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Original article

Assessment of enthesopathy in patients with fibromyalgia by using new sonographic enthesitis index

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ABSTRACT

Objective: The aim of the present study is to determine the frequency of enthesopathy in fibromyalgia (FM) by using a newly developed ultrasonography (US) method, the Madrid Sonography Enthesitis Index (MASEI).

Methods: This study was conducted on 38 consecutive patients with FM and 48 healthy sex- and age-matched controls. Six entheseal sites (olecranon tuberosity, superior and inferior poles of patella, tibial tuberosity, superior and inferior poles of calcaneus) on both lower limbs were evaluated. All US findings were identified according to MASEI. Scores of patients and controls were compared by Student's t-test and Mann-Whitney U-test. Validity was analysed by receiver operating characteristic curve. Values of $P < 0.05$ were considered significant.

Results: Total enthesitis score was 7.39 ± 4.99 (mean ± SD) among FM patients and 3.7 ± 3.22 among healthy controls ($P < 0.001$). The receiver operating characteristic curve established an ultrasound score of > 3.5 in the FM group as the best cut-off point to differentiate between cases and controls. No statistically significant correlation was found between the MASEI score and the FM disease duration, and the location of the tender points.

Conclusions: Misdiagnoses of FM are harmful to patients and the community, and the presence of enthesopathy among FM patients increases. Its detection with the MASEI score may help to discriminate FM patients presenting with ill-defined symptoms and signs, in order to prevent mistreatment.

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Avaliação de entesopatia em pacientes com fibromialgia por meio do novo índice ultrassonográfico de entesite

Palavras-chave:
Ultrassom
Fibromialgia
Entesopatia
Diagnóstico

RESUMO

Objetivo: Determinar a frequência de entesopatia na fibromialgia (FM) utilizando um método de ultrassonografia (US) recém-desenvolvido, o escore Madrid Sonography Enthesitis Index (MASEI).

Métodos: Este estudo foi realizado em 38 pacientes com FM consecutivos e 48 controles saudáveis pareados para idade e sexo. Seis sítios de ênteses (tuberosidade do olécrano, polos superior e inferior da patela, tuberosidade tibial, polos superior e inferior do calcâneo) nos dois membros inferiores foram avaliados. Todos os achados da US foram identificados de acordo com o escore MASEI. Os escores de pacientes e controles foram comparados usando-se o teste *t* de Student e o teste U de Mann-Whitney. A validade foi analisada pela curva receiver operating characteristic (ROC). Valores de $P < 0,05$ foram considerados significativos.

Resultados: O escore total de entesite foi 7,39 ± 4,99 (média ± DP) para os pacientes com FM e 3,7 ± 3,22 para os controles saudáveis ($P < 0,001$). A curva ROC estabeleceu um escore de US > 3,5 no grupo de FM como o melhor ponto de corte para diferenciar casos de controles. Não houve correlação estatisticamente significativa entre o escore MASEI e a duração da FM, e a localização dos pontos dolorosos.

Conclusões: Erros no diagnóstico de FM são prejudiciais aos pacientes e à comunidade, e a presença de entesopatia entre pacientes com FM é crescente. Sua detecção por meio do escore MASEI pode ser útil para discriminar pacientes com FM, cujos sintomas e sinais são mal definidos, para evitar equívoco de tratamento.

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Introduction

Fibromyalgia (FM) is an enigmatic disorder that is usually referred to as a syndrome, in view of the fact that these patients often have widespread pain and multiple somatic symptoms.[1,2] It is one of the most common reason of visits to rheumatologists after osteoarthritis, and is associated with substantial morbidity and disability, which means that it is also a substantial economic burden for national health systems.[3]

Diagnosing FM can be difficult because it encompasses a very wide range of symptoms that can be confused with those of other rheumatic and non-rheumatic diseases such as fatigue, headache, irritable bowel syndrome, sleep disturbances, paresthesias, muscle weakness, bladder dysfunction, depression, anxiety.[3] Therefore it requires differential diagnoses with a number of medical conditions. On the other hand, the finding of abnormal serology or radiographic changes does not exclude a diagnosis of FM.[3] This is an important point because FM may accompany rheumatic disorders such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS)[4,5] and, in this context, a late diagnosis or misdiagnosis is a common and underestimated problem.[3]

Recent developments of high-resolution transducers of ultrasonography (US) have made it possible to assess enthesitis more accurately than clinical examination. There are several reports describing the use of US in determining the features of lower limb enthesitis by using Glasgow Ultrasound Enthesitis Scoring System (GUESS).[6-8] Recently, a new US enthesis score has been developed -Madrid Sonography Enthesitis Index (MASEI)- and it contains additional parameters including power Doppler (PD) US and upper limb examinations when compared with GUESS.[9] In a recent study, entheseal involvements were investigated in patients with FM, however, results of their research do not fully satisfied.[10] This may be as a result of using the Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) in their study which has been reported moderate intraobserver agreement among spondyloarthropathy (SpA) patients, with an intraclass correlation coefficient of 0.56 (95% CI 0.34, 0.82).[11,12]

The aim of the present study is to determine the frequency of enthesopathy in primary FM with using MASEI scoring system.

Materials and methods

The study comprised 38 primary FM patients (mean age 38.8 ± 9.1 years, 36 females and 2 males) and 48 healthy sex- and age-matched controls (mean age 36.5 ± 9.91 years, 46 females and 2 males).

The diagnosis of FM was based on the American College of Rheumatology (ACR) 1990 classification criteria.[13] Exclusion criteria were as follows: Patients with concomitant FM and other confirmed diagnosis, clinical evidence of arthritis, age < 18 years, peripheral neuropathy of upper-lower limbs, history of recent severe trauma at entheses scanned, or knee, ankle or elbow surgery, corticosteroid injection of the examined structures.

Patients enrolled in this study were referred from outpatient clinic of rheumatology of our University Hospital. This study was approved by the local ethics committee of our hospital. Furthermore, the examination was explained to the patients and control subjects and written informed consent was obtained. The physical examination included a tender points (TP) count according to the ACR criteria, tender and swollen joint count, and a spinal examination for presence of pain. All US examinations were performed by an experienced radiologist trained in musculoskeletal sonography blinded to clinical data in a darkened room. US examinations were performed after a 20-minute rest in the US evaluation room, because studies showed that a simple walk exercise significantly has increased an US enthesis score in healthy patients.[14]

US examinations were performed using an Aplio XG machine (Toshiba Medical Systems, Co, Ltd, Ottowara, Japan) equipped with a 5-12 MHz PLT-1204AX linear transducer. Abnormalities were quantified using the MASEI score,[9] which systematically explores 6 enthesis locations bilaterally (i.e., proximal plantar fascia, distal Achilles tendon, distal and proximal patellar ligament, distal quadriceps, and brachial triceps tendons) in each patient. All ultrasound examinations for MASEI scoring system were performed using a standard technique as previously described in the literature.[15,16] The US exploration evaluated the following elemental lesions of enthesis at each site: thickness, structure, calcifications, bursae, erosions and PD US signal in bursa or enthesis full tendon (cortical bone profile, intratendon and paratendon on the enthesis insertion) (Figs. 1-4).[9] Bone erosion was defined as a cortical interruption with a step-down contour defect not due to traumatic tendon rupture (Figs. 1 and 4). In order to avoid acoustic fiber anisotropy, meticulous effort was taken to make sure that the scan planes were parallel to the tendon fibers. Blood flow was examined in each enthesis using PD, the settings of which were standardized with a pulse repetition frequency of 750 Hz and a low wall filter (Fig. 3). Color gain was adjusted to just below the level that reasoned the manifestation of noise artifacts.

The MASEI scores were also correlated separately with the FM disease duration using the Spearman's correlation coefficient.

The total MASEI scores and FM disease duration were compared between different subgroups in patients with FM according to location of someTPs including elbow and knee.

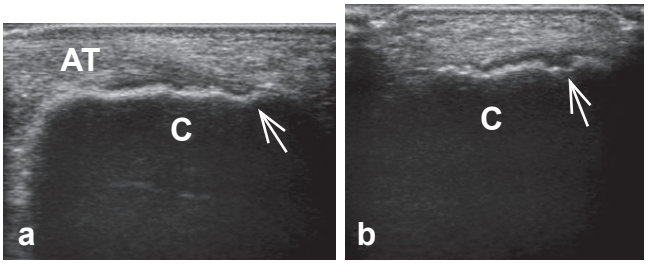

Fig. 1 – 35-year-old woman with erosion of Achilles tendon enthesis. (a) Longitudinal sonographic view of the Achilles tendon (AT) shows erosion (arrow) at the entheseal site; (b) transvere sonogram showing erosion (arrow).
C, calcaneus.

The descriptive statistics included the mean values and SD of the continuous variables, and the percentages and proportions of the categorical variables. The Student's *t*-test was used to compare symmetrically distributed continuous variables between groups and the Mann-Whitney test, for asymmetric distributions. Spearman's correlation coefficient was used for the analysis of correlation. Receiver operating characteristic (ROC) curve was used to calculate the different levels of positive predictive value (PPV), negative predictive value (NPV) sensitivity and specificity at every cut-off point using overall MASEI score. The statistical significance was set at $P < 0.05$ throughout.

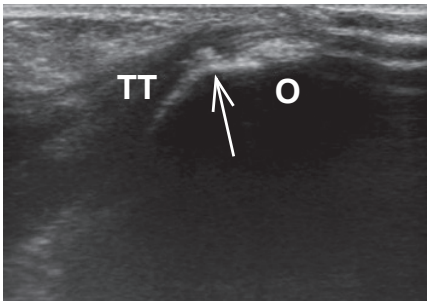

Fig. 2 – 39-year-old woman with calcification of triceps tendon enthesis. Longitudinal sonographic view of the triceps tendon (TT) shows calcification (arrows).
O, olecranon.

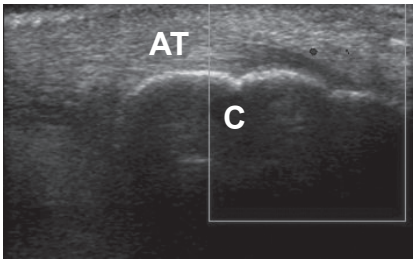

Fig. 3 – 29-year-old woman with abnormal Doppler signal of Achilles tendon enthesis. Longitudinal sonographic view of the Achilles tendon (AT) shows abnormal Doppler signal (arrow) at the entheseal site.
C, calcaneus.

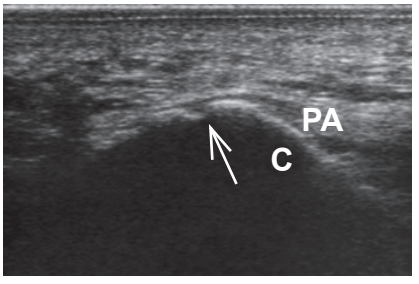

Fig. 4 – 34- year-old woman with erosion of plantar aponeurosis enthesis. Longitudinal sonogram of the plantar fascia (PA) shows an erosion (arrow) at the entheseal site.
C, calcaneus.

Results

The demographic characteristics and mean ± SD MASEI score for each group of patients and controls are shown in Table 1. Mean MASEI score between FM and control were statistically different, 7.39 ± 4.99 (range 1–23) and 3.7 ± 3.22 (range 0–15), respectively (P < 0.001).

There are several elemental lesions of enthesis at each entheseal site. The most common detected elemental lesions in each entheseal site were: olecranon enthesis calcification (34%) in triceps tendon enthesis, quadriceps tendon thickness > 6.1 mm (29%) in quadriceps tendon enthesis, patellar ligament thickness > 4 mm in proximal (8%) and distal (17%) patellar ligament enthesis, posterior pole of calcaneus enthesis calcification (54%) in Achilles tendon enthesis and inferior pole of calcaneus erosion enthesis calcification (11%) in plantar aponeurosis enthesis. Table 2 shows bilateral/unilateral involvement of the most common detected elemental lesions in each entheseal site. Overall, a total of 456 entheseal sites in 38 patients with FM were examined by US. All of the patients with FM had at least one lesion. The highest number of elemental lesion of entheseal sites was the calcification (106/456) (23%), followed by thickness (46/456) (10%), erosion (20/456) (4%), bursitis (3/456) (0.6 %) and PD (1/456) (0.2%).

Table 3 shows the MASEI score in each enthesis affected. FM patients have significantly higher mean ± SD scores than controls' when compared all entheseal sites except proximal patellar tendon enthesis and plantar aponeurosis enthesis (all P values < 0.05). There was no statistical difference among MASEI scores of proximal patellar tendon enthesis and plantar aponeurosis enthesis between patients with FM and controls (P > 0.05).

Mean disease duration was 5.6 ± 4.67 years. There were no statistically significant correlation between the MASEI score, the FM disease duration (r = 0.197; P > 0.05).

The localizations of some TPs including elbow and knee were analyzed in terms of entheseal involvement. The total MASEI scores and FM disease duration were compared between different subgroups in patients with FM according to localizations of some positive TPs including elbow and knee. There was no statistical difference among MASEI scores and FM disease duration between different subgroups in patients with FM according to these TP's involvements; for example, patients with knee involvement vs. patients without in FM group (all P values > 0.05).

Table 1 – Demographic data and results of the Madrid Sonography Enthesitis Index score.

	FM Group	Control group
Subjects (n)	38	48
Female/male (n)	36/2	46/2
Age, years (mean ± SD)	38.8 ± 9.1	36.5 ± 9.91
Age range, years	20-57	20-60
MASEI score (mean ± SD)	7.39 ± 4.99[a]	3.7 ± 3.22

FM, fibromyalgia; SD, standard deviation, MASEI, Madrid Sonography Enthesitis Index score.
[a]P < 0.001 vs. controls.

Our scores were lower when compared to SpA, because FM had minor enthesopathy frequency. Therefore we decided to reestablish the cut-off point to differentiate between cases and controls. ROC curve was performed using overall MASEI score. The area under the ROC curve was 0.75 (95% CI, 0.648 to 0.852) (P < 0.001). When a cutoff point of ≥ 3.5 was used, the sensitivity, specificity, PPV, and NPV were 74%, 58%, 58%, and 73%, respectively. This cut-off point was exceeded by 74% of the patients with FM and 41% of the subjects in control group.

The comparative tendon thickness measurements are evaluated and the mean tendon thickness values did not have a significantly difference from the controls' (all P values > 0.05).

Discussion

The major finding of this study was that the frequency of entheseal abnormalities was significantly increased in FM patients independent of TPs involvement when compared to healthy controls and no difference was observed between patients and MASEI scores as regards their disease duration.

Enthesitis has been regarded as the primary lesion in SpA.[9] Since radiographs and physical examination are not sensitive enough for the detection of early signs of entheseal involvement,[6,17] high-resolution US is widely used as an imaging technique in the diagnosis of enthesopathy.[18] Sensitivity of high-resolution US in the detection of enthesitis has been well established in patients with SpA.[9,19,20] There was only one study about entheseal involvement in patients

Table 2 – According to bilateral/unilateral involvement of the most common detected elemental lesions in each entheseal site.

Enthesis affected	Bilateral (n)	Unilateral (n)
Triceps tendon calcification	5	10
Quadriceps tendon thickness	8	—
Patellar ligament thickness proximal patellar ligament enthesis)	2	4
Patellar ligament thickness (distal patellar ligament enthesis)	5	4
Achilles tendon calcification	16	7
Plantar fascia calcification	2	2

n, number of patients.

Table 3 – Madrid Sonography Enthesitis Index scores by enthesis affected.[a]

Enthesis affected	FM group	Control group	P
Triceps tendon	0.71 ± 0.89	0.27 ± 0.67	0.003
Quadriceps tendon	2.02 ± 2.56	0.56 ± 1.0	0.002
Proximal patellar tendon	0.15 ± 0.36	0.33 ± 0.63	0.18
Distal patellar tendon	1.18 ± 1.52	0.43 ± 0.76	0.014
Achilles tendon	2.65 ± 2.08	1.43 ± 1.97	0.007
Plantar fascia	0.63 ± 0.99	0.66 ± 1.27	0.89

FM, fibromyalgia.
[a]Values are the mean ± SD.

with FM in the literature.[10] The authors had investigated the utility of PDUS in discriminating between psoriatic polyenthesitis and FM by using Outcome Measures in Rheumatology Clinical Trials (OMERACT) definitions of enthesopathy for their study.[21] Patients with primary FM and psoriasis or FM associated with psoriatic arthritis (PsA) and those with psoriatic polyenthesitis may have nearly the same clinical characteristics and are at hazard of misdiagnosis and management mistakes.[1]

The authors also have reported that PD US evaluation of the peripheral entheses distinguishes patients with PsA and patients with FM in terms of number and distribution of the involved sites.[10] In their study, plantar fascia insertion involvement has been seen only in one patient. Although, this tendon involvement was seen in our 10 patients with FM, this difference failed to reach statistical significance (Table 2). Similarly, in terms of proximal patellar tendon entheseal involvement, difference between groups was not statistically significant and this finding was consistent with this study.[10] However, the authors have reported that bony erosions were never found in entheseal sites in patients with FM, whereas they were present in 4% of the entheseal sites of those patients with FM in our study. On the other hand, hypoechoic aspect of tendon as a component of structural changes in MASEI scoring system was never found in our patients with FM when compared this study (7%).[10] These differences between two studies can be associated with entheseal assessments which are influenced by the patient position and scanning technique. As we mentioned previously in result section, meticulous effort was taken to make sure that the scan planes were parallel to the tendon fibers in order to avoid angle-dependent appearance of tissue structures (anisotropy). If this rule is not taken into consideration, tendon may become hypoechoic at greater angles and mistakenly take this for pathology.[22]

The MASEI scores were not homogeneously distributed in the six entheses examined (Table 2), scores being more frequently higher at Achilles enthesis in both groups, whereas relatively low scores at the proximal patellar tendon enthesis and plantar aponeurosis enthesis. These findings consisted with the data of a recent study.[10] These may be associated with mechanical, local anatomic factors at the foot-ground interface. It is possible that the occurrence of a thicker layer of both skin and subcutaneous tissue overlying the plantar aponeurosis may play an important role in decreasing the US sensitivity.[16] Higher scores at Achilles enthesis in both groups may result from higher frequency of tendon calcifications. The most common detected elemental lesion in Achilles tendon enthesis is calcification and it is very common in asymptomatic persons.

There is evidence supporting the issue that PD powerfully improves US correctness in the evaluation of enthesitis.[8] In the present study a lower frequency of PD signal (3%) was found in patients with FM. This finding conflicts with the data of a recent study[10] in which PD signal was detected in seven (23.3%) patients with FM. One possible explanation is that there is no consensus on the optimal Doppler settings for enthesitis in the literature.[23] The different types of ultrasound equipment used may also explain part of the differences observed, because no information regarding inter-equipment reliability for enthesitis assessment is available.[23]

FM is a well recognized and specific clinical characteristic syndrome, however, differential diagnosis with SpA, connective tissue disease and inflammatory arthritis may still be a challenge for general practitioners. Since some of its symptoms such as low back pain, are common to other diseases, they can be confusing, and there are no laboratory and imaging findings that can be considered diagnostic hallmarks.[3] Therefore new 2010 diagnostic criteria have recently been proposed that include cognitive problems and somatic symptoms that were not even considered in the 1990 ACR criteria.[3,24] However, with the exclusion of TP counts, these criteria are not constantly adopted by primary care physicians and or even rheumatologists.[3] The TPs count seemed to be useful for diagnosing FM, but it is well known that the counts are not always very precise. New diagnostic critera and investigation of these subclinical entheseal involvement with this MASEI scoring system may help for diagnosing FM.

Although body-wide pains occur, there are no obvious signs of tissue injury in FM patients. Studies showed that, patients who have chronic pain syndromes (FM, osteoarthritis) display a spread of pain sensation to much wider body areas after intramuscular injection of hypertonic saline compared with healthy control subjects, which strongly suggests central hypersensitivity.[25,26] On the other hand, enthesitis has historically been considered as a disorder of a focal attachment site; however, entheses together with adjacent tissues may form mini organs, named 'enthesis organs'.[27] The "enthesis organ" concept is clearly relevant for understanding Achilles insertional tendinopathies.[27] Studies showed that nerve fibres in Kager's fat pad, an integral part of the Achilles tendon enthesis organ, are obvious in conjunction with mast cells. The neural–mast cell interaction may lead to release of mast cell components that could modulate pain.[28] Perhaps, these pain mechanisms may explain entheseal organ involvement in patients with FM.

MASEI scores range from 0 to 136, and a value ≥ 18 is established as the best cutoff point to differentiate between cases and healthy controls (sensitivity of 83.3%, specificity 82.8%) in the literature.[9] However, our scores were lower when compared to SpA because of being lower entesopathy frequency in patients with FM. Therefore, we decided to reestablish cut-off point to differentiate between cases and controls. Although ROC curve established an ultrasound score of ≥ 3.5 in FM group, as the best cut-off point, lower specificity rate (58%) of this point may be questionable. It is not clear why the values obtained in this study are so low and why there is such a large difference from what is normally seen in other literature. A larger study using this cut-off value should be conducted to validate the cut-off.

In addition to the relatively small number of patients, our study has some other limitations. The groups were not matched for body mass index, a factor that might influence the enthesis score. Herewith, we did not detect clear differences between cases and controls for body mass index.

In conclusion, this is the first study to show significant enthesopathy in patients with FM. Misdiagnoses of FM are damaging for patients and the community, and the presence of enthesopathy among FM patients increases. Its detection by using MASEI score may be helpful to discriminate FM patients presenting with ill-defined symptoms and signs in order to prevent mistreatment.

Conflicts of interest

The authors declare no conflicts of interest.

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