Original paper

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Pain in bilateral knee osteoarthritis – correlations between clinical examination, radiological, and ultrasonographical findings.

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Abstract

Aims: The aim of the study was to evaluate the correlations between clinical symptoms (pain), physical examination, ultrasound (US), and radiological findings in patients with bilateral knee osteoarthritis (OA). **Material and methods:** Knee pain was appreciated during medial and lateral palpation of each knee joint and using visual analogue scale (VAS) and The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). US evaluation (osteophytes, meniscal protrusion, synovial fluid, femoral hyaline cartilage thickness) and radiological assessment (osteophytes, femoral-tibial space, Kellgren–Lawrence [K-L] score, enthesopathies) were performed by two examiners blinded to the clinical results and to each other. All these findings were scored with a five-point scale. **Results:** A total of 52 consecutive patients aged 63.44±9.49 were examined, 33 (80.5%) being females. In patients with bilateral knee OA the pain, evaluated by WOMAC score and VAS, was correlated with the presence of osteophytes and cartilage thickness but no association with medial meniscal protrusion and effusion was demonstrated. Pain produced by palpation of the knee was strongly associated with the presence of medial osteophytes. VAS and WOMAC scores increased with the severity of radiological and US findings. The presence of osteophytes and articular cartilage damage at US examination were strongly and positively correlated with radiological K-L score. US examiners agreement was good for osteophytes and moderate for meniscal protrusion, cartilage damage, and synovial fluid. The cartilage damage score was the only independent predictor for VAS scale; for WOMAC score the sex, cartilage damage, the presence of medial osteophytes and lateral meniscal protrusion were the independent predictors. **Conclusion:** Pain intensity was correlated with the severity of US findings, cartilage damage score being an independent predictor for both VAS and WOMAC scores. Medial osteophytes and lateral meniscal protrusion and are independent predictors for WOMAC score.

Keywords: pain, knee osteoarthritis, clinical examination, ultrasonography, radiography

Introduction

Pain is considered to be the main complain in patients with osteoarthritis (OA) [1] but is has been demonstrated that imaging findings do not always correlate with patients' symptoms [2-4]. The OA pain is multifactorial and the mechanism of its appearance is not completely understood [5-8]. The diagnosis of OA is mainly clinical, but imaging techniques are useful for identifying the structures involved in the pathological process, for prognosis, and follow-up [9]. At this point, despite the identification of the damaged joint components, the cause of the pain remains frequently unclear.

The first imaging method used for the diagnosis of OA was radiography, which evaluates the bone structure. It relies on identifying marginal osteophytes, narrowing of joint space, and assessing the severity of the disease, but has a low ability to visualize soft tissues and provides indirect evidence of cartilage damage [10,11]. Magnetic resonance imaging (MRI) can fully evaluate joint changes in OA, including osteophytes, bone mar-

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row lesions, subchondral cysts, bone attrition, meniscal tears, ligament abnormalities, synovial thickening, joint effusion, intra-articular loose bodies, and periarticular cysts [12], but cannot be used as a routine examination because of its high cost and relatively low availability. Computer tomography (CT) is useful for evaluating bone changes, but is rarely used in clinical practice in OA [13] and scintigraphy does not provide additional information to X-ray in patients with OA [14].

Ultrasonography (US) is an easily performed and non-invasive imaging technique, producing minimal discomfort to the patient and allowing the evaluation of the soft tissue changes in OA joint [15,16]. US has become the first-line imaging technique chosen by rheumatologists to obtain real-time imaging information in patients with painful joints [17]. The ability of US in assessing the periarticular and intra-articular abnormalities in knee OA [18], the reliability [19], and diagnostic performance [20] of the method were already demonstrated. In the last years many studies were performed in order to establish the possible correlations between US findings and patient symptoms (especially pain) in knee OA [2,5,7,18,21-23], but no clear conclusions were drawn. All the authors underlined the need for more work in this field.

The majority of the published studies were performed in patients with unilateral symptomatic OA knee (frequently the asymptomatic knee being considered to be the normal knee), but the authors found degenerative and/or inflammatory findings also in the contralateral, asymptomatic knee [7,24-26]. From clinical practice it is known that patients with painful knee reduce their physical activities in order to "protect" the symptomatic joint. In this way, it is possible that the former symptomatic knee becomes painless. Therefore, sometimes the patient does not describe with accuracy the level of pain. The aim of the study was to establish if the knee pain (reported by patients and established by rheumatologist by palpation) can be correlated with US and radiological findings in patients with bilateral painful knee OA.

Material and methods

Patients

During January and July 2015 a total of 86 consecutive patients who presented in the outpatient clinic or were hospitalized with bilateral knee OA were enrolled in this cross-sectional study. The inclusion criteria were primary knee OA according to the American College of Rheumatology (ACR) definition [27] and only patients with pain in both knees were selected. We excluded patients diagnosed with secondary knee OA (metabolic or traumatic) and knee pathology due to systemic or local inflammatory diseases (rheumatoid arthritis or other inflammatory arthropathies, crystal arthropathy, history of septic arthritis). Finally, we included 52 patients for clinical, radiological and US examination. Informed consent was obtained from each patient and the approval of the local Ethics Committee was obtained. All examinations (clinical, ultrasound and radiography) were performed the same day.

Clinical examination

All patients were clinically evaluated by a rheumatologist with 2 years experience. First, a total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score [28] and visual analogue scale (VAS) were calculated for each knee. The WOMAC score assesses pain, stiffness and physical function and comprises 24 items. Each category was from 0 to 4 according to the severity (none, slight, moderate, severe, extreme). The VAS scale measures pain intensity from score of 0 ("no pain") to score of 10 ("worst imaginable pain"). Secondly, with the patient lying down, the pain was appreciated as present or absent during medial and lateral palpation of the median skyline (lower edge of the patella) of the each knee joint.

Ultrasonography

US was performed by two examiners blinded to clinical findings. Both knees were examined with an Esaote-MyLab 50 machine using 12 MHz linear transducer. With the patient in supine position and complete extension of the knees, the size of tibial and femoral osteophytes was recorded. Osteophytes were defined as modification of the joint bone contour with protrusion seen in two planes [29]. Then, the medial and lateral meniscal protrusion was measured in the place with the most important protrusion, as considered by examiner; it was defined as the perpendicular distance between the joint line and the outer edge of the meniscus in a longitudinal scan. A 30° flexion was used to identify the synovial fluid in the suprapatellar recess defined as an abnormal hypoanechoic displaceable and compressible area without a Doppler signal, using a longitudinal scan [29]. All these findings (osteophytes, meniscal protrusion, and synovial fluid) were scored with a five-point scale: 0=normal, 1= from 0 mm to 2 mm, 2= from 2 mm to 4 mm, 3= from 4 to 6 mm and 4= more 6 mm (fig 1). In a transverse plane and with the knees in maximum flexion, the femoral hyaline cartilage was assessed and classified in 5 degrees: 0-normal, 1- loss of regular contour level interfaces or increased echogenicity cartilage, 2A- modification from degree 1 with decreasing the thickness of the cartilage <50% of his size, 2B-decreasing the thickness of the cartilage >50%, but under 100%, and 3- 100% focal loss of cartilage thickness [30] (fig 2).

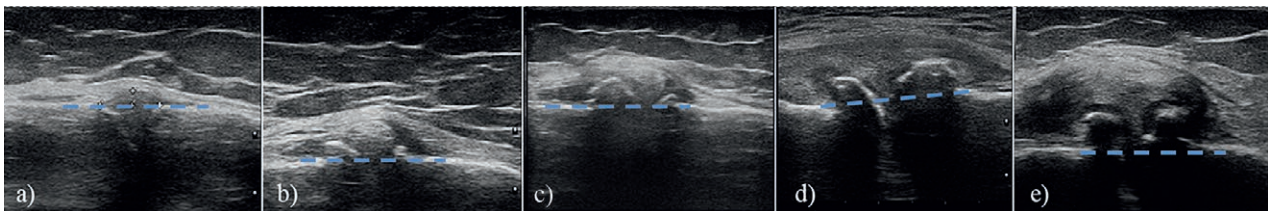

Fig 1. Longitudinal scan of the medial compartment showing the modality of grading the osteophytes: a) 0= normal; b) 1= from 0 to 2 mm; c) 2= from 2 to 4 mm, d) 3= from 4 to 6 mm; e) 4= more 6 mm. The blue dash line is the femuro-tibial bone contour.

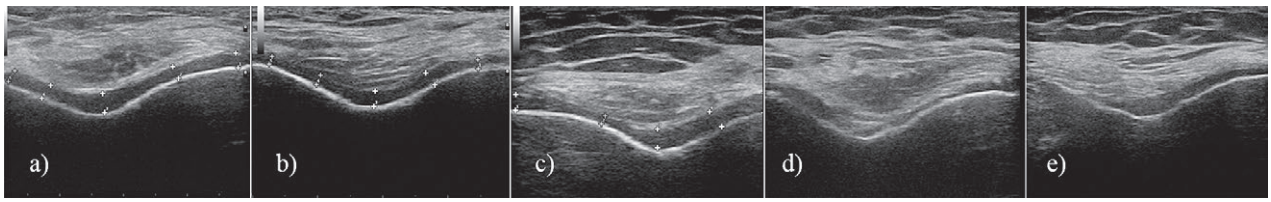

Fig 2. Transversal scan of the femural condyle for assessing the hyaline cartilage damage: a) grade 0; b) grade 1; c) grade 2A; d) grade 2B; e) grade 3 (details inside the text).

Radiological examination

All patients had weight-bearing anteroposterior and lateral knee radiographs which were interpreted by two radiologists, blinded to the clinical and US findings and to each other. They assessed osteophytes, femoral-tibial space, Kellgren–Lawrence (K-L) score and enthesopathies. K-L score evaluates the severity of knee OA using 5 grades from 0 (without radiological changes) to 4 (complex radiological changes) focusing on the presence of osteophytes and/or joint space narrowing [10]. The radiological soft tissue swelling with calcification seen at the site of insertion of a tendon or ligament was defined as enthesopathy.

Statistical analysis

All continuous data were assessed for normality using the Shapiro-Wilk test. The Chi-square and Fisher's exact test were used to assess the relationship between pain at palpation and US and radiological findings. When a significant association was found, the Cramer's V coefficient was calculated to determine the strength of association. The assessment of differences in pain scales (VAS and WOMAC) grouped by US and radiological findings categories was performed using the Kruskall-Wallis test and *post-hoc* analysis. The correlations between pain scales (VAS and WOMAC) and US and radiological findings were tested using Spearman's rho correlation coefficient. Inter-observer agreement between US examiners or radiologists was assessed using Cohen's kappa coefficient. Multivariate Linear Regression was used to determine which independent variables predict the intensity of pain. The significance level was 0.05 for all statistical analyses. Statistical analysis was performed using IMB SPSS Statistics version 22 and Microsoft Excel 2010.

Table I. Characteristics of the study population

Patients, N (F/M)	52 (33/19)
Number of examined knees, N	104
Average age, years	63.44±9.49.
BMI, mean ±SD, kg/m2	31.73 ±6.42
Abdominal circumference, mean ±SD, cm	109.81 ±13.94
Pain intensity scale	
VAS, mean ±SD	6.58 ±2.08
WOMAC, mean ±SD	54.9 ±16.7

N = number of patients; F = female; M = male; BMI = body mass index; SD = standard deviation

Results

The demographic features of subjects are presented in Table I.

Prevalence of radiological and ultrasound features

The most prevalent US findings were moderate synovial fluid, loss of regular contour of the cartilage interfaces, diffuse increased of the cartilage echogenicity, severe medial meniscal protrusion, and moderate lateral meniscal protrusion. VAS and WOMAC scores increased with the severity of radiological and US findings (Table II). Most of the patients had first grade K-L score on radiological examination, incipient osteophytes, and moderate narrowing of articular space.

Relationship between clinical examination and ultrasound findings

Pain produced by palpation of the knee was strongly associated with the presence of medial osteophytes (p=0.011, Cramer's V=0.250), but no association was found with lateral osteophytes (p=0.118) or medial and

Table II. Frequencies of radiological and ultrasound findings and corresponding average VAS and WOMAC score.

Parameter	N (%)		VAS*	WOMAC*
Ultrasound features				
Synovial fluid				
0	16 (15.4)		4.33 (2.77)	42.33 (21.63)
1	19 (18.3)		6.81 (2.07)	54.13 (10.07)
2	30 (28.8)		6.42 (1.92)	52.62 (17.10)
3	23 (22.1)		6.80 (1.70)	56.53 (19.19)
4	16 (15.4)		6.77 (1.59)	60.31 (11.77)
Articular cartilage damage				
0	5 (4.9)		3.75 (2.87)	29 (11.5)
1	43 (41.5)		5.65 (2.32)	46.85 (15.97)
2A	29 (28)		6.57 (1.6)	55.13 (12.15)
2B	18 (17.1)		7.29 (1.27)	63.79 (10.02)
3	9 (8.5)		8.29 (1.11)	72.00 (17.57)
Medial meniscal protrusion				
0	7 (6.7)		4.67 (3.06)	42.33 (16.83)
1	4 (3.8)		4.67 (2.31)	43.67 (18.82)
2	23 (31)		6.63 (1.77)	53.53 (15.77)
3	31 (29.8)		5.88 (2.45)	47.73 (16.11)
4	39 (37.5)		6.81 (1.85)	59.94 (16.20)
Lateral meniscal protrusion				
0	32 (30.8)		6.20 (2.45)	51.68 (18.39)
1	8 (7.7)		6.14 (2.19)	59 (14.28)
2	34 (32.7)		6.47 (1.91)	52.37 (16.11)
3	21 (20.2)		6.07 (2.34)	56.87 (17.55)
4	9 (8.7)		7 (1.58)	49 (17.85)
Medial osteophytes	Superior	Inferior		
0	33 (31.7)	39 (37.5)	5.37 (2.46)	45.71 (17.16)
1	15 (14.4)	14 (13.5)	6.24 (2.24)	49.88 (15.61)
2	26 (25)	32 (30.8)	6.62 (1.62)	54.60 (13.73)
3	22 (21.2)	12 (11.5)	7.28 (1.16)	63.24 (11.54)
4	8 (7.7)	7 (6.7)	8.22 (0.97)	75.22 (9.82)
Lateral osteophytes	Superior	Inferior		
0	50 (48.1)	53 (51)	5.77 (2.38)	49.44 (17.21)
1	19 (18.3)	17 (16.3)	6.85 (1.75)	53.63 (14.41)
2	23 (22.1)	21 (20.2)	6.86 (1.61)	58.22 (15.55)
3	11 (10.6)	13 (12.5)	7.21 (1.58)	63.00 (16.04)
4	1 (1)	0	7	70
Radiological features				
K-L score				
1	43 (41.5)		5.21 (2.42)	47.15 (15.6)
2	33 (31.7)		6.81 (1.55)	52.81 (15)
3	25 (24.4)		7.45 (1.36)	64 (16.13)
4	3 (2.4)		7.50 (2.12)	59 (28.28)
Osteophytes				
0	19 (18.3)		4.60 (2.20)	47.27 (18.66)
1	44 (42.7)		6.37 (2.25)	50.46 (15.99)
2	31 (29.3)		6.75 (1.51)	56.46 (14.78)
3	10 (9.8)		8 (0.93)	68 (15.46)
Articular space narrowing				
0	5 (4.9)		3 (1.15)	44.5 (16.74)
1	33 (31.7)		5.88 (2.47)	48.15 (15.81)
2	57 (54.9)		6.76 (1.75)	55.9 (16.71)
3	9 (8.5)		7 (1.73)	61.3 (17.94)
Enthesopathies				
0	47 (45.1)		5.97 (2.3)	52.65 (17.54)
1	56 (53.7)		6.57 (1.98)	53.95 (16.67)
2	1 (1.2)		8	52

N (%)= number of examined knees (percent); SD= standard deviation
*Data presented as mean (SD)

Table III. Correlation between clinical, radiological and ultrasound features

Radiological features		
	K-L score	
	Spearman's correlation	Pvalue
Pain		
VAS	0.432	<0.001
WOMAC	0.363	0.001
Ultrasound features		
Osteophytes	0.626	<0.001
Meniscal protrusion	0.370	<0.001
Cartilage damage	0.618	<0.001
Ultrasound features		
Pain	**Osteophytes**	
VAS	0.214	<0.001
WOMAC	0.247	<0.001
	Meniscal protrusion	
VAS	0.073	0.294
WOMAC	0.038	0.582
	Cartilage thickness	
VAS	0.387	<0.001
WOMAC	0.434	<0.001
	Synovial fluid	
VAS	0.108	0.277
WOMAC	0.142	0.149

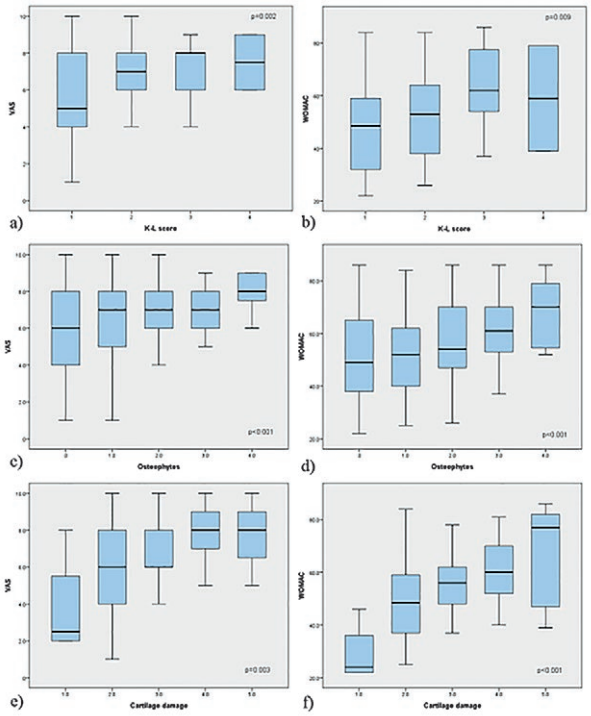

Fig 3. Comparison of pain intensity registered as VAS and WOMAC scores between different categories of radiographical – (a and b) K-L score – and ultrasonographical findings – (c and d) osteophytes and cartilage damage (e and f).

lateral meniscal protrusion (p=0.445, p=0.409 respectively).

Relationship between pain, radiological and ultrasound findings

The presence of osteophytes and articular cartilage damage at ultrasound examination were strongly and positively correlated with radiological K-L score, and meniscal protrusion was weakly correlated with K-L score.The intensity of pain assessed by VAS and WOMAC scales were weakly correlated with the presence of US detected osteophytes and moderately correlated with the cartilage damage (Table III).

As shown by fig 3 significantly higher VAS and WOMAC scores were registered as the K-L score increased. Also, the intensity of pain significantly increased with the severity of osteophytes and cartilage damage found on US examination.

Inter-observer agreement

The inter-observer agreement between the two ultrasound examiners was good in respect to osteophytes identification and scoring (k=0.618, p<0.001) and moderate for meniscal protrusion (k=0.500, p<0.001), cartilage damage (k=0.485, p<0.001) and synovial fluid scoring (k=0.451, p<0.001). The two radiologists obtained a very good agreement in calculating the K-L score (k=0.855, p<0.001), in osteophytes (0.965, p<0.001), articular space narrowing (k=0.938, p<0.001) and enthesopathies (k=0.951, p<0.001) identification and grading.

Multivariate analysis

The multivariate linear regression analysis (Table IV) showed that the cartilage damage score was the only independent predictor for VAS score when adjusting for age, sex, body mass index (BMI), abdominal circumference, radiological features, and ultrasound features. WOMAC score was independently predicted by sex, cartilage damage, the presence of medial inferior osteophytes and lateral meniscal protrusion when adjusting for age, sex, body mass index (BMI), abdominal circumference, radiological features and ultrasound features.

Discussions

In our study we found that in patients with bilateral knee OA the pain, evaluated by the WOMAC score and VAS, was correlated with the presence of osteophytes and cartilage thickness, but no association with medial meniscal protrusion and effusion was demonstrated. The pain at palpation strongly correlated with the presence

Table IV. Prediction of VAS and WOMAC scales

Model	β	95% CI*	p-value	Adjusted R square*
VAS				
Intercept	3.65	(2.44; 4.86)	< 0.001	0.205
Cartilage damage	0.94	(0.54; 1.34)		
WOMAC				
Intercept	34.74	(25.93; 43.55)		
Cartilage damage	6.98	(3.59; 10.37)		
Sex (M)	-10.93	(-18.10; -3.76)	< 0.001	0.427
Medial inferior osteophytes	3.68	(6.47; 0.49)		
Lateral meniscal protrusion	-2.40	(-4.76; -0.06)		

Data are given as regression coefficients (β) and 95% confidence intervals (95% CI); M- male; * Adjusted for age, sex, body mass index (BMI), abdominal circumference, radiological features and ultrasound features

of medial osteophytes but not with the meniscal protrusion. The K-L score showed a good correlation with pain, quantified by the WOMAC score, and VAS. The only independent predictor for the VAS pain scale was the cartilage damage. Instead, several predictors were identified for WOMAC score: the cartilage damage, medial osteophytes, and lateral meniscal protrusion. We found that pain intensity increased with the severity of these pathological findings.

Pain is the most important and disabling symptom in knee OA, but published studies offer contradictory results concerning the relationship between pain and structural changes. The problem of the moderate level of evidence showing correlation between structural changes of knee OA (evaluated by MRI) and pain, and the need for more research is underlined in the Yusuf et al systematic review [31].

It was demonstrated in a recent published study that US is a useful and reliable method in identifying knee osteophytes, medial meniscal protrusion, and morphological changes of the cartilage in the medial femoral condyle. US detects osteophytes and medial meniscal protrusion better than conventional radiography [22].

Comparing with published data our study showed some contradictory results.

First, we found a good correlation of the pain with osteophytes, but no correlation with medial meniscus protrusion. Kijima et al [26] correlated the pain with medial meniscus extrusion (the higher extrusion degree, the higher level of pain) in 38 patients with knee OA. They used the same modality as in our study for determining the meniscal protrusion and expressed the modification in milimeters. Of note, the authors did not take into consideration the presence of osteophytes at this level so their results could be biased. Podlipska et al [22], using the scale proposed by Koskiet al [32] for evaluating osteophytes and the distance from bone contour for meniscal protrusion, underlined the added value of US over radiography in knee OA management. One of the drawbacks of the study was that the authors did not correlate these findings with pain. Chan et al [2] positively correlated the presence of medial osteophytes and meniscal protrusion (medial and lateral) with pain on stair climbing but not with walking pain. In our study, we evaluated the global level of pain as we did not focus on specific physical activities, which probably explains the differences with other studies. Kaukine et al [33], using MRI as the imaging technique for investigation of the knee OA, found a strong correlation between the presence of osteophytes and pain level. Only the anterior extrusion of the medial meniscus was associated with medial pain after adjustment for other MRI findings. Osteophytes represent in fact new bone formation at the joint margins and periostitis can be associated with this process [34], possibly generating and explaining the intensity of the pain.

Secondly, we found no correlations between pain (VAS and WOMAC score) and joint effusion. Esen et al [7] correlated the inflammatory episodes in knee OA with suprapatellar effusion. Naredo et al [18] identified in symptomatic OA knees a correlation between effusion and Baker cyst. Pain during walking and stair climbing but not in sitting position was correlated with effusion [2]. Synovitis was considered to be an important predictor for pain [5]. In contrast to these findings, studies using MRI showed only moderate [31] or no [33] correlation/association between effusion/synovitis and pain. The presence of the 2 types of pain – mechanical pain during joint movements and inflammatory pain related to flares – can partially explain the differences between studies. In our study patients with large synovial fluid had higher VAS and WOMAC score, but no correlation was established. We cannot exclude the fact that our conclusions

are linked to the study group selection modality– patients with bilateral symptomatic OA.

Cartilage damages identified by US were previously correlated with degenerative cartilage changes found by arthroscopy, but the lack of US findings does not exclude degenerative changes [30]. The association of the hyaline cartilage damageor loss with pain was demonstrated in US and MRI studies [2,13,31-33]. In our study we found that cartilage damage was the most important predictor for knee pain, especially for pain evaluated by VAS.

As we already have demonstrated, we obtained a very good agreement between radiologists and a good or moderate agreement between US examiners. The lower agreement at US examination may be the result of comparing a senior and a beginner evaluator. Despite this, the results of agreement can be considered very good as the beginner had only one year of experience in musculoskeletal US. The main problem of the agreement is the impossibility to establish a constant place for grading the modifications: the position of the patient was the same for both examiners but the examiner had the liberty to select himself the place with the most important pathological findings. Notwithstanding the utility, high availability even bedside, and reproducibility, US is a real time, operator-dependent imaging technique with a reliability that ranges from moderate for the beginner examiners to good for junior examiners when compared with senior examiners [19], but the possibility of skills improvement based on the learning curve is in its favor.

Some limitations of our study should be taken into account. One of the major limitations of our study is the lack of data about the patients' treatment: chronic use of anti-inflammatory or antialgic drugs can modify the pain perception. We did not compare the obtained results with a control group (a non-pain group of patients with knee OA or patients with unilateral painful OA). An important limit is the lack of comparison of the US findings with MRI findings as we did not take into consideration the presence of bone marrow lesions as an important source of pain in knee OA. Moreover, the psychological factors that can interfere with pain in our patients were not evaluated. The number of participants was relatively small, especially those with more severe OA (K-L score 4), and we studied both knees of one patient as an independent sample.

The correlation of symptoms in knee OA and US findings is still unclear and controversial and require to be evaluated in larger studies.

Conclusions

Pain intensity in knee OA was correlated with the severity of US findings, cartilage damage score being an independent predictor for both VAS and WOMAC scores. Medial osteophytes were associated with pain at palpation and are independent predictors for the WOMAC score. Lateral meniscal protrusion was also a predictor for the WOMAC score.

Conflict of interest: none

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