J Musculoskel Neuron Interact 2003; 3(1):89-100

Original Article

Hylonome

Enthesial fibrocartilage – bone interaction: a radiographic study of selected sites of nonsynovial peripheral enthesopathy

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Abstract

Objectives: To assess radiological imaging and prevalence of pelvic (excluding sacroiliac joints), calcaneal, patellar and humeral enthesopathy (EN) in a cohort study. Materials-methods: Outpatients attending a state hospital rheumatology clinic for a continuous 4-year period, were consecutively screened for radiographic evidence of peripheral nonsynovial EN in pelvis, ankle, knee and shoulder regions and in particular sites within these regions regardless of symptoms. Imaging and prevalence were assessed in patients suffering from a variety of myoskeletal disorders by applying either of the following two plain X-ray criteria: a) tendon and/or ligament and/or fascia ossification, b) reactive bone proliferation resulting in excrescences and/or sclerosis and/or erosions. Results: A total of 3,670 patients were screened and a cohort of 585 patients (16%) with extraspinal peripheral EN was selected. Plain radiography provided good imaging of pelvic EN at iliac crests, greater trochanters, pubic symphysis and pubic rami, as well as of calcaneal, patellar and humeral head enthesopathic changes. Cohort recruitment by applying the two aforementioned criteria resulted in the formation of 2 groups: Group A, consisting of 169 patients (mean age in years 34 ± 8 SD) suffering from inflammatory myoskeletal disease represented by Seronegative Spondyloarthropathies (SSp); and Group B, including 416 patients (mean age 63 ± 7) suffering from degenerative/metabolic disorders classified as degenerative disease of the spine, hip or knee (70%), Diffuse Idiopathic Skeletal Hyperostosis (DISH) (11%) and rotator cuff (Rot/Cuff) syndromes (19%). Females were the predominant gender in the cohort and in Group B patients (both $p<0.001$ vs. males), while the opposite was true for the group of inflammatory diseases. Patients in Group A were younger and had shorter disease duration than those of group B ($p<0.001$ for both). Pelvic EN was the most frequent localization of EN within the cohort (46%, $p<0.001$) followed by both multiple site and patellar EN (24% & 22% respectively). Patients in Group A, had a significantly higher prevalence of pelvic EN compared to those in Group B (60% vs. 39%, $p<0.001$) and the former group was significantly associated with pelvic EN. On the contrary, although pelvis was also the predominant EN site in Group B, patellar and humeral head EN were significantly associated with noninflammatory diseases. In patients with SSps, pelvic EN predominance (60%) was followed by calcaneal involvement ($p<0.01$ vs. patellar and humeral head). These two were the skeletal sites that were significantly associated with individual diseases within Group A (pelvis with AS and Ps-Sp and calcaneus with RR). Within Group B, patients with knee OA, hip OA and Rot/Cuff showed EN site localization in absolute proximity with disease process, while in those with Deg/Sp or DISH pelvis was the predominant site involved. Conclusions: Plain radiography provides good imaging of peripheral nonsynovial EN at well defined skeletal sites. Within a general rheumatic population, pelvic EN is the most prevalent localization followed by multiple site and patellar reactive bone lesions. Apart from seronegative spondyloarthopathies, degenerative and metabolic myoskeletal disorders contribute substantially to local induction of abnormal fibrous tissue/fibrocartilage-bone interactions resulting in radiographically detectable EN.

Keywords: Enthesopathy, Enthesitis, Fibrocartilage, Bone Insertion, Radiographic Imaging

Introduction

The site of insertion of a tendon, ligament, fascia or articular capsule into bone is called an enthesis[1]. The term is derived from Greek (verb: εντίθεμαι, noun: ενθέσεις) where

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Accepted 5 August 2002

it signifies the process of "slip in and lie inside". Entheses can be either axial (spinal) or peripheral (extraspinal)[2].

Insertions of soft tissue elements into bone are divided into four histologically discrete zones[3-5]. These zones are: 1. collagen fibers of soft connective tissue (tendon, ligament or other), 2. unmineralized fibrocartilage, 3. mineralized fibrocartilage (fibrocartilaginous entheses) and 4. bone. Alternatively, at the end of the attachment the collagen fibers blend with those of bone matrix and are often referred to as Sharpey's perforating fibers (fibrous entheses).

Transmission and dissipation of tensile forces produced by muscular contractions is the main function of an enthesis[4,6]. It is now accepted that there is a good correlation between the distribution of fibrocartilage within an enthesis and the levels of compressive stress.[7]

Any pathological lesion at an enthesis is termed enthesopathy (EN) and ossification at this site is termed an enthesophyte[1,2,5,6]. Fibrocartilage, representing an intermediate form between fibrous connective tissue and hyaline cartilage, is an integral part of entheses, ENs may be considered as a pathological process affecting this stucture[6].

Traumatic, degenerative, inflammatory and metabolic diseases may all induce inflammatory or non-inflammatory EN. EN can also be classified regionally into the axial or spinal form involving the spine and peripheral forms, appearing at extraspinal locations such as synovial joints, cartilaginous articulations, syndesmoses and various extra- or juxta-articular nonsynovial sites. It has been postulated that in synovial sites, a joint ankylosis or a joint effusion, phenomena commonly observed in inflammatory disorders such as the seronegative spondyloarthritides (SSp), result from extrasynovial capsular inflammation and EN lesions at the articular capsule-synovial membrane interface[5,8,9].

Both axial and peripheral ENs may be simultaneously observed in inflammatory or non-inflammatory disorders, characteristic examples being SSp and Diffuse Idiopathic Skeletal Hyperostosis (DISH), respectively.

Histopathology of EN consists of an inflammatory lesion (enthesitis) characterized by marked capillary proliferation and cellular infiltration containing fibroblasts, dividing chondrocytes, plasma cells and lymphocytes,[2,5,6] the latter being mostly CD8+ T lymphocytes[10], though recent experimental evidence shows that EN may be a T cell independent process[11]. Entheseal inflammatory changes induce osseous erosions the healing of which, by reactive bone formation, leads to chondroid and bone tissue outgrowth at the enthesis, generating axial or peripheral bone excrescences and/or enthesophytes[5,6,11].

Myoskeletal locations of peripheral EN are numerous[1] but the most commonly observed nonsynovial sites in routine radiographs relate to the pelvic girdle, greater tuberosity of the humeral head, patella and calcaneum. Imaging of these enthesopathic sites can be assessed by plain X-rays, isotope bone scanning, axial tomography and magnetic resonance imaging (MRI) techniques[5,12].

The present study assessed radiographic prevalence and imaging of the aforementioned skeletal regions of abnormal fibrous tissue/ fibrocartilage-bone interaction in inflammatory and non-inflammatory disorders met in a busy rheumatology outpatients department. It was shown that in addition to SSp and DISH, degenerative diseases contribute significantly to the radiological appearance of nonsynovial peripheral EN in rheumatological clinical practice.

Materials and methods

Cohort recruitment

All adult (age>16 yrs) outpatients visiting the 5-weekly clinics of the Rheumatology Department of the hospital for the first time are routinely screened by radiological means for diagnostic and therapeutic purposes. For the purpose of the present study, outpatients attending the clinic from February 1997 until December 2000, were consecutively screened for signs of extraspinal nonsynovial EN in the pelvis, knee, ankle and shoulder by plain radiographs. No correlation to corresponding enthesopathic symptoms was attempted. A full clinical, laboratory and radiographic investigation on an inpatient basis followed the decision for study enrolment. It should be stressed that all patients were symptomatic in relation to their rheumatic disease and according to diagnosis based on currently accepted routine diagnostic criteria, patients were classified into two groups of myoskeletal disease: inflammatory (Group A) and non-inflammatory (Group B). Based on clinical grounds (presenting symptoms, reason for visiting the clinic, clinical, laboratory and radiological findings) and for reasons of clarity, only one primary diagnosis was assigned to each patient and was employed for classifying patients in either of the two groups.

Skeletal sites and criteria

The following skeletal regions and sites were studied from obtained radiographs:

Region	Sites
Pelvis	iliac crests, femoral trochanters, ischial tuberosities, pubic symphysis and pubic rami
Knee	Anterior and lateral views of the patella and tibial tuberosity
Ankle	calcaneal views, plantar area
Shoulder	humeral head, acromion, acromioclavicular joint

Sacroiliac joints were excluded from the pelvic area since these joints, representing part of the spine, were considered as axial or spinal EN. Moreover, it is well known that sacroiliac joints are fibrocartilaginous in their upper and synovial in their lower part[5].

In this respect, subsets of peripheral EN were designated as pelvic, calcaneal, patellar and humeral and the total number of multiple locations of EN (more than one skeletal

Patient characteristics	No. (per cent)
Total	585
Age	yr, mean (± SD)
Cohort	59 (±9.9)
Group A	34 (±8)
Group B	63 (±7)
Gender	
Cohort	
Females	349 (60%)
Males	236 (40%)
Group A	
Females	64 (38%)
Males	105 (62%)
Group B	
Females	285 (69%)
Males	131 (31%)
Disease duration	yr, mean (±SD)
Group A	4 (±5)
Group B	8 (±9)
Myoskeletal diseases	
Inflammatory- Seronegative spondyloarthropathies (Group A)	169 (29%)
Ankylosing spondylitis	28
Psoriatic arthropathy	119
Spondylitis only	40
Arthritis with or without spondylitis	79
Reiter's syndrome/Reactive arthritides/ Undifferentiated	22
Non-inflammatory (Group B)	416 (71%)
Degenerative disease	292
Degenerative spinal disease	105
Knee osteoarthritis	163
Hip osteoarthritis	24
Rotator cuff syndromes	80
Diffuse Idiopathic Skeletal Hyperostosis (DISH)	44
Co-existing axial (spinal) enthesopathy (discovertebral junction and sacroiliac joint involvement)	132 (23%)

Table 1. Nonsynovial peripheral enthesopathy – Basic demographic data and classification of the study cohort by disease association.

region) was also recorded without further analysis. Two or more sites within the same skeletal region were separately recorded only in the pelvis because of: (i) the large size of iliac bones, (ii) the inclusion of femoral heads and (iii) the polymorphism of enthesopathic lesions at this part of the skeleton.

Inclusion criteria

Two radiological criteria were applied for diagnosing peripheral EN at the designated skeletal regions and sites and for inclusion of patients in the cohort:

i. Ossification of tendon, ligament or fascia insertion

ii. Bone excrescences and/or bone sclerosis and/or bone erosion.

The first criterion was mainly applicable to patellar and calcaneal EN and the second one to all skeletal sites and all subsets of EN studied. It should be mentioned that enthesopathic bone erosions were defined as lesions observed at extra-articular nonsynovial sites, over and above subchondral erosions within the synovial cavity noted in inflammatory arthritis.

Radiographs and corresponding patient records were included in the study when either of the two criteria was satisfied with no correlation to symptoms. All X-rays were independently assessed by two investigators, one always being the radiologist, and patients included in the study on mutual agreement.

Skeletal region and sites	No.	%	% Region & site difference P
Pelvis			
Any site	355	46	*
Iliac crests	216		
Greater trochanters	233		
Pubic symphysis and/or Pubic rami	275		†
Knee (patella)	166	22	*
Ankle (calcaneum)	134	17	
Shoulder (humeral head)	117	15	
> 1 region	187	24	*

EN: Enthesopathy
† :<0.05
* :<0.001

Table 2. Subgroups and relative prevalence of 772 (585+187) peripheral EN * localizations in 585 patients.

	Group A 169+90=259		Group B 416+97=513		Group difference
Site	No.	%	No.	%	p
Pelvic (any single site)	155	60	200	39	<0.001
Iliac crests and/or	139	77			
Greater trochanters	125	108			
Pubic symphysis or pubic rami	152	123			
Patellar	32	12	134	26	<0.001
Calcaneal	50	19	84	16	NS
Humeral	22	8	95	18	<0.001
>1 region	90		97		NS

* EN=Enthesopathy
NS: not significant

Table 3. Prevalence of 259 skeletal sites with peripheral EN* in 169 patients with inflammatory (Group A) and 513 sites in 416 patients with non-inflammatory (Group B) myoskeletal disorders.

Exclusion criteria were concurrent or equivocal rheumatological diagnoses, bad health and pregnant women.

Approval by the Hospital Ethics Committee was obtained for all patients.

Statistical evaluation

The Pearson Chi-square test was used for the identification of association between individual diseases and enthesopathic site involvement, and for the assessment of association between disease group and site involvement. Binomial proportions were compared using normal approximations and the t-test was used when appropriate (significance of age differences, significance of disease duration). Differences were considered statistically significant at $p<0.05$. When multiple comparisons were conducted, the Bonferroni method was used.

Results

Cohort analysis

A total of 3,670 consecutive patients were radiographically screened during the study period and 630 of them were

Disorder	Total No. of patients	Total No. of localizations	Pelvic No.	%	Patellar No.	%	Calcaneal No.	%	Humeral No.	%
Group A	169	259	155	60*	32	12	50	19	22	9
Group B	416	513	200	39	134	26*	84	16	95	18*

*:p<0.001

Table 4a. Prevalence of pelvic, patellar, calcaneal and humeral EN localizations in myoskeletal disorders of the cohort. Statistically significant association between groups of patients and EN site involvement, flagged by the association of patellar and humeral EN with Group B and pelvic EN with Group A patients (p<0.001, Chi-square test).

Disorder	Total No. of pelvic EN localizations	Iliac crests No.	Greater trochanters No.	Pubic symphysis or pubic rami No.
Group A	155	139	125	152
Group B	200	77	108	123

Table 4b. Pelvic EN localizations as a whole and for each of the pelvic sites.

identified as satisfying the inclusion criteria of radiological EN at the selected skeletal sites. It is again emphasized that no connection between radiographic findings and symptoms was looked for.

Forty patients, 25 men and 15 women (19% in the cohort), suffering from microcrystalline arthropathies (gout, pyrophosphate disease, undefined) and fulfilling the radiological criteria of EN were excluded from the cohort and were not subjected to further analysis. The reason for this was that classification of such patients in the inflammatory group is debatable; despite the fact that all were diagnosed as suffering at the time from acute crystal-induced inflammation, many of them exhibited simultaneous radiographic signs of (secondary) degenerative disease with or without signs of articular chondrocalcinosis and enrolment into one of the two groups appeared problematic. Five patients (all female) suffering from rheumatoid arthritis were also excluded from the cohort due to similar reasons and their small number.

Basic demographic data and classification by disease association of the remaining 585 cohort patients are given in Table 1. Inflammatory EN in Group A consisted of SSp and non-inflammatory EN was represented by degenerative and metabolic arthropathies.

The mean age of patients with inflammatory arthropathies (34 ±8 yrs), was significantly lower (p<0.001) than that of patients with non-inflammatory disorders (63 ±7 yrs). This was apparently due to the fact that Group A consisted of patients suffering from SSp, a disease that affects younger ages.

Females exceeded males in the total cohort (60% vs. 40%, p<0.001), reflecting the larger Group B population, which included cases of degenerative and metabolic disorders. As shown by further intra-group gender analysis, there was a male gender predominance in Group A (62% vs. 38% females, p<0.001) whilst females predominated in Group B with degenerative EN (69% vs. 31% males, p<0.001).

Due to obvious prevalence differences in any rheumatic population, non-inflammatory compared to inflammatory disorders are represented in the study cohort by a significantly higher number (71% vs. 29%, p<0.001).

Mean disease duration was 4 years (±5 SD) in Group A. Intra-group analysis showed that this ranged from 3-9 years in AS, 1-7 for PsA, 2-4 for Ps-Sp and <1 – 8 years for RR.

Mean disease duration was significantly longer in Group B (8 years, ±9 SD, p<0.001 between groups). It ranged from 3-16 years for Deg-SP, 2-10 for knee OA, 1-5 for hip OA, 1-7 for Rot/Cuff and (estimated) 7-16 years for DISH.

SSp represented inflammatory arthropathies in Group A. Psoriatic arthropathy (franc spondylitis – 40 patients, arthritis with or without spondylitis – 79 patients) comprised 70% of the group (119/169). Prevalence of ankylosing spondylitis (AS) and all reactive arthritides (RR) were 17% and 13%, respectively. It can be seen that psoriatic arthropathy, either purely spondylitic (Ps-Sp) or mainly with peripheral arthritis (PsA), was the predominant enthesopathic disease in Group A (p<0.001).

Degenerative diseases, consisting of osteoarthritis (OA) of the knee or hip and degenerative spinal disease (Deg-Sp), represented the main category of myoskeletal disorders in Group B, comprising 70% of patients of the group (p<0.001 versus Rot/Cuff and DISH). Knee OA was the most frequent disease both in Group B and in all OA patients (39% and 56% respectively, both p<0.001). Patients with Deg-Sp were the second more frequent sub-group within degenerative disease patients (36%, p<0.001) and both Deg-Sp with Rot/Cuff syndromes were the diseases that followed knee OA in this group of non-inflammatory EN (25% and 19%

		Group A				F-M difference		Group B				F-M difference
		F		M				F		M		
Site	Total No.	No.	%	No.	%	p	Total No.	No.	%	No.	%	p
Pelvic	106	46	43	60	57	*	163	114	70	49	30	#
Patellar	15	4	27	11	73	*	110	85	77	25	23	#
Calcaneal	36	10	28	26	72	#	67	44	65	23	35	#
Humeral	12	4	33	8	67	*	76	42	55	34	45	NS
All sites	169	64	38	105	62	#	416	285	69	131	31	#

Table 5. Prevalence of pelvic, patellar, calcaneal and humeral EN* by gender in the two groups.

	Total Group A	AS	Ps-Sp	PsA	RR
Total No. of localizations	259	83	51	46	79
Pelvic	155**	60**	37**	22*	36**
Patellar	32	8	5	10*	9
Calcaneal	50*	6	4	12*	28**
Humeral	22	9	5	2	6

*:$p<0.01$
**:$p<0.001$

Table 6. Prevalence of inflammatory myoskeletal disorders in different enthesopathic regions and sites in SSp (Group A).

prevalence, respectively).

Rotator cuff (Rot/Cuff) syndromes (19% in Group B) related mostly to clinical cases of present or past episodes of "shoulder periarthritis" due to supraspinatus or other rotator muscles tendinitis of the humeral head area.

Non-axial involvement in DISH, requiring spinal involvement as a diagnostic criterion for the purposes of the study, was radiographically recorded at the selected skeletal sites in 11% of Group B patients.

Overall, axial EN was detected in 23% of the cohort patients. Spinal syndesmophytes (enthesophytes) were observed in all 44 patients with DISH, whilst sacroiliitis and spinal syndesmophytes in all 28 and all 40 patients with AS and Ps-Sp respectively, as well as in 20/22 patients with RR (data not shown).

Beyond enthesopathy, we have to state certain features of arthritis of individual diseases. Patients with PsA, who all had peripheral arthritis, showed 57% prevalence of knee synovitis. On the contrary, there were only 23% of RR patients with knee arthritis, whilst the majority of them (68%) had ankle synovitis. Finally, more than a third of AS patients (36%) had hip arthritis and only 11% of them showed knee synovitis.

The majority of patients in Group A (130/169) were receiving, during the study period, Disease Modifying Antirheumatic Drugs (DMARDs), 101 of them either methotrexate or sulphasalazine and 29 azathioprine. Almost all the patients of the cohort were also receiving analgesics and/or Non Steroidal Anti-inflammatory Drugs (NSAIDs) as part of their treatment. Since we did not believe that any kind of treatment might influence radiographic signs of EN (as opposed to clinical or MRI findings), this issue was not further explored.

EN imaging and prevalence analysis

Multiple regions of enthesopathic changes were recorded in 187 patients of the cohort (24%) and a total of 772 peripheral EN sites in the two groups were subjected to statistical analysis (Tables 2 and 3).

Pelvic EN at any skeletal site was the prevailing localization within the total 772 enthesopathic sites observed (46%, $p<0.001$, Table 2), followed by both multiple site and patellar EN (24% and 22%, respectively). No significant difference was observed between ankle and shoulder EN prevalence (17% & 15%, respectively, Table 2). This large prevalence of pelvic EN was expected since multiple skeletal sites, including a strictly anatomical non-pelvic site, namely the greater trochanters, were considered together as part of the pelvic girdle. In the pelvic girdle, pubic symphysis/pubic rami was the most prevalent site involved ($p<0.01$).

Enthesopathic changes in more than one skeletal region were the second most frequent localization, closely followed by patellar EN, without a particular pattern of sites associa-

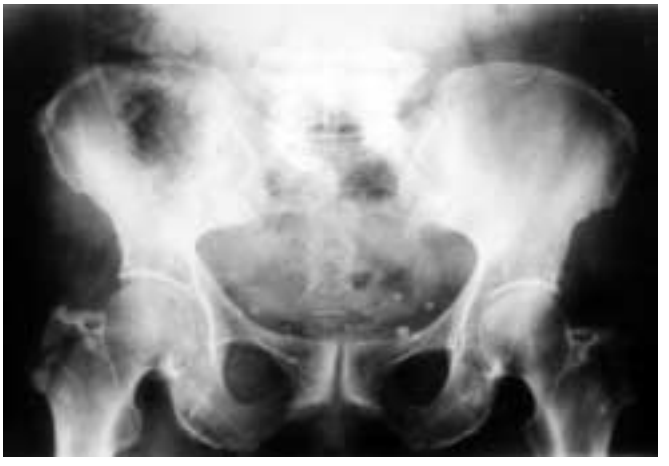

Figure 1. Pelvic enthesopathy. Frontal radiograph of the pelvic girdle in a woman suffering from degenerative spinal disease. Bone proliferation and excrescences are seen at iliac crests, greater trochanters and pubic rami. Bone sclerosis is also seen at the pubic symphysis ("pubic osteitis").

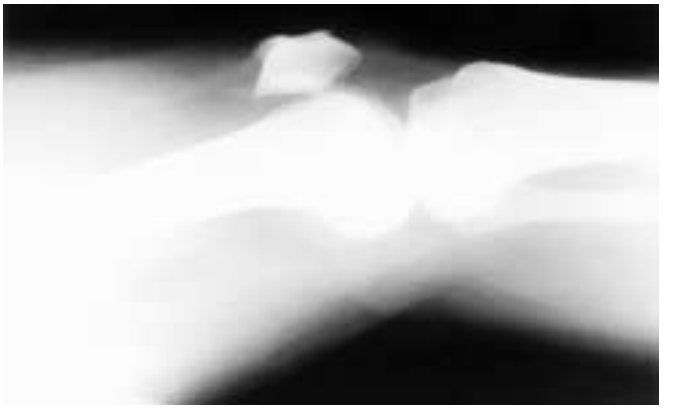

Figure 2. Patellar enthesopathy. Knee lateral X-ray of a woman suffering from knee OA. Quadriceps tendon ossification at the upper and lower ends of the extra-articular (anterior) aspect of the patella. A small osteophyte formation is also seen at the intra-articular (posterior) aspect of the patella.

tion; pelvic+calcaneal EN was recorded in 35/187 patients, pelvic +patellar in 46/187 and various associations of pelvic, patellar, calcaneal and humeral localizations were seen in the remaining 106 patients. Figures in these subgroups did not reach any statistical significance (data not shown).

Particular attention was paid to the imaging of EN at skeletal sites involved in each region. No significant predilection of reactive bone formation (ossification or bone sclerosis or bone excrescences) was noted between individual sites of overall pelvic EN. The pattern observed in most patients of both groups was that of multiple enthesopathic changes in iliac crests, greater trochanters, pubic symphysis ("pubic osteitis") and pubic rami (Figure 1), although a difference regarding iliac crests emerged in an inter-group analysis (see below). Besides, radiographic signs of EN in multiple sites within the same skeletal region were also frequently seen at other locations. This was the case for quadriceps tendon ossification at the upper and lower ends of the extra-articular aspect of the patella (Figure 2), or the formation of "spurs" in both the superior and inferior aspect of the calcaneum, where erosive lesions were also occasionally impressive (Figure 3) and, finally, the depiction of bone sclerotic and radiolucent (erosive) lesions at the supraspinatus insertion and the humeral head (Figure 4). Osseous erosions were also observed in some patients at the pubic symphysis where, as depicted in Figure 1, bone sclerosis usually predominated.

Inter-group prevalence

As shown in Table 3, pelvic EN had the largest prevalence in both inflammatory (Group A) and non-inflammatory (Group B) myoskeletal disorders (60% and 39%, respectively). Patients in Group A had a statistically larger prevalence of pelvic EN compared to those in Group B ($p<0.001$), while both patellar and humeral EN were significantly more prevalent in Group B (Table 3, $p<0.001$). On the contrary, no significant difference between the two groups was observed in calcaneal EN and in multiple site involvement (Table 3).

The above results indicate an association between site involvement and group of patients. Further statistical evaluation based on the Chi-square test revealed a significant association of patellar and humeral head EN with Group B patients, while pelvic EN was significantly associated with Group A patients ($p<0.001$, Table 4a). Concerning EN localization for each of the three pelvic sites in Group A, we noticed that the majority of patients had all three sites involved with a rather similar prevalence (Table 4b). On the contrary, in Group B patients pubic symphysis/pubic rami were the predominant pelvic sites involved, followed by greater trochanter and iliac crest localizations (Table 4b).

As already stated in the cohort analysis section, there was a male gender predominance in Group A ($p<0.001$), whilst the opposite was true for Group B patients ($p<0.001$). When further gender prevalence analysis was done, it was seen that the above gender predominance was true for any individual site of EN in each of the groups, with one exception; this was the case of humeral head EN in Group B, where the expected Group B female predominance was not observed (Table 5). Concerning gender prevalence analysis for the three distinct pelvic EN sites, no male/female differences were noted.

Intra-group regional prevalence

Radiographic regional EN prevalence was also compared between individual myoskeletal diseases within each group of the cohort population (Table 6). Pelvic EN was the most frequent overall location in Group A patients ($p<0.001$), followed by the calcaneal site ($p<0.01$ versus patellar and humeral EN). In the subgroup of patients with AS, the pelvis

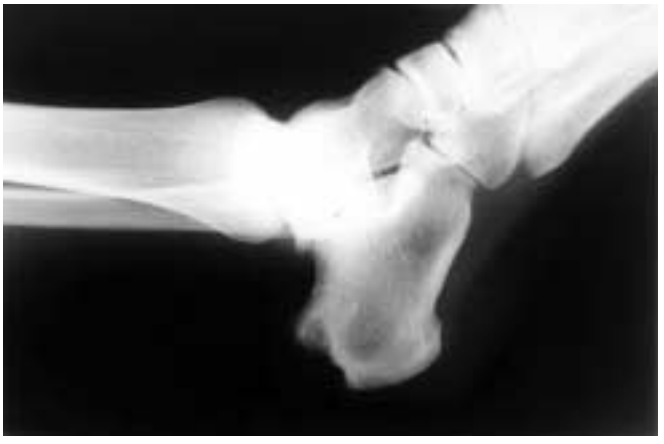

Figure 3: Calcaneal enthesopathy. Lateral radiographic view of the right ankle in a man suffering from Reiter's disease. Erosive lesions ("enthesitis") and a thin "spur" are observed at the superior aspect of the calcaneum.

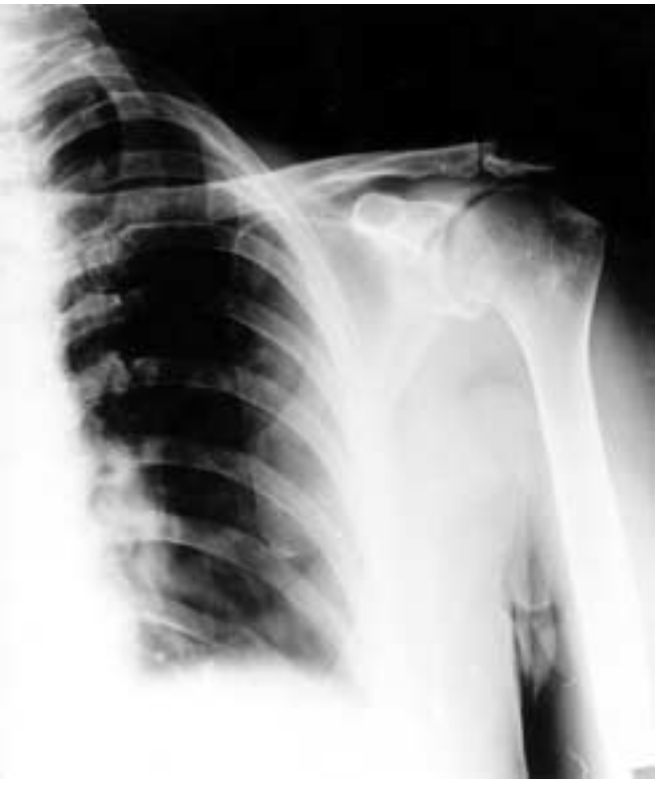

Figure 4: Humeral enthesopathy. Anterior radiograph of the left shoulder in a woman suffering from recurrent episodes of "shoulder periarthritis". Erosions and reactive bone sclerosis are clearly visible at the humeral head.

was beyond any doubt the predominant site involved ($p<0.001$ versus all other localizations). The same EN pattern was observed in patients with Ps-Sp, while in patients with PsA pelvic EN ($p<0.01$ versus all other localizations) was followed by both calcaneal and patellar EN (both $p<0.01$ versus humeral EN). A different pattern of EN involvement was observed in RR patients, where both pelvic and calcaneal EN prevailed over patellar and humeral EN ($p<0.001$).

As already noted, there was an association between Group A patients and pelvic EN. When the same statistical analysis (Chi-square) was applied to test for any association between individual diseases and EN site involvement in Group A, a significant association of AS and Ps-Sp with pelvic EN was shown, while the subgroup of RR was associated with calcaneal EN (Table 6).

Intra-group analysis in Group B showed that, as already stated, pelvic EN was the overall most prevalent subset ($p<0.001$ versus all other sites, Table 7), followed by patellar EN ($p<0.01$ versus humeral and calcaneal EN). When we further analyzed the site prevalence of EN for individual diseases, a quite variable pattern of EN in the subgroups of patients was found. Thus, in Deg-Sp patients, the pelvis was the prevailing EN region ($p<0.001$ versus other sites), followed by both patellar and calcaneal EN ($p<0.001$), in knee OA patellar predominance was noted ($p<0.0001$ versus other sites) and in patients with hip OA pelvic EN was again the predominant localization. In patients with DISH, enthesopathic changes contributed significantly to the overall prevalence of EN in Group B (160/513, $p<0.001$), pelvic predominance was noted ($p<0.001$). Finally, humeral head EN prevailed over other sites only in the Rot/Cuff subgroup ($p<0.001$).

Testing again for any association between individual diseases and site involvement by Chi-square test showed that knee OA was significantly associated with patellar EN and Rot/Cuff syndromes with humeral EN (Table 7).

Discussion

In this study we have attempted to use radiographic signs of EN, with no correlation to symptoms, as a criterion for recruiting a cohort of peripheral EN expressed in patients suffering from a variety of rheumatic diseases, which produce symptoms themselves. Such an approach may have several shortcomings, the most serious of them being selection bias, for a number of reasons.

Firstly, there is no validated method for measuring or quantifying radiographic EN changes, e.g., bone proliferation and sclerosis at iliac crests, size and extent of a bony spur or tendon ossification. This represents a disadvantage of plain radiography compared to MRI screenings whereby, as already mentioned, the intensity of inflammation at the enthesopathic region may be assessed[5,8]. By blind assessment of radiographs independently by two of us, one always being the radiologist, we tried to overcome, at least in part, this problem; moreover, the aim of our study was to assess imaging, not size or intensity, of EN lesions by simple, routinely used radiological means such as plain X-rays.

	Total Group B	Deg-Sp	Knee OA	Hip OA	Rot/Cuff	DISH
Total No. of localizations	513	93	107	76	77	160
Pelvic	200**	55**	10	51**	0	84**
Patellar	134*	21**	73**	7	4	29
Calcaneal	84	13*	18	15	9	29
Humeral	95	4	6	3	64**	18

*:$p<0.01$
**:$p<0.001$

Table 7. Prevalence of degenerative myoskeletal disorders in different enthesopathic regions and sites (Group B).

Secondly, bias selection might ensue when a cohort is recruited by patients assigned a single primary diagnosis; this was based on the clinical problem for which the patient was seeking medical help. This has certainly resulted in a highly selected cohort of EN, since patients exhibiting concurrent rheumatic diseases with enthesopathic findings were either excluded from analysis or classified into one of the two groups of the study on clinical grounds only. We deliberately avoided diagnostic overlaps so that a well-defined rheumatological cohort could be screened for radiological EN, this being our basic aim. Furthermore, this was why patient groups which could not be unequivocally classified as either inflammatory or non-inflammatory, such as the micro crystalline arthropathies, were also excluded from the study.

Notwithstanding the above arguments, we believe that the present cohort study has demonstrated that plain radiographs can provide satisfactory imaging and assessment of the most frequent skeletal sites of extraspinal EN encountered in rheumatological clinical practice. This is conceivable in view of the fact that reactive bone formation or ossification at sites of tendon or ligament insertions is the end-result of peripheral nonsynovial EN. This disorder, representing as indicated above, skeletal regions of fibrocartilage–bone interaction, can be ossifying/bone proliferative, erosive or both and such radiographic changes are easily assessed by plain X-rays. As already stated, the underlying early inflammation (enthesitis), either axial or peripheral, can be evaluated by several imaging techniques, such as bone scan, axial tomography and in particular by magnetic resonance imaging (MRI), where the degree of enhancement on T1 weighted gadolinium-enhanced imaging may be proportional to the degree of inflammation[5,12,13]. The intensity of inflammation may also be assessed by the MR signal on T2 – weighted images in which a higher T2 signal is associated with more intense inflammation[14]. In general, MRI allows better visualization of soft tissue and is better indicated in acute tendon inflammation. Such a lesion is often associated with swelling and may lead to traumatic or spontaneous rupture[5]. The cost-effectiveness ratio of MRI imaging in EN remains, however, a problem and the technique should perhaps be preserved as a good imaging modality for studying the pathology of the disorder.

With regard to gender, enthesopathic changes were as expected, more frequently seen in men in the SSps group whilst the reverse was true in degenerative and metabolic diseases where females predominated.

It should be stated that the overall radiological or clinical EN prevalence in a rheumatic population was not an aim of this study and the figure of 16% noted in our results relates exclusively to: a) patients seen in our clinic; the present study was not sensu stricto epidemiological nor population-based. It is almost certain that this rate is higher in rheumatic populations with overlapping inflammatory/non-inflammatory diseases, yet fulfilling criteria for radiological EN, b) the selected regions radiographically surveyed. It is conceivable that peripheral EN affects many other sites of the skeletal body. These, amongst others, include: (i) medial and lateral epicondylitis (golfer's and tennis elbow, respectively) in which, interestingly, insertion of collagen fibers in bone is identical to axial forms of the disorder involving the interface between vertebral bodies and intervertebral discs[33], (ii) inflammation at the serratus anterior muscle attachments to the anterolateral ribs, commonly causing chest pain in SSp, (iii) synovial sites which, according to current concepts, play a causative role in the inflammatory arthritis of the spondyloarthropathies[8,9].

The issue of symptomatic or asymptomatic EN is difficult to assess; it is noted that all patients of the cohort were symptomatic with symptoms arising from the main disease and causing them to visit the rheumatology clinic. Neither "enthesitis index"[15], probably useful in assessing drug therapy in AS nor any other clinical attempt to discriminate EN pain or inflammation was employed and this issue was not further explored in this radiographic study.

It has been suggested that EN is a phenomenon of aging[18]. We partly agree with such an assumption. This may be true for degenerative disorders which, themselves, are largely related to aging. In addition, a positive correlation has been found between enthesophytes and osteophytes which remains after correction of age and gender[34]. This does not seem to be the case for inflammatory myoskeletal diseases where, according to this study, the mean age was considerably lower in our Group A patients suffering from inflammatory disease compared to patients in Group B with degen-

erative or metabolic disorders. Moreover, mean disease duration was shorter in Group A compared to Group B patients, pointing to the fact that peripheral enthesopathic changes occur early in the process of inflammatory EN. It is widely accepted that EN, either axial or peripheral, constitutes one of the diagnostic criteria proposed for the classification of diseases regarding younger age groups of patients, such as the SSp 35 and the Seronegative Enthesitis-Arthropathy (SEA) syndrome[36]. Other facts arguing against EN being an age-related disorder are: a) certain enthesopathic sites are often encountered in the young, e.g., calcaneal EN is included among the most common causes of heel pain in children[37], b) the paucity of EN in RA is observed at any age, as noted in this study (5 out of 630 patients in the initial cohort) and by others[18] and c) conversely, purely enthesopathic disorders such as epicondylitis or shoulder "periarthritis" are not age-dependent.

As shown in our study, pelvic EN in skeletal sites other than the sacroiliac joints, is clearly the most common skeletal location of nonsynovial peripheral disease in both inflammatory and non-inflammatory conditions. Predomimant involvement of the pelvic girdle by EN may be due to a variety of reasons, including the large size of the iliac bone, the plethora of tendons and ligaments inserted at multiple sites such as the iliac crest, greater trochanters, pubic symphysis and pubic rami and finally, the functional association with the spine in transmitting mechanical loads. Other factors, such as ischaemia, traumatic effects and physical activity also play a causative role[19]. Furthermore, enthesopathic involvement of the greater trochanter site has also been described in systemic conditions including drug-induced, such as retinoid EN[20]. Entheses are strong regions structurally designed for the transmission of tensile forces[5] but at the same time and despite strengthening by fibrocartilage, represent skeletal sites of mechanical risk due to the forces exerted in the tendon or ligament junction to bone[16]. Of relevance is the suggestion that ligament insertions on the iliac crest which show lower resistance to mechanical overloads are more prone to EN[17]. It has been reported that up to 18% of iliac crests ossify in degenerative conditions[18]. A prevalence rate of 15% of iliac crest EN in patients with non-inflammatory disorders (Group B) found in this study, appears to agree with this previous report. On the other hand, the predominance of pelvic EN not only in patients with non-inflammatory diseases but also in the group of inflammatory diseases suggests that, besides mechanical effects, an inflammatory component might actively contribute to EN.

Consistent with this thought is the fact that, in the present study, SSp showed a larger prevalence of pelvic EN compared to degenerative/metabolic disorders as well as a statistically significant association with pelvic EN, over and above sacroiliac joint involvement. This was apparently due to the statistically significant association between pelvic EN and two of the subgroups within Group A patients, namely those of AS and Ps-Sp. By contrast, although pelvic EN was again significantly more prevalent compared to other sites in non-inflammatory disorders it was not shown to have a statistically strong association with this group of patients.

Pubic "osteitis" or "osteitis" pubis is a rather confusing term radiologically describing sclerotic and/or erosive lesions at the symphysis pubis following trauma, pelvic surgery, childbirth, infection or overuse[21,22]. It can be due to osteomyelitis[23] but it is mostly an aseptic condition, even following urological procedures which, when symptomatic, may be treated by steroids or nonsteroidal anti-inflammatory drugs[22,24]. It may also mimic malignancies because of "osteolytic" images obtained by plain radiography[25,26]. Pubic osteitis, in the radiographic form of erosive and sclerotic changes, is also commonly noted in SSp[27] and, according to the results of our study, is a fairly common finding in degenerative diseases as well. We believe that in most instances of radiological detection, pubic osteitis represents a true enthesopathic lesion, "benign" in nature, as also noted by others[22,24,26]. The same observations apply to the pubic rami bone-proliferative and erosive lesions which, apart from the "fluffy periostitis" frequently described in SSp, may give a similar appearance in degenerative and metabolic diseases, as also shown in this study. Ossification of fibrocartilage attachments to all of these skeletal sites occasionally give the pelvis the well known "whiskering" appearance which may not be specific for SSp[27].

Multiple sites EN, was besides patellar, the second most frequent localization of the cohort patients. When this was further analyzed, no particular pattern of EN association was found.

Putting aside enthesopathic involvement of more than one region, patellar EN was the second most prevalent localization in the study cohort. It was more prevalent in the group of patients with non-inflammatory diseases with whom a significant association was observed. This was mainly due to the high prevalence of patellar involvement in patients with knee OA, which was the only subgroup significantly associated with patellar EN. When prevalence of patellar EN in individual diseases was reviewed, it was found that PsA in Group A together with knee OA and Deg/Sp in Group B were the diseases with significant patellar prevalence. With the exception of Deg/Sp, it is noted that patellar EN was significantly associated with knee pathology, either inflammatory, as in the case of PsA where knee synovitis was present in over half of our cases or non-inflammatory, as in knee OA. It is now well accepted that knee pathology in PsA is strongly associated with enthesitis as well as with several other nonsynovial manifestations of this disease[9,28]. On the other hand, it has been reported that patellar enthesophytes develop in up to 25% of cases of degenerative disease[18]. This is also in accord with the results of the present study where an overall prevalence of 26% was noted in Group B patients with non-inflammatory disorders.

Quadriceps tendon at the upper pole and/or ligamentum patellae ossification at the lower pole, both involving the frontal extra-articular aspect of the patella, together with

"whiskering" of the structure, were the usual radiographic images we obtained. Ossification at the distal attachment of the patellar ligament to the tibia was also occasionally seen.

Calcaneal EN, radiographically visualized either as a spur or/and bone erosion, did not differ in prevalence between the two groups of our study. However, in the group of patients with inflammatory diseases, calcaneus was the second most frequently affected site following pelvic involvement. By further analysis it was shown that the subgroup of RR, including Reiter's syndrome, was significantly associated with calcaneal EN. A high prevalence of calcaneal localization of EN in SSp, particularly in Reiter's syndrome, was expected since bony spurs or erosions at the upper or lower aspect of the calcaneum constitute a common radiographic finding in this group of diseases[6,29].

Humeral head EN, although accounted the least for the overall EN in our cohort, was significantly associated with the group of patients with non-inflammatory disorders. This was apparently due to the significant association of Rot/Cuff subgroup with humeral head EN, an anticipated finding in the present study. The shoulder joint has the largest range of movements of any joint in the body and the rotator cuff is a composite tendon formed from four muscles, the tendons of which insert circumferentially around the humeral head[32]. Rotator cuff disorders are purely enthesopathic and radiographic findings are common, particularly in chronic or relapsing forms at any age.

Reviewing data related to degenerative disease, it becomes clear that patients with a mainly localized disease process like knee OA, Rot/Cuff syndromes and hip OA, present with a peripheral radiographic EN localization which lies in proximity with the disease process. This points to the impact of local factors which, as already noted, seem to play a dominant role in generating enthesopathic bone reactions, especially in non-inflammatory diseases. Thus, in such local disorders, EN lesions could perhaps be characterized as a "disease specific" phenomenon. However, it is obvious that in any skeletal site affected by either inflammatory or non-inflammatory stimuli (e.g., SSps and DISH, respectively), the same pattern of radiographic (and presumably pathological) enthesopathic lesions is roughly produced. In this sense, EN can be labeled as a "site specific" process.

Taking all facts into consideration, we would agree that EN is not a disease-specific lesion[18]. To our minds and on the basis of our findings, EN is a skeletal site-specific disorder of fibrocartilage-bone interaction. The target sites are determined by mechanical factors and local influences exert a major effect, as our radiographic data strongly suggest. Inflammatory, degenerative, traumatic, metabolic or other stimuli only serve as inducing factors at any age.

Identification and assessment of EN represents a conceptual advance in diagnosing both joint or bone disorders and musculoskeletal interactions.

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