

# Lower limb enthesopathy in patients with psoriasis without clinical signs of arthropathy: a hospital-based case–control study

P Gisondi,<sup>1</sup> I Tinazzi,<sup>2</sup> G El-Dalati,<sup>3</sup> M Gallo,<sup>3</sup> D Biasi,<sup>2</sup> L M Barbara,<sup>2</sup> G Girolomoni<sup>1</sup>

## ABSTRACT

**Background:** Psoriasis is associated with a form of spondyloarthropathy in 10–30% of cases. A major feature of psoriatic arthritis is enthesitis. In some patients with psoriasis the presence of enthesitis could be underdiagnosed.

**Objective:** To investigate the presence of lower limbs enthesal abnormalities in patients with chronic plaque psoriasis without signs and symptoms of psoriatic arthritis.

**Methods:** Thirty patients with psoriasis and 30 controls underwent ultrasonographic evaluation of Achilles, quadriceps, patellar entheses and plantar aponeurosis. Ultrasonographic findings were scored according to the Glasgow Ultrasound Enthesitis Scoring System (GUESS).

**Results:** Mean GUESS score was significantly higher in patients with psoriasis as compared with controls: 7.9 (0.6) vs 2.9 (0.3);  $p < 0.0001$ . In particular, the thickness of all tendons examined was significant higher in cases than in controls ( $p < 0.0001$ ), as well as the number of enthesophytes in all sites examined. In both cases and controls, the GUESS score was directly correlated with age ( $r = 0.22$ ;  $p = 0.008$ ), body mass index ( $r = 0.23$ ,  $p = 0.0067$ ) and waist circumference ( $r = 0.17$ ;  $p = 0.02$ ). In contrast, the GUESS score was not correlated with the duration and severity of psoriasis according to the Psoriasis Area and Severity Index ( $r = 0.03$ ;  $p = 0.8$ ) and body surface area involvement ( $r = 0.07$ ;  $p = 0.6$ ).

**Conclusions:** Enthesal abnormalities can be documented by ultrasonography in clinically asymptomatic patients with psoriasis. These findings could be related to a subclinical enthesal psoriatic inflammation. We suggest close follow-up of patients with psoriasis with enthesal abnormalities for early diagnosis of psoriatic arthritis.

Psoriasis is a chronic inflammatory skin disease that can be associated to a form of spondyloarthropathy, known as psoriatic arthritis (PsA). In most patients psoriasis precedes the onset of PsA, although there is no relationship between the severity of skin disease and the occurrence of PsA. Prevalence of PsA in patients with psoriasis varies from 7.6 to 36% according to different populations studied.<sup>1–7</sup> Moreover, 3–8% of patients with psoriasis had articular symptoms, including arthralgia, morning stiffness and paraesthesia in the absence of sufficient criteria for the diagnosis of PsA.<sup>8–9</sup> Enteses are the initial site of joint inflammation in spondyloarthropathy and enthesitis most commonly localises in the lower limbs.<sup>10–11</sup> In some patients with psoriasis the presence of enthesitis could be missed during clinical evaluation.

Musculoskeletal ultrasonography 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 sensitivity comparable with magnetic resonance imaging.<sup>12</sup> The aim of the present study was to investigate the presence of enthesal abnormalities by means of ultrasonography in patients with psoriasis without clinical signs of PsA, compared with patients with skin disease other than psoriasis. The results indicate that enthesal abnormalities can be documented in clinically asymptomatic patients with psoriasis. These patients may need a closer follow-up for the early detection of PsA.

## METHODS

### Study population

This was a hospital-based case–control study involving a series of 30 patients with chronic plaque psoriasis and 30 age- and sex-matched controls consecutively admitted to the outpatients clinic. The source population for cases and controls was the same, including patients referred to the University Hospital of Verona. Inclusion criteria for cases were: age  $> 18$  years; diagnosis of chronic plaque psoriasis lasting  $> 1$  year; absence of any 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); absence of radiological signs of spinal hyperostosis and absence of any systemic treatment for psoriasis in the previous 3 months prior to clinical and ultrasound evaluation. In particular, no patients had ever received retinoids (acitretin or etretinate) for psoriasis. Controls were enrolled among patients referred to the same hospital for dermatological diseases other than psoriasis, including skin carcinomas (55%), atopic or contact eczema (32.5%) or chronic urticaria (12.5%). Articular examination was performed according to standard procedures. Severity of psoriasis was scored according to the Psoriasis Area and Severity Index (PASI) and body surface area (BSA) measurements.<sup>13</sup> A target nail was selected for each case patient and psoriatic nail involvement was graded according to Nail Psoriasis Severity Index (NAPSI), that is a numeric (ranging from 0 to 32), reproducible, objective, simple tool for the evaluation of nail psoriasis.<sup>14</sup> Registered socio-demographic characteristics of the study population included body mass index (BMI), waist

<sup>1</sup> Department of Biomedical and Surgical Sciences, Section of Dermatology and Venereology, University of Verona, Verona, Italy; <sup>2</sup> Department of Experimental and Clinical Medicine, Section of Rheumatology, University of Verona, Verona, Italy; <sup>3</sup> Department of Biomedical and Morphological Sciences, Section of Radiology, University of Verona, Verona, Italy

Correspondence to: Paolo Gisondi, Department of Biomedical and Surgical Science, Section of Dermatology and Venereology, University of Verona, Piazzale A. Stefani 1, I-37126 Verona, Italy; paolo.gisondi@univr.it

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circumference, co-morbidities and age of onset of psoriasis. Venous samples were taken at the enrolment visit after the subjects had fasted overnight (at least 8 h). Serum cholesterol, triglycerides and uric acid were measured with enzymatic procedures. Plasma glucose was measured using a glucose oxidase method. This study was approved by the Ethical Committee.

### Ultrasonography

Real-time ultrasonography was performed by both an experienced radiologist and a rheumatologist, using an ATL HDI 3000 machine with a linear 10–15 MHz probe. The rheumatologist received a certified university training in musculoskeletal ultrasonography and she was very familiar with the routine use of ultrasound for the detection of early rheumatoid arthritis. Both the radiologist and the rheumatologist were blinded, that is, they were not aware if patients were affected by psoriasis or other skin diseases, and the ultrasonographic examination was performed in a darkened room. Examination of the superior pole of the patella (quadriceps tendon insertion), the inferior pole of the patella (patellar ligament origin) and the patellar ligament insertion at the tibial tuberosity was performed with the patient in the supine position with the 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. Ultrasonographic assessment of structure, thickness and the presence or absence of bony erosions, enthesophytes and bursitis was recorded at each site. Ultrasonographic findings were scored according to Glasgow Ultrasound Enthesitis Scoring System (GUESS), which was validated by Balint *et al*<sup>15</sup> in order to compare ultrasonography with clinical examination in the detection of enthesal abnormalities of lower limbs in patients with spondyloarthritis. GUESS is an easily reproducible standardised measure of lower limb enthesal ultrasonographic abnormalities, ranging from 0 to 36.<sup>15</sup> It incorporates the assessment of tendon thickness, and the presence of bone erosions, enthesophytes and bursitis recorded at the Achilles, quadriceps and patellar tendons and plantar aponeurosis. Clinically, enthesitis is suspected and afterwards better confirmed by power Doppler ultrasonography and/or magnetic resonance.<sup>16</sup> Validation ultimately comes down to histological confirmation,<sup>17</sup> but this is very rarely performed in clinical practice.

### Plain radiography

A SIEMENS OPTI 150/30/50 HC-100, model 4803388 instrument was used (Malvern, PA, USA). A plain radiography of spinal, knee and foot was performed in both cases and controls, in order to detect the presence of hyperostosis, calcifications, bone erosions and bone apposition. Examination of the superior pole of the patella (quadriceps tendon insertion), the inferior pole of the patella (patellar ligament origin), and the patellar ligament insertion at the tibial tuberosity was performed with the patient in the supine position with the knee flexed at 30°. The Achilles tendon and the plantar aponeurosis were examined with the patient lying supine with the feet at 90° of flexion. Radiographies were useful to confirm the presence of enthesophytes detected by ultrasound and to exclude spinal hyperostosis suggestive of diffuse idiopathic skeletal hyperostosis.<sup>18</sup> The number of calcifications evident by plain radiography were measured and GUESS was re-scored (GUESS modified) without including these in the computation. The main advantage of not

considering radiological calcifications is to take into account only enthesophytes due to inflammatory processes.

### Statistical analysis

Analysis was made using the STATA (version 6.0 Stata-Corp LP, College Station, TX, USA) and Graphpad (version 4.0 GraphPad Software, El Camino Real, San Diego, CA, USA) software packages. Standard descriptive statistics such as mean and standard deviation were computed. Associations between the presence of psoriasis and various covariates were tested by using the Fisher exact test for categorical variables and t test for continuous variables. Linear correlation between covariates were analysed according to Spearman test for non-parametric variables and Pearson for parametric variables. The intraobserver agreement was calculated using a  $\kappa$  test. Analysis of covariance (ANCOVA) was also performed. All p values are two-sided and  $p < 0.05$  was considered statistically significant.

### RESULTS

Descriptive characteristics of study population are reported in table 1. Cases had mild to severe chronic plaque psoriasis with a PASI score ranging from 1.6 to 30.2 with a median 7.54 (95% CI 7.4 to 9.6); 17 patients (56.6%) had a PASI score  $< 10$ , whereas 13 had a PASI score  $\geq 10$ . BSA involvement ranged from 1 to 45%, with a median of 10.6 (95% CI 14.9 to 19.1); 18 patients (60%) had a BSA  $< 10\%$ , whereas 12 had a BSA  $\geq 10\%$ . Mean NAPS score was 10.3 (95% CI 7.9 to 15.1). Controls included 15 females and 15 males with a mean age of  $56.7 \pm 13.9$  (age ranged from 29 to 78 years). There were no significant differences in sex distribution, mean age, BMI, waist circumference, glycaemia, cholesterolaemia, triglyceridaemia and uric acid plasma levels between cases and controls (table 1).

GUESS score and main sonographic findings are reported in table 2. Mean GUESS score was significantly higher in patients with psoriasis as compared with controls: 7.9 (0.6) vs 2.9 (0.3),  $p < 0.0001$  (fig 1a). Moreover, also rescoring GUESS without including calcifications evident with plain radiography (ie, GUESS modified) the difference between cases and controls was still statistically significant: 5.0 (2.1) vs 2.8 (0.3),  $p < 0.01$  (fig 1b). In particular, the mean thickness of all tendons examined was significantly higher in cases than in controls ( $p < 0.0001$ ) as well as the mean number of enthesophytes in all sites examined (fig 2a,b). We found that thickening was preferentially (almost 70% of cases) associated with loss of fibrillar echogenicity than to hypoechoic change (fig 2b,c). In both cases and controls GUESS score was directly correlated with age ( $r = 0.22$ ;  $p = 0.008$ ) (fig 1c), BMI ( $r = 0.23$ ;  $p = 0.0067$ ) (fig 1d), and waist circumference ( $r = 0.17$ ;  $p = 0.02$ ). Although there were no differences in BMI between cases and controls, we performed a covariate analysis to adjust the statistical

**Table 1** Description of the study population

	Cases	Controls	p value
N	30	30	1
Sex distribution (M:F)	18:12	15:15	0.8
Age (years), mean (SD)	55.8 (13.2)	56.7 (13.7)	0.7
BMI, mean (SD)	28.5 (4.2)	28.4 (2.4)	0.8
Waist circumference (cm), mean (SD)	104.5 (12.8)	102.4 (9.1)	0.1
Glycaemia (mg/dl), mean (SD)	116 (15.6)	105 (16.8)	0.08
Cholesterolaemia (mg/dl), mean (SD)	245 (10.2)	230 (12.8)	0.9
Triglyceridaemia (mg/dl), mean (SD)	208 (12.2)	201 (14.8)	0.9
Uric acid (mg/dl), mean (SD)	6.1 (2.2)	5.6 (2.3)	0.7

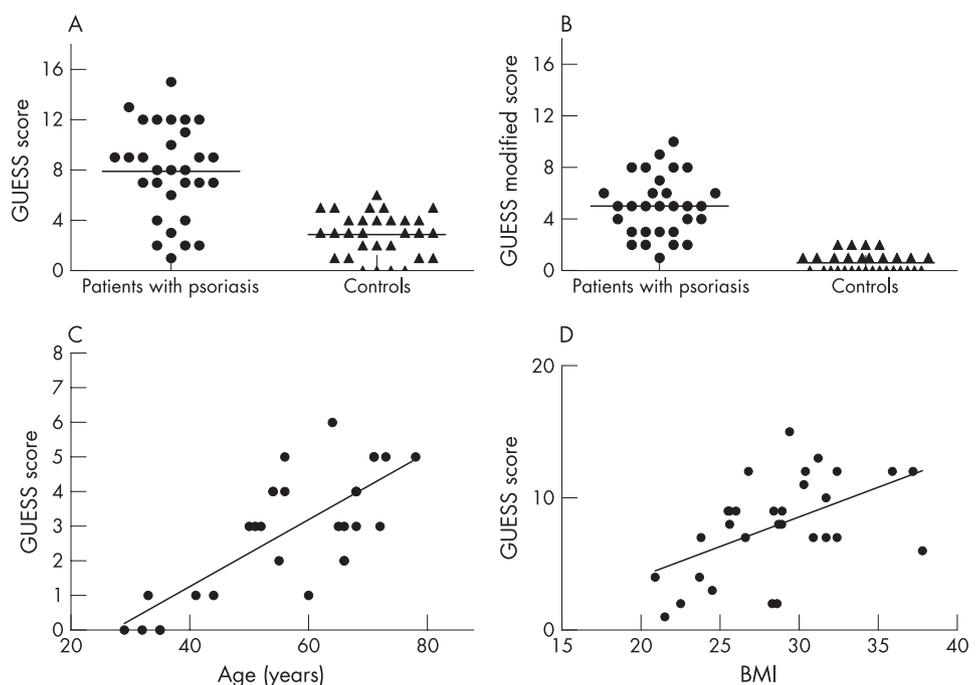
evaluation for BMI and body weight. According to the adjustment in BMI, the difference in GUESS score was still statistically significant: 7.5 (0.5) vs 2.8 (0.2),  $p < 0.0001$ . In contrast, the GUESS score was not correlated with either the duration or the severity of psoriasis according to the PASI index ( $r = 0.03$ ;  $p = 0.8$ ), BSA involvement ( $r = 0.07$ ;  $p = 0.6$ ) as well as to severity of nail psoriasis ( $r = 0.05$ ;  $p = 0.7$ ). We did not observe bone erosions neither in cases nor in controls, whereas we found six patients with psoriasis with retrocalcaneal bursitis, but no bursitis in controls ( $p = 0.0001$ ) (fig 2c). The intraobserver  $\kappa$  value for analysis of all sites was 0.9. The  $\kappa$  values for the analysis of separate lesions were as follows: tendon thickness  $\kappa = 0.91$ ; bone erosions and bursitis  $\kappa = 0.98$ ; enthesophytes  $\kappa = 0.88$ .

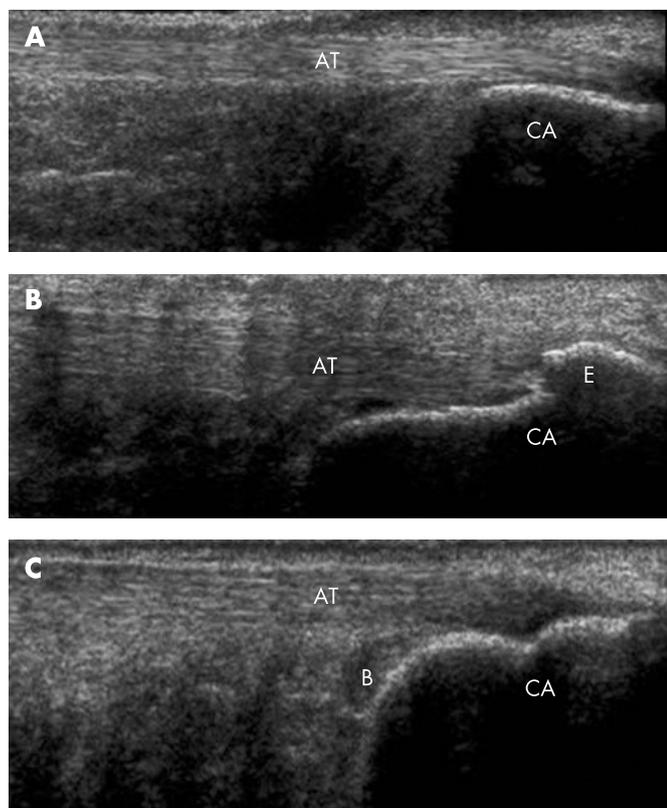
**DISCUSSION**

This study found that enthesal abnormalities can be documented by ultrasonography in clinically asymptomatic patients with psoriasis. In particular, thickness of lower limb entheses examined and number of enthesophytes were significant higher in patients with psoriasis than in controls. Bone erosions were not observed neither in cases nor in controls, whereas six patients with psoriasis had retrocalcaneal bursitis. Similar findings were rarely reported by other authors. In particular, De Filippis *et al*<sup>19</sup> found that enthesal abnormalities not detected at clinical examination were present in six of 24 (25%) patients with psoriasis who underwent ultrasonography. Similarly, Ozcakar *et al*<sup>20</sup> found that the mean thickness of the Achilles' tendon was significantly higher in patients with psoriasis (without clinical sign of enthesitis) than in healthy volunteers. Achilles sonographic abnormalities in 35 of 59 patients with psoriasis (59.2%) were also reported by De Simone *et al*.<sup>21</sup> However, in this study, 15 of 58 patients with PsA were included. Finally, Galluzzo *et al*<sup>22</sup> found a high prevalence of involvement of the tendons and entheses of the ankle in clinically asymptomatic PsA patients, suggesting that clinical evaluation underestimates these manifestations. Our data

confirm that enthesal abnormalities are common in patients with psoriasis without clinical sign of articular involvement and we suggest that these findings could be related to a enthesal psoriatic inflammation, which is not clinically apparent. We measured the enthesal abnormalities according to the GUESS score and the modified GUESS score, which takes into account only enthesophytes due to inflammatory processes excluding those due to degenerative processes. Moreover, we found a small but significant correlation between GUESS score and BMI, waist circumference, and age in both cases and controls, whereas there was no correlation between GUESS score and duration and severity of psoriasis. Apart from inflammatory tendinitis other disorders that are known to increase tendon thickness include trauma, diabetes, familiar hypercholesterolaemia and gout tophi, all conditions that were excluded in our patients.<sup>23 24</sup> Another relevant factor that may affect tendon thickness is the BMI. It has been reported that there is an association between the thickness of the Achilles tendon and BMI either in healthy individuals but also in female patients with diabetes.<sup>25 26</sup> We did not observe any statistically significant difference between patients with psoriasis and controls in terms of BMI as well as mean glycaemia, cholesterol, triglycerides and uric acid levels. Even if we adjusted the GUESS score according to all of the above-mentioned confounding factors, the adjusted GUESS score value was still significantly higher in cases than in controls, which supported that the presence of enthesopathy in our patients is independent from the confounding. As far as iatrogenic causes of enthesopathy, retinoids are known to induce hyperostosis, most notably when they are used in high dosages and over long periods;<sup>27</sup> therefore, we included in the study only patients that never received retinoids. The role of ageing on tendon thickness is uncertain, although more recently it has been reported that Achilles tendon thickness was similar in young and middle-aged people.<sup>28</sup> We suggest that psoriasis is an independent factor, which may favour either tendon thickness and enthesophyte production possibly due to subclinical enthesal psoriatic inflammation.

**Figure 1** (A) Glasgow Ultrasound Enthesitis Scoring System (GUESS) scores of patients with psoriasis and controls (p). (B) GUESS modified score in patients with psoriasis and controls (p). (C) Linear correlation between GUESS score and age according to Pearson test ( $r = 0.22$ ;  $p = 0.008$ ). (D) Linear correlation between GUESS score and BMI according to Pearson test ( $r = 0.23$ ;  $p = 0.0067$ ).





**Figure 2** (A) Ultrasonographic image of normal Achilles tendon (3.8 mm) in a control subject. (B) Ultrasonographic image of a thickened Achilles tendon (7.1 mm) and enthesophyte in a psoriatic patient. (C) Ultrasonographic image of a thickened Achilles tendon (6.8 mm) associated to a retrocalcaneal bursa (diameter 6.9×2.4 mm) in a psoriatic patient. AT, Achilles tendon; B, retrocalcaneal bursa; CA, calcaneus; E, enthesophyte.

**Table 2** GUESS score in the study population

	Cases	Controls	p value
Quadriceps tendon thickness >6.1 mm; N* (%)†	18 (30)	2 (3.3)	0.0001
Suprapatellar bursitis; N (%)	1 (1.6)	0	0.8
Superior pole of patella erosion; N (%)	0	0	1
Superior pole of patellar enthesophyte; N (%)	41 (68.3)	24 (40)	0.005
Patellar ligament thickness >4 mm (inferior pole of patella); N (%)	22 (36.6)	14 (23.3)	0.02
Inferior pole of patella erosion; N (%)	0	0	1
Inferior pole of patella enthesophyte; N (%)	20 (33.3)	12 (20)	0.01
Patellar ligament thickness >4 mm (insertion at the tibial tuberosity); N (%)	21 (35)	10 (16.7)	0.01
Infrapatellar bursitis; N (%)	0	0	1
Tibial tuberosity erosion; N (%)	0	0	1
Tibial tuberosity enthesophyte; N (%)	14 (23.3)	1 (1.6)	0.0001
Achilles tendon thickness >5.29 mm; N (%)	10 (16.6)	1 (1.6)	0.0001
Retrocalcaneal bursitis; N (%)	6 (10)	0	0.0001
Posterior pole of calcaneus erosion; N (%)	0	0	1
Posterior pole of calcaneus enthesophyte; N (%)	54 (90)	20 (33.3)	0.0001
Plantar aponeurosis thickness >4.4 mm; N (%)	3 (5)	0	0.8
Inferior pole of calcaneus erosion; N (%)	0	0	1
Inferior pole of calcaneus enthesophyte; N (%)	23 (38.3)	22 (36.6)	0.8

\*N is the number of enthesal sites resulted abnormal according to the GUESS score.  
 †(%) is the prevalence enthesal sites abnormalities in the case and control population respectively.

The major limitation of our study is the small number of patients investigated and the absence of long-term follow-up, which may show whether some of the patients could later develop PsA. As enthesopathic changes have been suggested as being the unifying and early feature of PsA, these patients need a closer follow-up for the early detection of PsA.<sup>29-30</sup> PsA can be associated with a progressive and irreversible damage of the entheses in a relatively short time.<sup>31</sup> Therefore, we suggest the routine use of ultrasonography in the early diagnosis of patients with tendon enthesopathy, as these factors may have implications for therapy and the prevention of progression of PsA.

**Competing interests:** none

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