Clinical overlap between fibromyalgia tender points and enthesitis sites in patients with spondyloarthritis who present with inflammatory back pain

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ABSTRACT

Objectives. *To assess the extent of co-existence of inflammatory back pain (IBP) with fibromyalgia (FM) features in patients with spondyloarthritis (SpA), and to assess the degree of overlap of FM tender points (TeP) and enthesitis sites (ES) in patients with SpA.*

Methods. *We evaluated 61 consecutive patients who presented with IBP. Anterior and posterior anatomic diagrams were used as an aid to record assessments of TeP typically seen in FM and ES.*

Results. *Of the patients assessed (n=61), 60 patients (97.9%) fulfilled criteria for IBP (male: female=17:43 (28.3%:71.7%); mean age=47.9 years (SD=11.5) and were included in the analysis. Of those who returned the questionnaire (n=47 (78.3%), 76.6% had onset of symptoms at ≤40 years (mean age=33.5±12.5 years), 87.2% had back pain of ≥3 months duration, 91.5% had morning stiffness (mean duration=70±66 minutes), and 60% showed improvement of pain with exercise. Eating disorders were reported by 21.3% of subjects, and stress was identified as a disease trigger by 40.4% of the respondents. Other symptoms related to FM were reported by 68.1% of the interviewed subjects.*

Of the 60 patients assessed, 18 (30%) fulfilled the clinical criteria for FM (at least 11 out of 18 TeP). Using regression analysis, a significant correlation was identified between FM TeP and ES.

Conclusions. *One third of patients with IBP fulfilled the criteria for FM. There is a significant degree of overlap between FM TeP and ES in patients with IBP.*

Introduction

Spondyloarthritis (SpA) constitutes a group of diseases that includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), undifferentiated SpA, enteropathic arthritis or arthritis associated with inflammatory bowel disease, reactive arthritis, juvenile SpA, arthritis associated with uveitis, and other less common associations. These diseases demonstrate overlapping symptoms, particularly in their early stages (1). As a group, SpAs display variable onset times, presentations, and progression. The diseases in this spectrum share common characteristics, such as back pain at an early age (<40 years), morning stiffness, improvement with exercise but not with rest, insidious onset, and axial and/or peripheral disease (1-4). Clinical history was suggested as a screening test by Calin in 1977 (5) and by Rudwaleit (6).

Although axial involvement and/or back pain are common features of SpAs, a positive diagnosis is often delayed, possibly by the lack of specific diagnostic tests and the concomitant presence of fibromyalgia (FM) features.

FM emerged as an entity in 1950, when it was first described by Graham (7). Fibrositis (or FM) was thought to be a rheumatologic disorder because it was characterised by musculoskeletal pain similar to that of other rheumatologic diseases. In 1990, the American College of Rheumatology (ACR) established classification criteria based on the scoring of 11 out of 18 specific sites as tender (8). Recently preliminary diagnostic criteria have been developed which do not include tender point examination but the other associated symptoms remain the same (9). In general, FM is characterised by generalised chronic muscle pain and diffuse tenderness at discrete anatomical sites in the absence of inflammatory or structural musculoskeletal abnormalities (10).

The prevalence of FM varies from 0.3 to 13% of the population, depending on the definition used and the popula-

tion studied (11-13). Other associated symptoms include sleep, cognitive, and emotional disturbances (depression and anxiety), fatigue, headaches and skin sensitivity, migraines, interstitial cystitis, irritable bowel syndrome (14). The onset of FM is generally gradual and follows an illness or operation. Some authors consider FM a diagnosis of exclusion (13), while also acknowledging the possibility of other concomitant disease. There is female predominance, with a female/male ratio of 4:1. There are no genetic or biochemical markers for the diagnosis of FM.

According to the 1990 ACR classification criteria, which were originally developed for research purposes, and have subsequently been used and applied to the clinical diagnosis of FM in routine clinical practice (14), FM has been shown to be present in roughly one third of patients with other autoimmune rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and familial Mediterranean fever (15). As far as the group of SpAs is concerned, the presence of FM features has previously been evaluated in psoriasis (16) and PsA (17) and in female patients with AS (18). However, the association between FM and SpAs in general, has not been investigated and the overlap between the enthesitis (ES) and FM tender points (TeP) has not been explored.

The aim of the present study was to assess the concomitant presence of SpAs and FM from the clinical perspective and to investigate the presence of potential overlap between the defined characteristic FM TeP and pain at ES in patients with IBP.

Methods

This study (classified as a scientific audit) was conducted at a District General Hospital in North-East London between March and April 2009. Inclusion criteria included: Onset of back pain at an age of below 40 years and present of more than 3 months, buttock pain, morning stiffness of more than 30 minutes, pain exacerbated by rest and improved by exercise, good response to non-steroidal anti-inflammatory drugs, back pain of insidious onset, presence of psoriasis, uveitis, inflammatory bowel disease and age of onset of more than 16 years of age. Exclusion criteria included: Back pain onset at a greater age of 40 years, mechanical back pain, pain improving by rest. Such patients who have been given the diagnosis of SpA and seen consecutively in the outpatients' clinic over 8 weeks were evaluated, with regards to the enthesitis sites and as to whether they fulfil FM criteria based on the 18 tender point rule (1990 ACR classification criteria). A brief description of the FM criteria used in the present study is provided in Table I. General demographic characteristics, including clinical diagnoses at the time of assessment of patients studied, are shown in Table II. The new ASAS criteria for SpA (19, 20) were applied to patients' data retrospectively.

Clinical information regarding FM TeP was obtained by the standard procedure of pressure application with the thumb pad of the examiner's dominant hand. Survey sites were first located visually, followed by light palpation. Thumb pad pressure was applied perpendicularly to each survey site for a total of 4 seconds once only, to an equivalent pressure of 4 kg (aiming to achieve whitening of the assessor's nail bed). Three control sites were used to determine the threshold of each patient's pain perception (as a clinical negative control). Using the criteria described above, we assessed which TeP were present for each patient.

Enthesitis sites assessed were the ones as described by Mander *et al*. (21) and were the following: nuchal crests, manubriosternal joint, costochondral joints, greater tuberosity, medial and lateral epicondyles, humerus, iliac crests, anterior superior iliac spine, greater trochanter of the femur, medial and lateral condyles of the femur, the insertion of Achilles tendon and plantar fascia to the calcaneus, the cervical, thoracic and lumbar spinous processes, the ischial tuberosities, and the posterior superior iliac spines. Most of the sites were assessed individually whereas others were assessed as a group. The sites assessed as a group were: nuchal crests, costochondral joints, cervical thoracic lumbar spinous processes.

The information obtained from clinical assessment of FM TeP and ES for each patient was recorded on anterior and posterior anatomic diagrams on the assessment form, which were marked with tender site characteristic of both diseases. The diagrams used were the one used by the American College of Rheumatology 1990 for the criteria for the classification of FM (8) and its simplified form as found in the booklet intended for physician and healthcare professionals on fibromyalgia (22) and the one used for the Mander enthesitis index (MEI) for enthesitis evaluation described above (21). Printed diagrams shown in Figures 1 and 2 were used to record all clinical assessments. Appropriate blood tests, radiographs and magnetic resonance imagine (MRI) were obtained as evidence for the diagnosis of IBP and to exclude the presence of other conditions as part of routine clinical care.

In addition to the form regarding FM TeP and ES assessment, clinicians also completed printed questionnaires based on the Calin (5) and Rudwaleit (6) criteria for IBP, a modified FM impact questionnaire (including selected points from the FM Impact Questionnaire (FIQ) (23, 24), and questions obtained from the rating scale for FM and chronic fatigue syndrome (the Fibro Fatigue scale) (25).

Each patient has been given to fill in the questionnaire containing the following information (in addition to age, gender obtained during clinical assessment): effect of the disease on everyday living, age at onset of back pain, duration of morning stiffness, effect of exercise, presence of buttock pain, and presence of pain upon lying on the affected areas. We also requested information regarding evidence of previous eating disorders or mood disturbance, onset of symptoms related to stress, poor concentration, headache, diffuse abdominal pain, and alteration of bowel habits. This composite questionnaire was given to patients to fill in at the time of the clinician's assessment of FM TeP and ES. Patients unable to spare time (parking constrains) or having difficulty in filling the questionnaire (not having reading glasses or having language

Table I. American College of Rheumatology 1990 criteria for the classification of fibromyalgia* (*both criteria must be satisfied).

1. History of widespread pain
Definition: pain is considered widespread when all of the following are present.
- Pain in the left side of the body
- Pain in the right side of the body
- Pain above the waist
- Pain below the waist
- In addition, axial skeletal pain, (cervical spine or anterior chest, or thoracic spine or low back) must be present

Note: In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 out of 18 tender point sites on digital palpation
Definition: pain on digital palpation must be present in at least 11 of the following 18 tender point sites.

Location of TeP according to the 1990 ACR classification criteria
Occiput (bilaterally at the sub-occipital muscle insertions)
Low cervical (bilaterally at the anterior aspects of the inter-transverse spaces at C5–C7)
Trapezius (bilaterally at the midpoint of the upper border)
Supraspinatous (bilaterally at origins above the scapular spine near the medial border)
Second rib (bilaterally at the 2nd costo-chondral junction just lateral to the junctions on the upper surfaces)
Lateral epicondyle (bilaterally 2 cm distal to the epicondyles)
Gluteal (bilaterally in the upper outer quadrants of the buttocks in the anterior fold of the muscle)
Greater trochanter (bilaterally posterior to the trochanteric prominence)

Table II. Demographic and clinical characteristics of total 60 patients assessed for enthesitis and fibromyalgia TeP.

Variable	Value	Percentage / range
Age (mean ± SD)	47.9 (± 11.5)	23-75
Age of onset of IBP*	33.5 (+ 12.5)	15-72
Males: females (n)	17 : 43	28.3% : 71.7%
Male: female (ratio)	1:2.5	
New ASAS criteria	54/60	90%
Axial disease	n=10	18.5%
Peripheral disease	n=38	70.3%
Both (axial & peripheral	n=6	11.1%
Unclassified	n=6**	11.1%
Sacroiliitis	n=10	16.6%
HLA B 27		
Done	22 (of 60)	36.6%
Positive	3	13.6%
Negative	19	86.3%
AS	n= 9	15%
PsA	n=20	33.5%
Undifferentiated(USpA)	n=11	18.3%
Enteropathic	n= 6	10%
Juvenile onset	n=2	3.3%
Uveitis	n=2	3.3%
USpA+fibromyalgia	n=10	16.6%

*IBP: inflammatory back pain.
**from those unclassified according to the new ASAS criteria 3 patients fulfilled CASPAR criteria for PsA based on past psoriasis or family history of psoriasis, 1 patients had developed bowel symptoms following the onset of arthritis and the remaining 2 were not having signs and symptoms enabling classification according to ASAS criteria.

barriers) while in clinic, were able to take it at home and return it back to the department within 2 months.

Patients were consecutively selected for assessment for FM TeP and ES by both clinicians involved in the study (ER and CC). Assessments and data acquisition were performed by the same assessor (CC) throughout the study. Conception of the study, final assessment score for each patient, data entry, and analysis were performed by ER.

Regression analysis was performed using the SPSS statistical package. A *p*-value of below 0.05 was considered as statistically significant.

The study was registered with the Audit Department of the Barking, Havering and Redbridge University Hospitals NHS Trust.

Results

From 61 patients assessed 60 were included in the study based on IBP which has been used as the main inclusion criterion. Patients' characteristics, the diseases they were suffering from, the HLAB27 status and radiologic evidence of sacroiliitis are shown in Table II. A retrospective evaluation as to whether these patients fulfil the new ASAS criteria for SpAs has shown that 54 of 60 patients could be classified according to the new ASAS criteria as having axial, peripheral or both axial and peripheral disease (Table II).

Inflammatory back pain

According to the Calin (5) and Rudwaleit criteria (6) for IBP, all patients but one (97.9%) fulfilled either both criteria [38 of 47 patients (80.9%)] or one of the criteria [8/47 (17%)]. In the present cohort, 76.6% had onset of back pain below the age of 40 years (mean age of 33.5 years (standard deviation of ± 12.5 years), 87.2% had back pain of more than 3 months duration, 91.5% had morning stiffness with a mean duration of 70 minutes, and 60% reported an improvement of pain with exercise. Buttock pain was present in 80.9% of subjects, while alternating buttock pain was present in 40%. Table III shows the epidemiological and clinical features of our cohort with regards to IBP.

Of the 60 patients clinically evaluated for IBP, 27 patients (44%) returned the questionnaire straight away while in clinic, and 34 (56%) took it away to fill it in and return it by post. A total of 47 patients (87.2%) returned the questionnaire; therefore, detailed clinical characteristics were derived only from these patients. Mean age of the group was of 47.9 years with a range of between 23–75 years (Table II). Features associated with IBP according to Calin and Rudwaleit criteria are shown in Table III, while disease characteristics related to SpAs and FM are shown in Table IV.

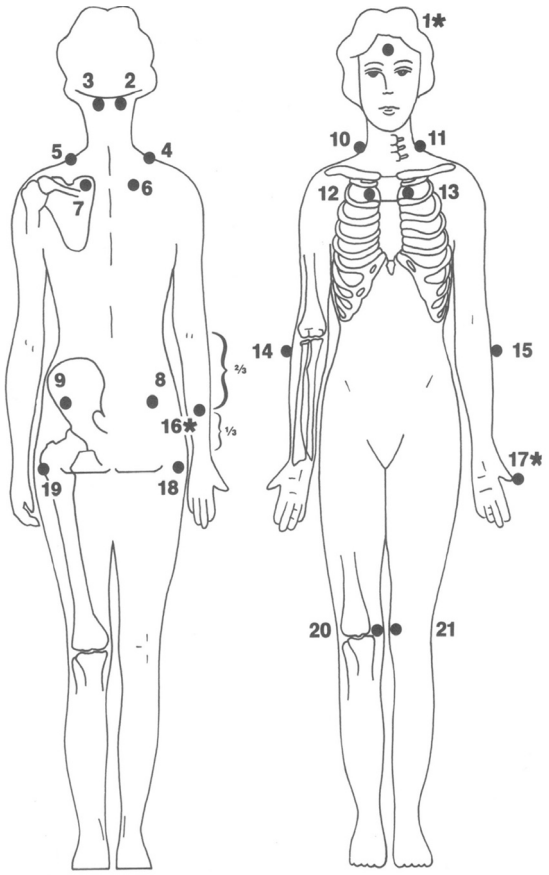

Fig. 1. Anterior and posterior anatomic diagrams showing the fibromyalgia (FM) tender points used in evaluation of patients in the study.

Footnote:

2, 3 At sub-occipital muscle insertion
10,11 At anterior aspect of C5–C7 intertransverse spaces
4, 5 Trapezious bilaterally at mid-point of upper border
6, 7 Supraspinatus at origins above medial border of scapula
12,13 Second costochondral junction
14,15 Two centimeters distal from epicondyles
8, 9 Upper outer quadrant of buttocks
18,19 Posterior to trochanteric prominence
20,21 Knees at medial fat pad proximal to joint line

*Control sites

1 Forehead
16 Junction of proximal 2/3 and distal 1/3 of forearm
17 Control site, unilateral left thumbnail

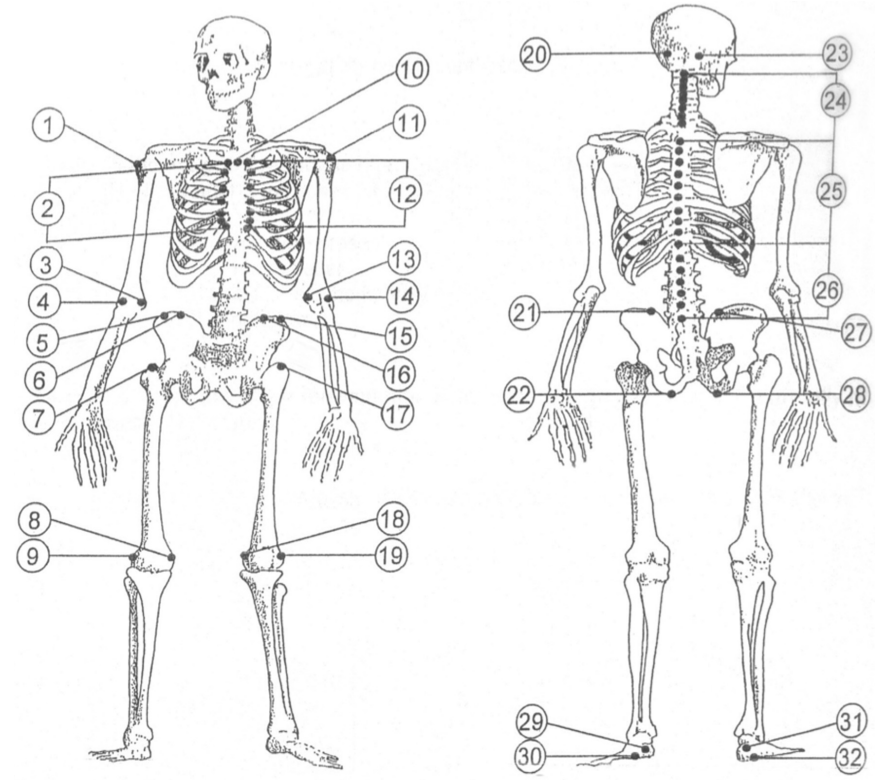

Fig. 2. Mander enthesitis index. Reproduced with permission of the copyright holders from reference 21. Anterior and posterior anatomic diagrams showing the enthesitis sites used in evaluation of patients in the study.

Enthesitis

Thirty-two patients (53.3%) had at least 1 ES, of whom 17 (28.3%) reported pain present at 1–4 enthesitis sites. Nine patients (15%) had no clinical entheseal disease.

Fibromyalgia

Regarding the criteria for widespread back pain, 46 (97.9%) of the 47 responders reported back pain, fulfilling at least one of the two ACR criteria for FM. Six patients had unilateral disease: 4 on the left side and 2 on the right.

Regarding the criterion for pain in at least 11 of 18 specific tender point sites, 18 patients (30%) fulfilled this diagnostic criterion for FM by taking into consideration that the first diagnostic criterion was fulfilled, because all of the patients reported back pain, therefore the final diagnosis depended on the presence of specific TeP. Further analysis revealed that of the 60 patients with IBP, (in addition to the 18 patients (30%) who fulfilled the tender-points criterion for the diagnosis of FM) 15 patients (25%) exhibited no FM TeP; and 25 patients had a variable number of TeP, but below 10 points and 3 patients had 10 TeP. Regarding the other FM associations, eating disorders were reported by 10 of 47 patients (21.3%), TeP upon lying reported by 24 of 47 (51.1%), and stress as a disease onset trigger reported by 19 of 47 (40.4%). Other symptoms related to FM, such as poor concentration, headache, diffuse abdominal pain, and altered bowel habits were reported by 32 of 47 (68.1%).

Psoriatic arthritis (PsA) subgroup

Of the total 60 patients, 20 patients (33.3%) fulfilled the CASPAR criteria for PsA (26), 14 of whom (70%) returned the questionnaire. Of the responders, half (7/14) fulfilled the TeP criterion for concomitant FM. This result suggests that FM occurred in 50% of our analysed patients with PsA based on the strict definition of the 11 tender point evaluation as proposed by the 1990 ACR classification criteria.

Overlap between FM TeP and ES

There was overlap of FM TeP and ES in 75% of patients. Of the 60 patients,

Table III. Patients (in absolute numbers and percentages) who fulfilled the criteria for inflammatory back pain.

Calin criteria (JAMA 1977)	Number of patients fulfilling item and percentages	*Rudwaleit criteria (Arthritis Rheum 2006)*	Number of patients fulfilling item
Age of onset of back pain <40 years	36 (76.6%)	Alternating buttock pain	24 (40%)
Back pain >3 months	41 (87.2%)	Pain at 2nd half of the night / early morning	23 (51.1%)
Insidious onset	37 (80.4%)		
Morning stiffness	43 (91.5%)	Morning stiffness of >30 min	33 (78.5%)
Improvement with exercise	27 (60%)	Improvement with exercise not with rest	26 (56.5%)
Number of patients fulfilling criteria	32 (68%)	Number of patients fulfilling criteria	32 (69.5%)
Total patients fulfilling criteria	17 (36.1%) fulfilled 5/5 15 (31.9%) fulfilled 4/5		14 (29.7%) fulfilled 4/4 8 (17%) fulfilled 3/4 10 (21.2%) fulfilled 2/4

For a patient to fulfil the Calin criteria, ≥4 positive signs of the total of 5 are required.
For a patient to fulfil the Rudwaleit criteria, ≥2 positive signs of the total of 4 are required.

32 had at least 1 ES, with 17 (28.3%) of these patients having between 1 and 4 tender enthesitis sites; 9 patients (15%) had no tenderness overlying the ES.

Of patients with IBP, 30% fulfilled the criteria for FM, while only 1 in 4 (25%) of the patients exhibited no FM TeP.

According to the diagnostic criteria, there were 13 areas where enthesitis sites as described in MEI coincided with the FM TeP. These were: occiput on the right (R) and left (L), trapezious both R and L, 2nd rib on the R, lateral humeral epcondyle R and L, gluteal muscle R and L, greater trochanter R and L, medial fat pad knee R and L. Figure 3 shows graphic representation of the percentage of those patients with SpA showing positive tests on the FM tender points and the corresponding ES in the above-mentioned anatomical areas.

Regression analysis, using total enthesitis sites as a constant and the total number of FM TeP as a dependent variable, revealed a statistically significant correlation ($p<0.005$, $df=1$, $F=26.926$). There was borderline significance of the correlation between the presence of clinical enthesitis and gender, with enthesitis being more common in females. Figure 4 shows scatter plot representation of the values obtained, and linear association as derived from the regression analysis of the two clinical diagnostic features namely FM TeP and ES.

Discussion

We present here the findings of an evaluation of patients with IBP who attended the rheumatology outpatients' clinic in our hospital for routine clinical care. Patients were assessed as to whether they fulfilled the criteria for FM and/or clinical enthesitis. FM TeP and ES were assessed in all patients included in the study. There is high prevalence of FM in patients with SpA.

Clearly, enthesitis sites described in the Mander index are different anatomically from the fibromyalgia points. However, correlation of the clinical findings of the co-existence and overlap between FM and clinical enthesitis revealed that, although the localisation of TeP specific for FM and enthesitis sites differs anatomically, in clinical practice however, the discriminatory capacity of the examiner is limited and there is clear identification of a degree of overlap at certain sites.

One third of the patients with IBP assessed for TeP in our analysis exhibited concomitant FM, while a quarter of patients did not. The remaining patients showed a variable degree of FM signs, without fulfilling the diagnostic criteria for FM.

There is a possibility that selection bias could have influenced the study results, because our hospital is a tertiary referral centre for inflammatory back pain. Most of the patients were referred to us following assessment by their general practitioner or experienced physiotherapist; therefore, inflammatory back pain predominates in our cohort, while patients with primary FM may have been diverted to other centres.

The female predominance in our cohort is not unusual and it is a consistent finding in our patients. It has been noticed before, that from 10% to 20% more

Table IV. Summary of the disease characteristics related to spondyloarthritis (SpA) and FM of patients in the present study.

Spondyloarthritis		Fibromyalgia	
Age of onset of back pain ≤40 years	36 / 47 76.6%	Eating disorder	10 / 47 21.3%
Back pain for >3 months	41 / 47 87.2%	Tenderness upon lying	24 /47 51.1%
Morning stiffness	43 / 47 91.5%	Stress as disease trigger	19 / 47 40.4%
Buttock pain	38 / 47 80.9%		
Alternating buttock pain	24 / 47 40%		
Improvement with exercise	26 / 47 56.5%	No improvement with exercise	20 / 46 43.3%
Duration of morning stiffness	70 minutes		

Data derived from 47 patients who returned the questionnaire.

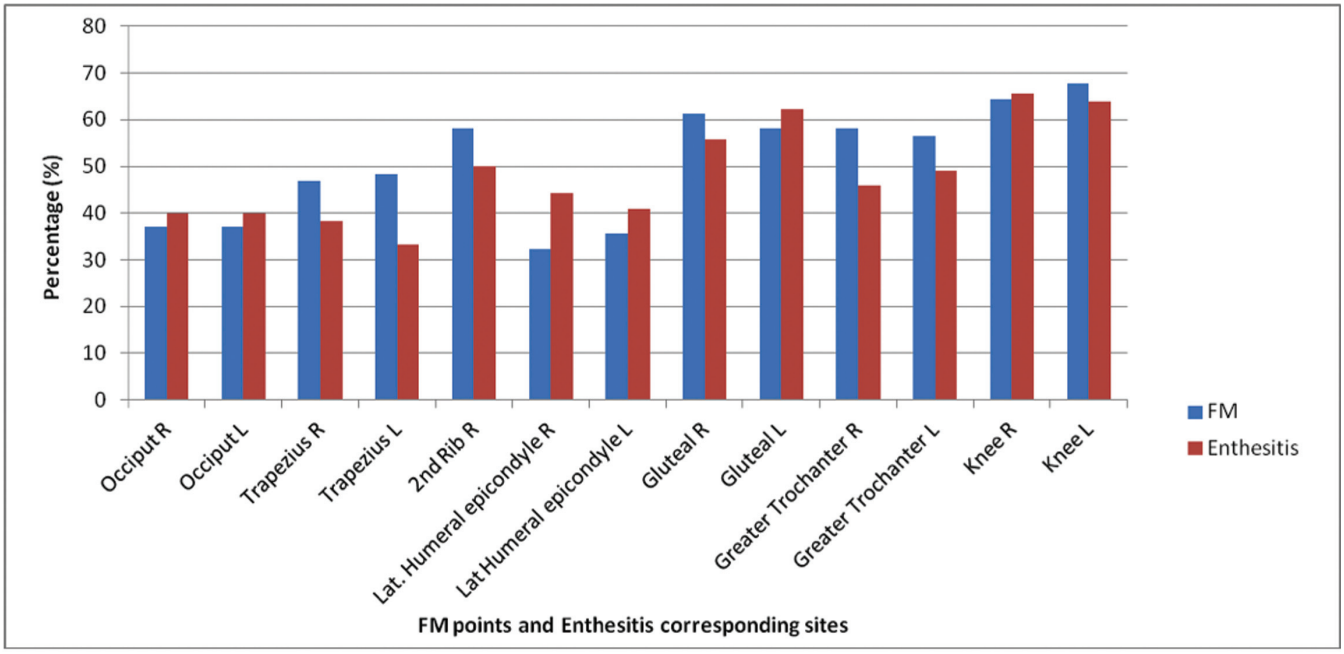

Fig. 3. Graphic representation of the percentage of Fibromyalgia tender points and corresponding enthesitis sites as obtained from the 60 patients assessed.

female patient referrals are addressed to the female consultant compared to the referrals made to the male consultant practising in the same hospital. We believe that the female preponderance is cultural-related, since we serve a diverse cultural population in which gender of the consultant to whom the patients are referred to, is considered important.

In clinical assessment, we took care to differentiate ES from FM TeP. Both assessments were subjective, and were potentially affected by assessment bias and the assessor's discriminatory ability. The amount of pressing force for examination of FM TeP should have been the equivalent of 4 kg, with a positive assessment reported when the individual indicated pain. We avoided the problem of inter-individual variability by using only one assessor.

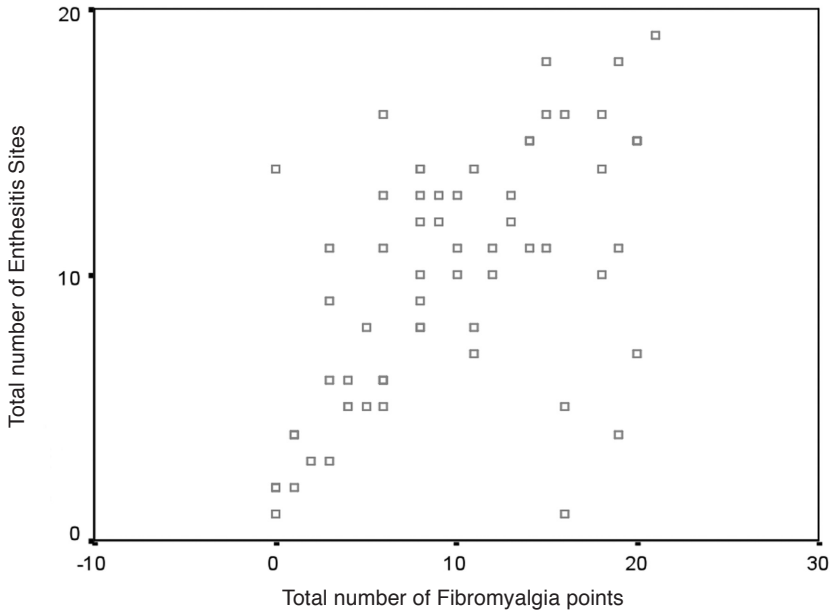

Fig. 4. Scatter plot of the total number of fibromyalgia points and total enthesitis sites obtained from the 60 patients evaluated in the study.

The manual tender-point examination has historically been considered a key feature in the depiction of the clinical features of FM, along with widespread pain (8). Because the distinction between primary FM and secondary concomitant FM has been abandoned, the actual diagnosis is influenced by the examiner's perception and his/her special interest. The 1990 ACR criteria for FM take into consideration the possibility of secondary FM. This is recognised in patients with other diseases that exhibit FM TeP, and by definition accepts co-existent diseases. According to the present results, these diseases may be part of the SpA spectrum, particularly if patients have scalp psoriasis that may be hidden or not easily identified, psoriatic nail disease that may only be obvious if the clinician is aware of it and looks for it, past psoriasis or family history of psoriasis or axial SpA in the early stages, before there is radiographic evidence of AS. This may also explain the variability in prevalence (0.3%–13%) reported in different studies, suggesting that prevalence depends on the definition used and the population studied (12-13).

According to Clauw and Crofford (27), the definition of FM, which requires 11 out of 18 TeP and chronic widespread pain, identifies only 20%

of individuals with the disease. They wondered what designation should apply to the other 80%. In contrast, it is reported that 20%–25% of people with Lupus, RA, or AS have co-morbid FM (15). We were able to identify a greater percentage of individuals with FM in the present study of patients with IBP than that reported in studies of other autoimmune diseases. Bearing in mind that both FM and SpA can present with normal blood tests, it is interesting to consider the percentage of patients who become "lost" in the interface and are misdiagnosed, and who are subjected to proper diagnosis based on the special interest of the examiner.

The tender point examination has been previously questioned (28) with regard to its discriminatory ability as an outcome measure; however, the "coincidence" between FM TeP and enthesitis sites has not been challenged and the high prevalence of FM in SpA may cause confusion in assessing enthesitis. Taking into consideration that patients with IBP and SpAs have axial pain which is one of the FM criteria by definition, (8) fatigue, sleep disturbance (29) improvement with exercise (30) which are common to both conditions and with arthritis and enthesitis seen in SpA patients being able to be interpreted as "widespread pains" required by FM criteria, one wonders the degree by which SpA patients are mislabelled as FM preventing them of getting appropriate clinical care and therapeutic interventions.

The new preliminary diagnostic criteria for FM that have been recently developed (9) do not include tender point evaluation, they are not validated as yet and have not been tested in other rheumatic conditions. Their clinical application over time will show whether they capture FM cases adequately and have better discriminatory ability than the 1990 ACR criteria. Our study has taken place and finalised prior to the publication of the new preliminary diagnostic criteria, therefore we are unable to comment on the application of those to patients with SpA.

In summary, we presented here the findings of our study of a SpA cohort in which all patients fulfilled the criteria for IBP. We demonstrated that 30% of the patients displayed FM signs and symptoms that suggest similar or a greater overlap (co-existence) of the two conditions than has previously been reported between FM and other rheumatic diseases. It remains unknown whether rheumatic diseases generate abnormal hypothalamic responses that lead to FM, whether FM predisposes to other rheumatic diseases, and whether what is perceived as FM is actually enthesitis.

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