Concise report

Ultrasound discloses entheseal involvement in inactive and low active inflammatory bowel disease without clinical signs and symptoms of spondyloarthropathy

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Abstract

Objective. To investigate the presence of lower limb entheseal abnormalities in IBD patients without clinical signs and symptoms of SpA and their correlation with IBD clinical variables.

Methods. A total of 81 IBD patients [55 Crohn’s disease (CD) and 26 ulcerative colitis (UC), 43 females and 38 males, mean age 41.3 (12.4) years, BMI 24 (2)] with low active (12) and inactive (67) disease were consecutively studied with US (LOGIQ5 General Electric 10-MHz linear array transducer) of lower limb entheses and compared with 40 healthy controls matched for sex, age and BMI. Quadriceps, patellar, Achilles and plantar fascia entheses were scored according to the 0–3 Glasgow Ultrasound Enthesitis Scoring System (GUESS) and power Doppler (PD). Correlations of GUESS and PD with IBD features [duration, type (CD/UC) and activity (disease activity index for CD/Truelove score for UC)] were investigated. The intra- and inter-reader agreements for US were estimated in all images detected in patients and controls.

Results. Of the 81 patients, 71 (92.6%) presented almost one tendon alteration with mean GUESS 5.1 (3.5): 81.5% thickness (higher than controls \(P < 0.05\)), 67.9% enthesophytosis, 27.1% bursitis and 16.1% erosions. PD was positive in 13/81 (16%) patients. In controls, US showed only enthesophytes (5%) and no PD. GUESS and PD were independent of duration, activity or type (CD/UC) of IBD. The intra- and inter-reader agreements were high (\(> 0.9\) intra-class correlation variability).

Conclusions. US entheseal abnormalities are present in IBD patients without clinical signs and symptoms of SpA. US enthopathies is independent of activity, duration and type of gut disease.

Key words: Spondylarthropathies, Ultrasonography, Tendons, Gastrointestinal disease.

Introduction

Enthesitis is categorized as inflammation of insertion of ligaments, tendons, joint capsule or fascia to bone and is a frequently under-diagnosed distinctive feature of SpA [1, 2]. In fact, out of 130 patients with IBD, clinical examination revealed enthesitis only in 5.4% of the cases [3]. Detection of entheseal involvement is important to prevent disability because initial acute oedema, inflammatory infiltration and fibrocartilage microlesions may evolve into chronic endochondral ossification and bone erosions in late disease [4]. Recent studies have shown that new imaging techniques are deemed essential for a sure diagnosis of enthesitis: US discloses entheseal thickness, enthesophytes, bursitis and erosions [5] and assesses vascularization on tendons, through flow signal scoring with Power Doppler (PD) [6]. A growing body of evidence has demonstrated the validity of US in SpA [5, 7], whereas
in IBD-related SpA, the value of US enthesis assessment has not been specifically evaluated.

The aim of the present study was to investigate US enthesis abnormalities in IBD patients without signs and symptoms of SpA (joint, entheses and spine) and their correlation with IBD clinical variables (duration, DAS) and the difference between Crohn’s disease (CD) and ulcerative colitis (UC).

**Methods**

From September 2008 to July 2009, 55 CD and 26 UC patients [43 females and 38 males, mean age 41.3 (12.3) years, min 18 years and max 68 years, BMI 22 (3.1), min 17 max 25, Caucasian race], without joint, entheses or spine inflammatory symptoms and signs of SpA, were studied with US of lower limb tendon insertion to cortical bone (entheses) by a rheumatologist trained in US (F.B.), using LOGIQ5 General Electric 10-MHz linear array transducer (Medical Systems, Milwaukee, WI, USA), unaware of clinical examination and history of the patients, at the Division of Rheumatology of the University of Florence, Florence, Italy.

Forty healthy controls without clinical signs of SpA or familiarity for IBD, psoriasis and SpA, matched for sex (22 females and 18 males), age [49.6 (11.1) years] and BMI [24 (2)] were used as controls and examined with US. The ethics committee of the University of Florence approved the study and informed consent (according to the Declaration of Helsinki) was signed by patients and controls.

Patients and controls answered negatively to questionnaires (HAQ modified for SpA, BASFI and pain VAS 0–100) and did not show pain at entheses, joints and spine at clinical examination, performed separately by an experienced rheumatologist (L.G.). They had not been referred for inflammatory pain at entheses, joint and spine in the past, did not receive major trauma or steroid injection or previous surgical intervention on joint and entheses and did not perform any agonistic sport.

Insertion of tendons at the superior pole of patella (quadriceps), inferior pole of patella (proximal rotuleus), tibial tuberosity (distal rotuleus), heel (Achilles tendon and plantar fascia) were examined with, respectively, supine (knee flexed at 30°) and prone (feet hanging over the edge of the examination table at 90° of flexion) patient position.

Entheses thickness (expressed in millimetres and defined with Balint cut-off for quadriceps >6.1, proximal and distal rotuleus >4.4 mm, Achilles >5.29, plantar fascia >4.4 mm) and presence of enthesophytes, bursitis and erosions at bone insertion (evaluated in transverse and longitudinal scan) were recorded at each site (in patients and controls) and were scored with US according to Glasgow Ultrasound Enthesitis Scoring System (GUESS), ranging from 0 to 36, which was validated by Balint et al. [5].

PD was standardized with pulse repetition frequency of 750 Hz and a gain of 53 dB, and the temperature of the room was set to 20°C [6]. Vascularity, studied at insertion of enthesis at the cortical bone, was scored as a binary item (negative if absent and positive if any signal was present) and was also semi-quantitatively graded [no flow (Grade 0); mild (only one spot detected) (Grade 1); moderate (two spots) (Grade 2); severe (more than three spots) (Grade 3)], as validated by D’Agostino et al. (Fig. 1) [7]. Finally, a total PD (tPD) was calculated by summing semi-quantitative PD scores of each tendon [8].

Intra- and inter-reader variability was established by recording the 10 entheses US of all patients and controls in a digital archiving computer system. The saved images were read and re-measured by the same rheumatologist who performed US examination (F.B.) 2 months after the initial scanning and by another rheumatologist trained in US (L.C.), both blind to previous results, and the identity of patients was mixed with controls.

All patients were scored with IBD disease activity indices (CD activity index (CDAI); Truelove score for UC) as remission in CD as CDAI <150 score and in UC as absence of symptoms. Of 81 patients, 79 (97.5%) were treated for IBD with: antibiotics (22/81), steroids (12/81), mesalazyn (12/81), SSZ (17/81), MTX (3/81), AZA (2/81) and anti-TNF-α (8/81). Seventy-seven (95%) received in the past: antibiotics (9/81), steroids (55/81), mesalazyn (53/81), SSZ (10/81), MTX (4/81), AZA (16/81) and anti-TNF-α (9/81). Twenty-three (28.4%) patients underwent bowel surgery before IBD.

**Statistical analysis**

Intra- and inter-reader agreement on patients and controls was evaluated with intra-class correlation (ICC) with 95% confidence interval. Difference in tendon thickness between IBD patients and healthy controls was calculated with Mann–Whitney test. Correlation between US scores (GUESS and PD) and disease duration was assessed with Pearson linear coefficient and not Spearman’s linear rho; difference in US parameters between IBD remission (low activity) and CD/UC were estimated with Kruskal–Wallis test. Data were presented as mean (s.d.) and percentage. $P < 0.05$ was considered significant.

**Results**

Intra-reader [ICC 0.99 (0.98–1) for GUESS and 0.97 (0.90–1) for PD] and inter-reader [ICC 0.97 (0.90–0.99) for GUESS and 0.95 (0.89–1) for PD] US variabilities were significantly low. Of 81, 12 (14.8%) IBD were low active and 67 (82.7%) inactive, with a disease duration of 8.8 (7.6) years (min 1 year; max 33 years).

**GUESS**

Of 81 patients, 71 (92.6%) had GUESS >1 [mean 5.1 (3.5)/36, min 0 and max 16; Table 1]. Of 810, 317 (39%) entheses had one alteration and 163 (20%) were symmetrical.

US revealed the presence of thickness, enthesophytes (Fig. 1), bursitis and erosions, in different percentages (Table 1) of patients, while only in 2/40 healthy controls (5%), one asymmetric enthesophyte was found in right Achilles tendon and no other abnormalities were found.
Enthesis thickness was found in 66/81 (81.5%) patients, enthesophytes in 55/81 (67.9%), bursitis in 22/81 (27.1%), erosions in 13/81 (16%) patients and none in controls. Thickness of tendons in IBD patients was higher than in controls at each site investigated (\(P < 0.05\)) (Table 1) and was most frequently found in the right distal rotuleus [47/81 (58%)], enthesophytes in the left Achilles tendon [34/81 (42%)], bursitis in right distal rotuleus [17/81 (21%)], erosions equally on bone insertion of right quadriceps and bilateral proximal rotuleus [3/81 (3.7%)]. Two patients had erosions at three and two different sites, respectively.

PD was positive in 13/81 patients (16%), in 50/920 entheses (5.4%) and was more frequent in left quadriceps, Achilles and fascia insertion [4/81 (5%)] (Table 1). No PD signal was found in healthy controls. The semi-quantitative score was mild in 10/13 (76.9%), moderate in 2/13 (15.3%) and severe in 1/13 (7.7%) patients and the tPD was 2.4 (2.1)/30 (min 0, max 8) (Fig. 1).

**Discussion**

Enthesitis is a specific and sometimes isolated [9] sign of presentation of IBD associated with SpA overall in young people [10], under-diagnosed [11], often mistaken for overuse pathology [12] and discovered by clinical examination only in a small percentage [4]. In agreement with Balint, who found that clinical entheses examination in SpA had a low sensitivity (22.6%) compared with US [5], our study showed that US discloses frequent subclinical enthesitis of lower limb in IBD patients without sign and symptoms of SpA.

In IBD, asymptomatic sacroiliitis was also recognized [13] but, up to now, IBD subclinical enthesopathy has not been investigated. Only in patients affected by psoriasis without any sign and symptom of joint involvement, US was able to recognize entheses subclinical abnormalities [14].

In disagreement with Kiris et al. [8] who demonstrated that enthesal pain was highly correlated with vascularity shown by PD, 16% of our patients were positive at PD signal on entheses without symptoms. It’s difficult to define the role of previous treatments on clinical manifestation, even if our patients did not refer any inflammatory signs or symptoms before beginning treatment. Furthermore, probably past steroid therapy might also prejudice PD signal in negative entheses, as already demonstrated in synovitis [15].

In our study, thickness was the most frequent modification and more specific than enthesophytes, which was most frequently found in the left Achilles tendon [34/81 (42%)], enthesophytes in the right distal rotuleus [17/81 (21%)] and erosions at right distal rotuleus [77/81 (95%)]. Bursitis was equally frequent at the left quadriceps and bilateral proximal rotuleus [3/81 (3.7%)]. Two patients had erosions at three and two different sites.

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**Table 1** Percentage of components of GUESS (thickness in millimetres) and PD in IBD patients and healthy controls

<table>
<thead>
<tr>
<th>GUESS (total)</th>
<th>Thickness</th>
<th>Enthesophytes</th>
<th>Bursitis</th>
<th>Erosions</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD, %</td>
<td>Controls, %</td>
<td>IBD, %</td>
<td>Controls, %</td>
<td>IBD, %</td>
<td>Controls, %</td>
</tr>
<tr>
<td>92.6</td>
<td>5</td>
<td>81.5</td>
<td>69.7</td>
<td>27.1</td>
<td>16</td>
</tr>
<tr>
<td>Right, %; mean (S.D.), mm</td>
<td>Left, %; mean (S.D.), mm</td>
<td>Right, %; Left, %</td>
<td>Right, %; Left, %</td>
<td>Right, %; Left, %</td>
<td>Right, %; Left, %</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>34.5; 6.3 (0.9)</td>
<td>0; 5 (0.4)</td>
<td>25.9; 6.3 (0.9)</td>
<td>0; 4.8 (0.5)</td>
<td>23.5; 6.3 (0.9)</td>
</tr>
<tr>
<td>Proximal rotuleus</td>
<td>42; 4.1 (0.8)</td>
<td>0; 3.3 (0.3)</td>
<td>33.3; 4.1 (0.8)</td>
<td>0; 3.4 (0.4)</td>
<td>29.2; 4.1 (0.8)</td>
</tr>
<tr>
<td>Distal rotuleus</td>
<td>58; 4.3 (0.8)</td>
<td>0; 3.4 (0.4)</td>
<td>59.2; 4.3 (0.9)</td>
<td>0; 3.2 (0.01)</td>
<td>56.8; 4.3 (0.8)</td>
</tr>
<tr>
<td>Achilles</td>
<td>9.9; 4.9 (0.8)</td>
<td>0; 3.7 (0.4)</td>
<td>9.9; 4.9 (0.8)</td>
<td>0; 3.8 (0.5)</td>
<td>9.9; 4.9 (0.8)</td>
</tr>
<tr>
<td>Plantar fascia</td>
<td>16; 4.1 (0.8)</td>
<td>0; 3.9 (0.7)</td>
<td>13.6; 4.1 (0.8)</td>
<td>0; 2.9 (0.5)</td>
<td>13.6; 4.1 (0.8)</td>
</tr>
</tbody>
</table>

Demographic characteristics of IBD and healthy controls: IBD: 43 females: 38 males, aged 41.3 (12.3) years, BMI 22 (3.1); controls: 22 females: 18 males, aged 49.6 (11.1) years, BMI 24 (2).
was the only alteration present in minimal part also in healthy controls. The rotuleus tendon was the most involved entheses, in agreement with another US study of Balint et al. [5] who demonstrated that thickness of distal rotuleus [39/69 (56.5%)] was the most frequent alteration in SpA patients, followed by plantar fascia. These data were in disagreement with previous issues on small populations on clinical presentation of symptomatic enthesitis, which considered the Achilles to be the most frequent clinically affected tendon [16-18] followed by proximal and distal rotuleus.

Some studies confirmed the relationship between subclinical gut inflammation and joint [10, 19, 20]. In 11 SpA patients, Mielants et al. [10] demonstrated that clinical remission was always associated with normal gut histology at more than two follow-up ileocolonoscopies, and flares of joint disease were correlated temporally with the reappearance of gut inflammation. Our study indicates that entheses may be involved independently of the gut flares as we found tendon alterations also in remittent IBD without any difference from low active disease.

In the literature, there is no other specific study of entheses US on IBD and Mielants et al. [10] described only a connection between gut and axial/joint peripheral involvement. In our study, we analysed only remittent and low active IBD and probably patients with active and highly active IBD should be considered in future studies. The treatment might also influence the gut disease activity but we could not discontinue drugs for IBD before US for ethical reasons.

Furthermore, our data suggested that enthesal involvement may also be present in early IBD disease. Otherwise, patients examined showed a wide range of disease duration (min 1 and max 33 years) and given that the enthesal involvement is related neither to duration nor to disease activity, US findings cannot be considered a predictive sign of joint disease in this study. Probably in future, early IBD should be specifically investigated for joint/enthesal and axial involvement with prospective imaging follow-up.

The relevance of this study is to show the high subclinical frequency of enthesopathy in IBD patients and in lower percentage of PD-positive enthesitis with an important role in diagnosis of US investigation. These findings might also influence the choice in IBD of disease-modifying drug (in particular, SSZ and anti-TNF-α) effective both for gut and SpA and elucidate the importance of strict collaboration between gastroenterologists and rheumatologists.

Rheumatology key messages
- US discloses a high percentage of enthesopathy in IBD patients without clinical signs and symptoms of SpA.
- Enthesopathy is independent of activity and duration of gut disease, in these subjects.

Disclosure statement: The authors have declared no conflicts of interest.

References