Concise report

The occurrence of lower limb enthesopathy in coeliac disease patients without clinical signs of articular involvement

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Abstract

Objective. Coeliac disease (CD) is a systemic autoimmune condition induced by gluten consumption in genetically predisposed people, affecting ~1% of the general population. In the literature, there are many studies that report the association between CD and different kinds of arthritis. The aim of this study was to investigate the presence of enthesal abnormalities by US in patients with CD without clinical signs of articular involvement as compared with healthy control subjects.

Methods. Sixty patients with CD attending the gastroenterology outpatient clinic of the University Federico II of Naples and 60 healthy control subjects matched for age and sex were enrolled in this study. Coeliac patients and healthy controls underwent clinical and US examination.

Results. Among 60 CD patients, 24 (40%) presented at least one enthesal alteration as compared with 6 (10%) control subjects (P<0.01). In CD patients, the enthesal site more frequently involved was patellar (distal and proximal), while in the healthy controls the enthesopathies were all localized at the Achilles tendon.

Conclusion. In conclusion, the results of this study underline the ability of US to detect signs of subclinical enthesopathy and indicate the presence of a higher prevalence of subclinical enthesopathies in asymptomatic CD patients.

Key words: coeliac disease, enthesopathy, ultrasound.

Introduction

Coeliac disease (CD) is a systemic autoimmune condition induced by gluten consumption in genetically predisposed people, affecting ~1% of the general population and is not limited to the digestive tract, but is rather a systemic disorder [1]. In the literature, there are many studies that report the association between CD and different kinds of arthritis [2, 3]. Enthesitis, commonly localized in the lower limbs, represents one of the frequent and early features of this arthritis. However, in some patients with CD the presence of enthesitis may be missed during clinical evaluation. Available data show that US is more sensitive and specific than clinical examination in the detection of enthesitis of the lower limbs and may provide a more objective and reliable index of enthesitis than clinical examination [4]. US is widely available and inexpensive, and readily demonstrates superficial tissue inflammation such as fluid collections, soft tissue lesions, enthesal and tendon abnormalities, as well as bone surface lesions with a comparable sensitivity to MRI [5]. The aim of this study was to investigate the presence of enthesal abnormalities by US in patients with CD without clinical signs of articular involvement as compared with healthy control subjects.
Patients and methods

Study population/inclusion criteria
In an 8-month period, 60 patients with CD (females/males 42/18; mean age 31.8 years, range 19–53 years; BMI mean 22.6, range 20–26) attending the gastroenterology outpatient clinic of the University Federico II of Naples and 60 healthy control subjects, matched for age, sex and BMI (females/males 42/18; mean age 31.8 years, range 18–50 years; BMI mean 22.6, range 20–26), were enrolled in this study. The healthy control subjects were recruited among helpers of patients and hospital employees. The ethics committee of the University Federico II of Naples approved the study and informed consent was signed by patients and controls. Inclusion criteria for cases approved the study and informed consent was signed by patients and controls. Inclusion criteria for cases were age >18 years; diagnosis of CD lasting >1 year; absence of clinical signs and symptoms of articular involvement (including axial and peripheral involvement); absence of clinical signs and symptoms of enthesopathy (including Achilles, quadriceps, patellar and plantar aponeurosis enthesitis); and never having received NSAIDs. Prior to the US examination, both CD patients and healthy controls underwent a clinical examination by an expert rheumatologist, who recorded tenderness elicited by pressure, mobilization and contraction against resistance of the corresponding entheses to confirm the absence of entheseal involvement. None of the patients or controls performs any agonistic sport.

US assessment

US examinations were performed at the Rheumatology Unit of the University Federico II of Naples immediately after the clinical examination using an Esaote My Lab 70 machine (Esaote Biomedica, Genoa, Italy), with a linear 10–18 MHz probe and Doppler frequency ranging from 5.9 to 14.3 MHz according to the target. All US examinations were performed in the same session, consecutively, by two experienced sonographers (M.A. and A.C.) blinded to clinical data. Patients and healthy subjects underwent US assessments randomly and were asked not to talk about their clinical condition with the US examiners. Each enthesis was scanned in grey scale to detect morphostructural changes and subsequently with power Doppler (PD) technique to detect abnormal blood flow. The following US findings indicative of enthesopathy were investigated and documented in both transverse and longitudinal views at each enthesis: thickening, calcifications, bone erosions, enthesophytes and bursitis [6]. Examination of the superior and inferior pole of the patella (quadriceps tendon insertion and patella ligament origin) and of the patella ligament insertion at the tibial tuberosity was performed with the patient in the supine position with knee flexed at 30°. The Achilles tendon and the plantar aponeurosis were examined with the patient lying prone with the feet hanging over the edge of the examination table at 90° of flexion. The total number of sites examined for each patient was 10. US assessment of structure thickness and the presence or absence of bone erosions, enthesophytes and bursitis were recorded for each site. Fascia and tendon thickness were measured at the point of maximal thickness on the bony insertion. The following criteria were used for abnormal structure thickness: quadriceps tendon >6.1 mm, proximal and distal patellar tendon >4 mm, Achilles tendon >5.29 mm and plantar aponeurosis >4.4 mm. US findings were scored according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS), ranging from 0 to 36 [6]. GUESS is a reproducible score that allows the measurement of abnormalities at the enthesis of the lower limbs with a numerical value between 0 and 36 [6]. GUESS evaluates the thickness of tendons and the presence of bone erosions, enthesophytes and bursitis in the Achilles tendons, quadriceps and patellar tendons and plantar aponeurosis. Higher values indicate more frequent and relevant abnormalities. PD was standardized with pulse repetition frequency of 750 Hz and a gain of 52 dB, and the temperature of the room was set to 20°C [7]. Vascularity, studied at the insertion of the enthesis at the cortical bone, was scored as a binary item (negative if absent and positive if any signal was present). Finally, for each patient a total PD score was calculated by summing semi-quantitative PD scores of each tendon [8].

Statistical analysis

Statistical analysis was performed using SPSS software, (SPSS Inc., Chicago, IL, USA). Descriptive statistics included mean values and s.d. of the continuous variables and percentages and proportions of the categorical variables. To compare continuous variables and dichotomous ones, Mann-Whitney and χ² tests were performed, respectively. Possible correlations with GUESS have been calculated using the Spearman test. To check the effects of possible confounding variables, the coefficients of partial correlation were computed. Assuming that some variables can affect GUESS, we computed the partial correlation coefficients, checking the effects of sex, age, disease duration and familial CD. As reported in the methods, the US examinations were performed in the same session, consecutively, by two experienced sonographers. The interobserver agreement was calculated using a kappa (κ) test (unweighted for dichotomous scoring). A value of 0–0.20 was considered poor, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 good and 0.81–1.00 excellent, while a κ-value of >0.8 for the intraclass correlation coefficient (ICC) was considered significant.

Results

Among 60 CD patients, 24 (40%) presented at least one entheseal alteration as compared with 6 (10%) control subjects (P < 0.01). Table 1 shows the anatomical localization of enthesal abnormalities of patients with CD and healthy controls. In CD patients, the entheseal site more frequently involved was patellar (distal and proximal). The Achilles tendon was the second most frequent, even if, as in our case, this site showed a frequency of involvement comparable to the controls. Less frequent was localization to quadriceps and the plantar fascia. Among CD patients, 78.6% of entheseal alterations were represented by...
thickness, 8.9% by retrocalcaneal bursitis (Fig. 1), 10.7% by enthesophytes and 1.8% by erosions. In the healthy controls, the enthesopathies were all localized at the Achilles tendon and were represented by thickness in 83.3% and by enthesophytes in 16.6% of subjects. We did not observe bone erosions and bursitis in controls. The thickness of tendons (mm) in CD patients is greater than in controls at each site investigated (P < 0.005). Patients with CD showed a higher GUESS than controls. In particular, the mean GUESS was 1.07 (s.d. 1.47) vs 0.2 (s.d. 0.65) (P < 0.0001). There was no correlation between the presence of enthesopathy or GUESS score with sex, age and BMI in both cases and controls. In addition, composite indices have been proposed to assess and score these abnormalities, especially those located at the lower limb level [14]. However, clinical examination could underestimate asymptomatic enthesial involvement. Thus the development of imaging methods adapted to the detection of enthesis is strongly needed. This would be especially helpful for the early diagnosis of SpA, considering the low specificity of clinical findings in this disease and the long period of time often required to observe significant radiographic changes [15]. MRI can identify both inflammation and structural changes caused by inflammation, but it is expensive and not easy to perform [16]. US has an increased and relevant role in the evaluation of entheses, mainly for its ability to asses joint and periarticular soft tissue involvement and because it is non-invasive, safe and easy to repeat [17]. It permits the assessment of morphostructural features and abnormal vascularization at enthesal sites. Several studies have described, using B mode, the US aspect of lower limb enthesitis in SpA, revealing the high frequency of clinically asymptomatic, abnormal US findings [4, 18, 19]. US may be used to detect early signs of enthesopathy, therefore it could represent, in future studies, a useful tool to predict the clinical onset of enthesial involvement and contribute to the early diagnosis of arthritis.

The present study shows for the first time the evidence of a significantly higher prevalence of enthesopathy in subjects with CD, yet asymptomatic, as compared with healthy controls. The presence of enthesopathy was

**Table 1** Anatomical sites involved by enthesopathy

<table>
<thead>
<tr>
<th>Site</th>
<th>CD patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal patellar</td>
<td>10 (42)</td>
<td>0</td>
</tr>
<tr>
<td>Distal patellar</td>
<td>14 (58)</td>
<td>0</td>
</tr>
<tr>
<td>Achilles</td>
<td>9 (37)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Quadriceps</td>
<td>5 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Plantar fascia</td>
<td>3 (12)</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are presented as n (%).

**Fig. 1** Achilles enthesitis in a coeliac patient.

Achilles enthesis on a longitudinal scan of a coeliac patient. Hypoechoegenicity (due to intratendinous oedema) generated an increase in the thickness of the enthesis. Note the bursitis associated with the intense PD signal.

Discussion

An association between CD and other autoimmune disorders has been described and joint involvement is reported to be related to CD [9, 10]. Furthermore, subclinical gut inflammation has been described in patients with SpAs [11]. Rheumatic diseases occur among patients with CD more commonly than in the general population, but the exact frequency of the coexistence of CD and different rheumatic diseases is not fully known [3, 12]. The articular involvement found in patients with CD is more frequently a non-erosive, non-deforming oligopolyarthritis associated with axial and/or SI joint involvement, a picture closely similar to that of other enteropathic arthritides, which in turn belong to the larger family of the seronegative SpAs [10]. Enthesitis is a major feature of SpAs more frequently localized in the lower limb [13]. Peripheral enthesitis is observed in all SpA subtypes, and it may sometimes be present for a long period of time as an isolated clinical manifestation [13]. In rheumatological practice, enthesial inflammatory signs are detected by clinical examination; in addition, composite indices have been proposed to assess and score these abnormalities, especially those located at the lower limb level [14].

The present study shows for the first time the evidence of a significantly higher prevalence of enthesopathy in subjects with CD, yet asymptomatic, as compared with healthy controls. The presence of enthesopathy was
documented with US, by both grey scale and PD. CD patients showed a significantly higher GUESS as compared with controls. These findings strongly suggest the presence of subclinical entheseopathy in a large proportion of CD patients with negative clinical examination. It is interesting to note that US findings showed non-uniform distribution of entheseopathy in the examined groups. In our study, thickness was the most frequent alteration of entheses in coeliac patients and it is localized at the distal patellar tendon, while in controls, though less frequent and not significantly different from cases, it is mainly localized at the Achilles tendon. A possible explanation of this aspect may be related to both mechanical and local anatomic factors. Limits of the present study are related to the dichotomous way to report the US findings in terms of presence/absence. In this way, very small and focal irregularities of the new bone formation had the same value of high and multiple enthesophytes. In addition, the relatively low prevalence of pathological US findings at the plantar fascia may be due to the presence of a thicker layer of skin and subcutaneous tissue overlying the fascia, which may decrease the US sensitivity.

In agreement with results obtained by Balint et al. [6], the present study confirmed that clinical entheses examination has a low sensitivity as compared with US. In particular, our results show in patients with CD that US discloses frequently subclinical entheseopathy of the lower limbs in subjects without signs or symptoms. A high interobserver reliability was found for all US single abnormal entheseal findings. The absence of PD signal in healthy controls confirms a high specificity of this imaging technique.

In CD patients, the presence of entheseopathy did not correlate with diet duration or serum level of anti-transglutaminase (anti-TG2) antibodies. TG2 are enzymes that play a critical role in the pathogenesis of CD [20]. TG2 expression can be induced by pro-inflammatory cytokines such as TNF-α, which is involved in the inflammatory cascade. TNF-α is the main cytokine involved in the pathogenesis of SpA. Therefore TNF-α could be considered a possible link between CD and SpA and this may represent a promising area for further studies.

In conclusion, the results of this study underline the ability of US to detect signs of subclinical entheseopathy and indicate the presence of a greater prevalence of subclinical entheseal abnormalities in asymptomatic CD patients. This condition may represent an early phase of SpA. Further longitudinal studies may confirm this, indicating the importance of an adequate follow-up of this subgroup of patients that will provide further information regarding the predictive value of US findings in the development of SpA in CD.

**Rheumatology key messages**

- This is the first study that shows a greater prevalence of enthesitis in asymptomatic subjects with CD.
- Enthesopathy did not correlate with diet duration or serum levels of anti-TG2 antibodies.

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**References**