovisco et al: in 76 patients with IBD without musculoskeletal manifestations 84.1 % had at least one GS entheseal abnormality and 13.9% more than one PD-positive entheseal site[48]. Therefore, all in three studies US demonstrated frequent subclinical entheseal involvement, particularly of lower limbs, in IBD patients without signs and symptoms of SpA.

Rovisco et al also evaluated at US subclinical joint involvement that was observed in 42.1% of 76 IBD patients without musculoskeletal manifestations[48]. In our study at least one joint of the lower limbs with US abnormalities was more frequently observed in patients with IBD and SpA, however it was also observed in 12% of 92 patients without SpA. Therefore, approximately one out of 10 patients with IBD without SpA in our study had evidence of subclinical enthesitis or arthritis.

Most studies showed a similar prevalence of SpA findings in both CD and UC[6,12,13], however a recent systematic review concluded that the prevalence of AS, sacro-iliitis and peripheral arthritis was higher in patients with CD compared to those with UC[1]. In our study, we observed an increased frequency of a positive history for at least one musculoskeletal SpA feature and current oligoarthritis and enthesitis in the patients with UC, although the prevalence of patients satisfying ASAS classification criteria for SpA was similar in UC and CD. Differences in case ascertainment, medical setting and disease expression in different geographical area can explain this heterogeneity in prevalence estimates.

The influence of smoking on disease activity in IBD is well defined, however the association between smoking and extra-intestinal manifestations is less defined. Observing an increased

frequency of current smokers in the patients with SpA compared to those without SpA, we confirmed in a Mediterranean population the results of the study of Severs et al that observed an association between smoking and joint manifestations in a cohort of Dutch patients with IBD[49].

Our study has several limitations, but also some strengths. A recall bias may have occurred. In this cross-sectional study patients were interviewed about possible previous musculoskeletal manifestations and they may have forgotten symptoms experienced a long before. However, all patients were also interviewed and visited by a Rheumatologist, thus minimizing the possibility that some musculoskeletal symptoms may have been overlooked. About one-fifth of the patients were treated with biological agents, mainly TNF blockers. This treatment may have masked the symptoms/imaging related to SpA, leading to an underestimation of the prevalence of this condition. A limitation of this study is also that we did not test for other arthritis, or non-inflammatory musculoskeletal conditions, nor included healthy subjects as controls. We did not use MRI for the evaluation of peripheral enthesitis, but we used PDUS that is considered a reliable and accurate imaging technique to detect inflammation at entheseal level[26]. However, both imaging techniques are not very specific and do not distinguish accurately between mechanic and inflammatory enthesitis, furthermore, abnormalities at entheseal level are often found by MRI and PDUS in healthy controls[50]. Therefore, not having controls represents a limit for the interpretation of our imaging results. Another limitation is that our patients with CD and UC were not matched for BMI, a factor that might influence the enthesitis scores, however no differences were found between the two groups of patients in this regard. Strengths of the study are the following: 1) arthritis and enthesitis were defined in all IBD patients using both clinical and US assessments; 2) US evaluation was performed by experienced musculoskeletal ultrasonographers using the same high-quality US machine and a standardized protocol, defined in a specifically organized training meeting; 3) musculoskeletal manifestations were evaluated considering the rheumatological history, the current rheumatological inspection, and the US. Because of the fluctuating course of SpA

symptoms it is important to consider symptoms experienced by the patient in the past but no longer present at the moment of the current evaluation.

In conclusion, in this cohort of Italian IBD patients we confirmed a high prevalence of musculoskeletal manifestations. Using ASAS classification criteria, more than 1/3 of patients were classified as SpA. We also confirmed that dactylitis is infrequent in entheropathic arthritis. US entheseal assessment showed a frequent presence of entheseal abnormalities in IBD patients, although the presence of entheseal PD signal, a more specific US sign of inflammation, was less frequently observed and its frequency was similar to the observed frequency of enthesitis at clinical examination (around 1/3 patients). A combined clinical and US evaluation is probably the best approach to evaluate the presence of enthesitis in patients with IBD and to plan an appropriate multidisciplinary treatment for these patients. PD sign of inflammation in the entheaseal sites and US evidence of joint abnormalities were more frequently observed in ASAS+ patients, however these alterations were also observed in ASAS- patients (around 1/10). The clinical significance of these US lesions in patients without evidence of SpA is unclear and must be evaluated in a long-term follow up study.

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Table 1. Demographic, clinical and laboratory findings, comorbidities, and extra-intestinal manifestations*

	Total n= 148	CD n= 68	UC n= 77	P
Age (years)	41± 14	40.5± 13.3	41.5± 14.5	NS
Male, n (%)	72 (48.6)	41 (60.3)	29 (37.7)	0.006
Age at disease onset (years)	31.4± 13.3	29.7± 12.5	32.7 ± 13.7	NS
Age at diagnosis (years)	33± 13.3	31.9± 12.6	33.9 ± 13.7	NS
IBD duration (months)	107.5± 129	111.3± 142.3	106.9± 118.9	NS
IBD duration, n (%)				
≤ 12 months	53 (35.8)	29 (42.6)	23 (29.9)	NS
> 12 months	95 (64.2)	39 (57.4)	54 (70.1)	NS
Comorbidities, n (%)				
Diabetes	5 (3.4)	1 (1.5)	4 (5.2)	NS
Dislypidemia	17 (11.5)	2 (2.9)	15 (19.5)	0.03
Hypertension	16 (10.8)	9 (13.2)	6 (7.6)	NS
Cardiovascular	13 (8.8)	7 (10.3)	5 (6.5)	NS
Psoriasis	6 (4.1)	2 (3.0)	4 (5.2)	NS
Extra-intestinal manifestations, n (%)				
Erythema nodosum/pyoderma gangr.	3 (2.0)	0	1 (1.3)	NS
Oral aphthosis	4 (2.7)	2 (2.9)	3 (3.9)	NS
Acute anterior uveitis	1 (0.7)	1 (1.5)	0	NS
Primary sclerosing cholangitis	3 (2.0)	1 (1.5)	3 (3.9)	NS
Perianal disease	14 (9.0)	11 (16.2	2 (2.6)	0.007
BMI	23.6± 4.8	23.1± 4	24.1± 5.5	NS
ESR, mm/h	21.1± 20.1	23.8± 22.2	18.8± 18.2	NS
CRP, mg/dl	1.74± 3.6	2.23± 4.73	1.3± 2.13	NS
Hb, gr/dl	13.1± 1.86	13.1± 1.93	13.10± 1.84	NS
Fecal calprotectin, mg/Kg	193±178	190±159	203±196	NS
Regular phisical activity, n (%)	63 (42.6)	26 (38.2)	35 (45.4)	NS

*Data are mean±SD, except where otherwise indicated; IBD = inflammatory bowel disease; BMI = body mass index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; fecal calprotectin was measured in 51 patients with IBD, specifically in 23 with Crohn disease and 27 with ulcerative colitis.

Table 2. Activity scores of the IBD[*]

HBI (CD = 68)	4.5 ± 4.3
HBI classification, n (%)	
Remission	45 (30.4)
Low activity	14 (9.5)
Moderate activity	7 (4.7)
High activity	2 (1.4)
Full Mayo score (UC = 56)	3.0 ± 3.3
Full Mayo score classification, n (%)	
Remission	32 (21.6)
Low activity	10 (6.8)
Moderate activity	12 (8.1)
High activity	1 (0.7)
Partial Mayo score (UC = 77)	2.2 ± 2.4
Partial Mayo score classification, n (%)	
Remission	42 (28.4)
Low activity	18 (12.2)
Moderate activity	13 (8.8)
High activity	4 (2.7)

[*]Data are mean±SD, except where otherwise indicated; IBD = inflammatory bowel disease; HBI = Harvey-Bradshaw index; CD = Crohn disease; UC = ulcerative colitis;

Table 3. Rheumatological clinical evaluation of the study population[*]

Rheumatological findings	Total n= 148	CD n= 68	UC n= 77	p
History				
Inflammatory back pain	20 (13.5)	6 (8.8)	14 (18.2)	NS
Gluteal pain	13 (8.8)	3 (4.4)	10 (13)	NS
Peripheral arthritis	22 (14.9)	9 (13.2)	13 (16.9)	NS
Thoracic wall pain	11 (7.4)	3 (4.4)	8 (10.4)	NS
Peripheral enthesitis	21 (14.2)	5 (7.4)	15 (19.5)	NS
Dactilytis	4 (2.7)	2 (2.9)	2 (2.6)	NS
At least one rheumatological manifestation	60 (40.5)	20 (29.4)	3.9 (50.6)	0.033
Cutaneous Psoriasis,	9 (6.1)	4 (5.9)	5 (6.5)	NS
Clinical examination				
LEI (mean; min-max)	0 (0-6)	0.4 (0-8)	0.7 (1-2)	NS
LEI ≥1	43 (29.1)	15 (22.1)	26 (33.8)	NS
MASES (mean; min-max)	0 (0-13)	0.5 (1-5)	0.8 (2-5)	NS
MASES≥1	29 (19.6)	12 (17.6)	15 (19.5)	NS
Painful joints ≥1	29 (19.6)	9 (13.2)	18 (23.4)	0.036
Oligoarthritis < 5	18 (12.2)	5 (7.4)	13 (16.9)	0.001
Polyarthritis ≥ 5	11 (7.4)	4 (5.9)	5 (6.5)	NS
Swollen joints ≥1	2 (1.4)	1 (1.5)	1 (1.3)	NS
Dactylitis	0	0	0	NS
Painful enthesis ≥1	49 (33)	17 (25)	29 (37.7)	0.012
Painful enthesis ≤5	36 (24.3)	12 (17.6)	22 (28.6)	0.057
Painful enthesis >5	13 (8.8)	5 (7.4)	7 (9.1)	NS
Swollen enthesis ≥ 1	0	0	0	NS
Axial ASAS criteria	12 (8.1)	4 (5.9)	8 (10.4)	NS
Peripheral ASAS criteria	44 (29.7)	17 (25.0)	24 (31.2)	NS
ASAS +	56 (37.8)	21 (30.8)	32 (41.5)	NS

[*]Values are the number (%), except where otherwise indicated; CD = Crohn disease; UC = ulcerative colitis; LEI = Leeds Enthesitis Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; ASAS = Assessment of SpondyloArthritis international Society.

Table 4.Ultrasonographic evaluation in the total IBD patients and in the CD and UC patients[*]

	Total n= 148	CD n= 68	UC n= 77	p
At least one alterated enthesis&	130 (87.8)	57 (83.8)	70 (90.9)	NS
Number of alterated enthesis/patient (mean±SD)	5.29± 3.08	5.29± 2.98	5.32±3.19	NS
At least one PDUS enthesitis	39 (27.1)	14 (21.5)	24 (31.6)	NS
Number of PDUS enthesistis/patient (mean±SD)	0.63± 1.29	0.44± 1.09	0.81± 1.44	0.087
Number of acute entheseal alteration/patient (mean±SD)	2.77± 2.46	2.8 ±2.26	2.73± 2.62	NS
At least one acute entheseal alteration	63 (43.8)	28 (42.4)	34 (45.3)	NS
At least one chronic entheseal alteration	124 (83.8)	54 (79.4)	67 (87)	NS
At least one joint with US abnormalities	29 (19.7)	10 (14.7)	18 (23.7)	NS
US score				
GUESS (mean±SD)	5.12± 3.62	5.02± 3.35	5.22± 3.8	NS
GUESS ≥ 1	134 (92.4)	64 (94.1)	70 (90.9)	NS
MASEI (mean±SD)	8.58± 6.64	8.4± 6.24	8.81± 7.1	NS
MASEI ≥ 1	12.9 (90.8)	61 (92.4)	68 (98.5)	NS

* Values are the number (%), except where otherwise indicated; &altered enthesis= presence of at least one acute or chronic alteration; IBD = inflammatory bowel disease; CD = Crohn disease; UC = ulcerative colitis; PDUS = Power Doppler Ultrasonography; US = Ultrasonography; GUESS = Glasgow ultrasound enthesitis scoring system; MASEI = Madrid sonography enthesitis index.

Table 5. Rheumatological clinical and US evaluations of ASAS+ and ASAS- patients[*]

	ASAS+n=56	ASAS-n=92	P
Clinical rheumatological findings			
At least one painful joints	25 (44.6)	4 (4.3)	< 0.001
At least one painful joints in the lower limbs	21 (37.5)	2 (2.2)	< 0.001
At least one painful enthesis	38 (68)	11 (12)	< 0.001
Positive rheumatological hystory	45 (80)	15 (18)	< 0.001
BASDAI (mean ±SD)	2.65 ± 2	1.65 ± 1.6	0.001
LEI≥ 1	33 (59)	10 (10.9)	< 0.001
MASES ≥1	23 (41.1)	8 (8.7)	< 0.001
US evaluation			
At least one alterated enthesis&	49 (91)	78 (86.7)	NS
At least one chronic entheseal alteration	48 (86)	76 (93)	NS
At least one acute entheseal alteration	33 (59)	32 (34)	0.004
At least one PDUS enthesitis	29 (52)	12 (13)	<0.001
Number of PDUS enthesistis/patient (mean±SD)	1.2± 1.5	0.3± 1	< 0.001
Number of acute entheseal alteration/patient (mean±SD)	3.0± 2.7	2.5± 2.2	NS
At least one joint with US abnormalities	18 (32.7)	11 (12)	0.002
US score			
GUESS (mean±SD)	5.1± 3.7	5.1± 3.5	NS
GUESS ≥	52 (93)	85 (92)	NS
MASEI (mean±SD)	9± 6.9	8.3± 6.4	NS
MASEI ≥ 1	48 (87)	84 (93)	NS

* Values are the number (%), except where otherwise indicated; &altered enthesis= presence of at least one acute or chronic alteration; US = Ultrasonography; ASAS = Assessment of SpondyloArthritis international Society; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; LEI = Leeds Enthesitis Index; MASES = Maastricht Ankylosing Spondylitis Enthesitis Score; PDUS = Power Doppler Ultrasonography; GUESS = Glasgow ultrasound enthesitis scoring system; MASEI = Madrid sonography enthesitis index.