9

IN EROSIVE HAND OSTEOARTHRITIS MORE INFLAMMATORY SIGNS ON ULTRASOUND ARE FOUND THAN IN THE REST OF HAND OSTEOARTHRITIS

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ABSTRACT

Objective

To compare inflammation as assessed by ultrasound between patients with the subset erosive hand osteoarthritis (EOA), versus non-EOA.

Methods

Consecutive hand osteoarthritis (HOA) patients (fulfilling ACR criteria) were included. Eighteen interphalangeal joints were scored on radiographs using the Verbruggen-Veys anatomical phase score; E and R-phases were defined as erosive. Patients were assigned to EOA when at least one joint was erosive. Effusion, synovial thickening and power Doppler signal (PDS) were scored with US on a 4-point scale. Generalized estimated equation were used to compare ultrasound features between EOA and HOA, and to associate ultrasound features with anatomical phases; odds ratios (OR) with 95% confidence intervals (95%CI) were calculated with adjustments for patients effects and confounders.

Results

Of 55 HOA patients (mean age 61 years, 86 % women) 51% had EOA. In 94 erosive joints, synovial thickening, effusion and PDS were found in 13%, 50% and 15%, respectively; in 896 non-erosive joints in 10%, 26% and 8%, respectively. In summated scores of PDS, effusion was higher in EOA than in non-EOA. Effusion and synovial thickening were more frequent in S, J, E and R-phases compared to N phase. PDS was only associated with E phase (OR 5.3 (95%CI 1.3 to 20.5)) not with other phases. Non-erosive joints in EOA demonstrated more PDS (OR 3.2 (95%CI 1.6 to 6.4)) and effusion (OR 2.2 (95%CI 1.2 to 3.8)) in comparison to joints in non-EOA.

Conclusions

Inflammatory signs are more frequent in EOA than in non-EOA, not only in erosive joints but also in non-erosive joints, suggesting an underlying systemic cause for erosive evolution.

INTRODUCTION

Erosive hand osteoarthritis (EOA) is considered a subset of hand osteoarthritis (HOA) associated with a higher clinical burden than non-erosive disease[1,2]. Whether EOA is a separate disease entity or a severe stage of HOA has been unclear until now. The diagnosis of EOA is based on subchondral erosions on radiographs in interphalangeal joints (IPJs). Unfortunately, the processes that lead to erosive evolution are still unknown. In an earlier study we showed that erosive evolution in EOA is clustered in certain patients and in certain families, suggesting that underlying systemic processes are involved[3].

The clinical course of EOA is characterised by episodes of inflammatory symptoms and signs, as assessed during physical examination[4]. Due to these frequent inflammatory signs EOA is sometimes referred to as inflammatory HOA[5]. Recent studies using ultrasound demonstrated that inflammatory signs, such as Power Doppler Signal (PDS), greyscale synovitis, synovial thickening and effusion, are frequently seen in both HOA and EOA[6-10]. Two studies, examining the frequency of inflammatory US signs in patients with EOA compared to HOA, showed a trend toward more inflammatory signs in EOA, but were not conclusive[9,10].

Based on the observations that underlying systemic processes may be involved in EOA and that during the clinical course inflammatory signs are often seen in EOA, we hypothesized that inflammatory signs are implicated in erosive evolution. We therefore investigated the presence of inflammatory signs assessed by ultrasound in erosive and non-erosive IPJs in patients with EOA in comparison to IPJs from patients with non-EOA.

PATIENTS AND METHODS

Patient population and osteoarthritis diagnosis

Consecutive patients with HOA consulting the rheumatology outpatient clinic of the Leiden University Medical Centre in Leiden, the Netherlands, were recruited from May 2008 until February 2010. For HOA this centre serves as a secondary consultation centre for the region. Approval for this study was obtained from the local medical ethics committee.

Patients could participate when they met the American College of Rheumatology (ACR) criteria for HOA and were at least 45 years of age[11]. Exclusion criteria were trauma or operation on the hands 6 months before inclusion, positive rheumatoid factor, intra-articular injection within 3 months, or oral corticosteroids within 1 month before inclusion. Other inflammatory joint diseases or disorders such as carpal tunnel syndrome were not allowed. All patients gave informed consent.

Radiographic assessment and definition of EOA

Dorsal-volar radiographs of both hands were obtained within at most 16 weeks from the ultrasound assessment. All IPJs were scored by one experienced reader (MCK) following the anatomical phase score developed by Verbruggen and Veys[12]. This score consists of five phases representing the evolution of HOA: N, normal joint; S, stationary OA with osteophytes and joint space narrowing; J, complete loss of joint

space in the whole or part of the joint; E, subchondral erosion and R, remodelling of subchondral plate. EOA was defined by the presence of at least 1 joint in E or R phase. Films were blinded for patient characteristics and ultrasound outcomes. The intrareader variability for the assessment of radiographic severity depicted by the intraclass coefficient was 0.80 for the anatomical phases. The intrareader variability was based on the re-examination of 10 (20%) randomly selected radiographs.

Ultrasound procedure

Ultrasound was performed on the same day as the clinical assessment by one ultrasonographer (MCK) and scored together with a second ultrasonographer (WYK) in consensus using a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHZ linear array transducer. PDS was assessed with a pulse repetition frequency of 13.2 KHz and a medium wall filter. Gain was adjusted until background signal was removed.

All 18 IPJs were scanned from the dorsal and lateral side only in longitudinal and transverse planes, in accordance with a workshop held by a group of experts in order to develop a scoring system for US for HOA[13]. Features had to be present in both planes. Each joint was scored for PDS, effusion, synovial thickening and osteophytes. Synovial thickening and effusion were scored in accordance with the scoring system for inflammatory signs in rheumatoid arthritis described by Szkudlarek *et al*[14]. The definition of synovial thickening and effusion followed the Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) definitions[15].

All ultrasound features were scored on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe). Summated scores could range from 0 to 54.

Intra-observer variability was tested by performing a second ultrasound in 10% (five) of all patients on the same day after at least 5 hours. Between the first and the second ultrasound at least one other ultrasound assessment was performed. These patients were randomly selected throughout the study. The ultrasonographers were blinded to clinical findings and hand radiographs. The intra-observer variability, taking into account the severity of the score, depicted by the intraclass coefficient was 0.71 for osteophytes, 0.73 for effusion, 0.73 for synovial thickening and 0.57 for PDS.

Clinical assessment

Demographic characteristics were collected by standardized questionnaires. All patients filled in a 100-mm visual analogue scale (VAS) to assess hand pain over the past 48 hours. In addition, hand pain and function were assessed over the past 48 hours by the subscales of the Australian Canadian osteoarthritis hand index (AUSCAN)[16]. AUSCAN responses are rated on a 5-point Likert scale (0, none to 4, extreme). Scores ranged from 0 to 20 for pain and 0 to 36 for function.

During physical examination 1st IPJs, proximal IPJs and distal IPJs from both hands were examined for pain upon lateral pressure (0, none; 1, tender; 2, wincing; 3, withdrawal) using the Doyle Index for the hands and for soft tissue swelling (present/absent)[17].

No analgesics were allowed 72 hours before the clinical and ultrasound assessments.

Statistical analysis

Data were summarized using the mean (standard deviation (SD)) for normally distributed, continuous variables, and the median (range) for non-normally distributed or ordinal variables. Differences in demographics, self reported pain or function, and summated ultrasound features between patients with and without erosive joints were calculated using Mann-Whitney U test. The distribution in the grades of inflammatory ultrasound signs in erosive joints was compared with the frequencies in non-erosive joints using the χ^2 test.

Generalized estimated equation analyses were performed to study the association between ultrasound inflammatory signs as independent variables and the presence or absence of erosive disease as dependent variable in individual joints. Relative risks were presented as odds ratios (OR) with 95% confidence intervals (95% CI). In multivariate analyses adjustments were made for confounders (age, gender and body mass index).

Generalized estimated equation analysis was also performed to study the association between the N, S, J, E and R phases according to the Verbruggen-Veys score (dependent variable) and ultrasound inflammatory features (independent variables).

Data were analyzed using SPSS for Windows, version 17.0 (SPSS, Chicago, Illinois, USA).

RESULTS

Study population

Sixty-four patients were recruited consecutively. One patient received an intra-articular injection in a finger joint between screening and the ultrasound and in eight patients the time between ultrasound and radiographs was more than 16 weeks. So, finally 55 patients were studied (table 1). Their mean age was 61 years, 86% were women. Median symptom duration was 5 years. Median VAS and AUSCAN pain were 51 and

Table 1: Demography of 55 patients with osteoarthritis of the hands and separately for patients with EOA and non-EOA.

	All patients	EOA* patients (n=28)	Non-EOA patients (n=27)
Age, years; mean (SD)	61.4 (9.3)	65 (8.5)	58 (8.9)
Female, no. (%)	47 (85.5)	25 (89.3)	22 (81.5)
BMI, kg/m^2; median (range)	27.3 (19.7-39.5)	27.6 (21.5-39.5)	26.9 (19.7-38.7)
AUSCAN pain, median (range)	9.5 (0-19)	12 (1-19)	8 (0-15)
AUSCAN function, median (range)	17 (0-33)	19 (5-33)	12 (0-30)
VAS pain, mm; median (range)	51 (0-99)	54 (22-99)	47 (0-79)
Tender joints**			
Summated score, median (range)	8 (0-31)	12 (0-31)	5 (0-18)
No. of joints, median (range)	6 (0-13)	8 (0-18)	4 (0-12)
Soft tissue swelling, no.; median (range)	1 (0-9)	2 (0-9)	0 (0-5)

* EOA, defined as at least one interphalangeal joint with erosion.
** Tender joints at physical examination as assessed by the Doyle index for hands.
AUSCAN, Australian Canadian osteoarthritis hand index; BMI, body mass index; EOA, erosive hand osteoarthritis; VAS, visual analogue scale.

9.1, respectively. Patients who were excluded did not differ significantly from patients twho were included (data not shown).

In 28 patients (51%) at least one IPJ was erosive. In 18 patients (33%) more than one IPJ was erosive. Of the 94 erosive joints, 12 joints were in the E phase and 82 joints were in the R phase.

Patients with EOA, as defined by at least one erosive IPJ, were significantly older ($p<0.004$) and experienced more pain in comparison to patients with non-EOA ($p<0.04$ for AUSCAN pain and $p<0.01$ for VAS pain) (table 1).

Also IPJs were significantly more painful on palpation ($p<0.02$ for summated score and for number of tender joints) and more often showed soft tissue swelling ($p<0.02$) in patients with EOA when compared to patients with non-EOA.

When EOA was defined as the presence of more than one erosive IPJ the results remained statistically significant (data not shown).

Inflammatory signs as assessed by US in EOA and non-erosive HOA

The 94 erosive joints in particular showed inflammation. Ultrasound inflammatory signs in erosive and non-erosive joints are depicted in table 2.

In patients with EOA, as defined by at least one erosive IPJ, the summated score as well as the number of affected joints per patient of PDS and effusion were significantly

Table 2: Ultrasound inflammatory signs in erosive and non-erosive joints of 28 patients with EOA and 27 patients with non-EOA.

	Erosive joints (n=94)	Non-erosive joints (n=896)	P-value (χ^2 test)
PDS			
No. of affected joints (%)	14 (15)	72 (8)	0.02
Distribution of grades, no. (%)			
0	80 (85)	824 (92)	
1	10 (11)	56 (6)	
2	4 (4)	13 (2)	
3	0 (0)	3 (0.3)	0.07*
Synovial thickening			
No. of affected joints (%)	12 (13)	92 (10)	0.45
Distribution of grades, no. (%)			
0	82 (87)	804 (90)	
1	3 (3)	55 (6)	
2	7 (7)	30 (3)	
3	2 (2)	7 (1)	0.08*
Effusion			
No. of affected joints	47 (50)	230 (26)	<0.001
Distribution of grades, no. (%)			
0	47 (50)	666 (74)	
1	32 (34)	174 (19)	
2	13 (14)	42 (5)	
3	2 (2)	14 (2)	<0.001*

*p Value for comparison of the distributions.
EOA, erosive hand osteoarthritis; PDS, power Doppler signal.

higher than in patients with non-EOA (table 3). Only summated scores for synovial thickening were significantly higher in patients with EOA, the number of joints with synovial thickening was not.

The summated scores for osteophytes were higher in EOA patients. The number of joints with osteophytes in patients with EOA did not differ from patients with non-EOA.

When EOA was defined as the presence of at least two erosive joints the results were similar for PDS, effusion and osteophytes; there was no difference in synovial thickening between patients with erosive versus non-erosive disease (data not shown).

Association of inflammatory signs and the anatomical phases of the Verbruggen-Veys score

Synovial thickening was significantly more frequent in S, J, E and R phases when compared to the N-phase (table 4). Synovial thickening showed the highest association

Table 3: Signs of inflammation and osteophytes as assessed by ultrasound in IPJs of patients with EOA* and non- EOA.

	EOA patients (n=28)**	Non-EOA patients (n=27)**	P-value
PDS			
Summated score	3.0 (0-9)	1.0 (0-3)	<0.001
No. of joints affected	2.0 (0-5)	1.0 (0-3)	<0.001
Synovial thickening			
Summated score	2.5 (0-19)	0 (0-14)	0.05
No. of joints affected	1.5 (0-10)	0 (0-8)	0.09
Effusion			
Summated score	9.0 (0-16)	4.0 (0-17)	0.02
No. of joints affected	7.0 (0-12)	3.0 (0-10)	0.007
Osteophytes			
Summated score	41.5 (20-49)	37.0 (9-47)	0.009
No. of joints affected	18.0 (9-18)	17.0 (9-18)	0.45

*EOA, defined as at least one IPJ with erosion.
**Depicted are median (range), comparison analysis by Mann-Whitney U test.
EOA, erosive hand osteoarthritis; IPJ, interphalangeal joint; PDS, power Doppler signal.

Table 4: Association analysed by generalized estimated equations of Verbruggen-Veys anatomical phases and ultrasound inflammatory signs in IPJs of 55 patients with HOA.

Phase	Synovial thickening*	Effusion*	PDS*
N	1	1	1
S	4.7 (2.5 to 8.8)	3.7 (2.3 to 5.8)	1.4 (0.7 to 2.8)
J	10.6 (4.2 to 26.8)	5.9 (2.7 to 12.7)	3.1 (1.0 to 9.6)
E	7.1 (1.5 to 34.1)	2.8 (0.8 to 9.7)	5.3 (1.3 to 20.5)
R	4.6 (1.8 to 11.9)	8.8 (4.4 to 17.6)	2.1 (0.8 to 6.1)

*Depicted are OR (95% confidence interval), adjusted for age, gender and body mass index.
HOA, hand osteoarthritis; IPJ, interphalangeal joint; PDS, power Doppler signal.

with the J phase. Effusion was demonstrated significantly more often in the S, J and R phases, but not in the E phase. Effusion showed the highest association with the R phase. PDS was more frequent in the J phase and significantly found more often in the E phase; the highest association was seen with E phase.

Inflammatory signs as assessed by ultrasound in non-erosive joints: comparison of patients with EOA to patients with non-EOA

After the exclusion of joints with erosions, the IPJs without erosions of patients with EOA demonstrated more PDS (OR 3.2 , 95% CI 1.6 to 6.4) and effusion (OR 2.2, 95% CI 1.2 to 3.8) compared to the IPJs of patients with non-EOA (table 5).

Therefore, we concluded that effusion and PDS are independently more frequent in IPJs of patients with EOA, although these joints themselves were not erosive.

No increased frequency was seen for synovial thickening or osteophytes in non-erosive joints of patients with EOA.

Table 5. Comparison between ultrasound features in non-erosive IPJs in 28 patients with EOA versus 27 patients with non-EOA analysed by generalized estimated equations.

Ultrasound features	Adjusted OR (95% CI)*
PDS	3.2 (1.6 to 6.4)
Synovial thickening	1.3 (1.0 to 5.5)
Effusion	2.2 (1.2 to 3.8)
Osteophytes	0.7 (0.3 to 1.8)

*Adjusted for age, gender and body mass index.
EOA, erosive hand osteoarthritis; IPJs, interphalangeal joints; PDS, power Doppler signal.

DISCUSSION

The present study showed that IPJs of patients with EOA demonstrate more PDS and effusion, but not more synovial thickening, in comparison to IPJs from patients with non-erosive HOA. Further detailed investigation revealed that especially erosive IPJs showed inflammatory signs. Remarkably, also IPJs without erosions in patients with EOA demonstrated more inflammatory ultrasound signs in comparison to IPJs of patients with non-EOA. The anatomical phases S, J, E and R showed more signs of inflammation compared to IPJs in the N phase, but PDS was only significantly associated to the E phase.

This study demonstrates for the first time that non-erosive IPJs of patients with EOA have more inflammation, as reflected by PDS and effusion, than IPJs in patients with non-EOA. These findings confirm our hypothesis that inflammatory signs might be implicated in erosive evolution. The present study suggests that EOA is a phenotype affecting all IPJs in a patient, not only the erosive ones, and could explain why erosive evolution is more often seen in those patients that already have erosions[3]. Whether it means that non-erosive joints with inflammatory signs in EOA patients are at an

increased risk of developing erosions in the future can not be answered in the present cross-sectional study. To answer that question longitudinal studies are necessary.

The present study showed that signs of inflammation were frequent in HOA, but significantly more frequent in EOA. Further investigation revealed that especially the E phases were associated with active synovitis as reflected by positive PDS. Inflammation was also more frequently seen in EOA at physical examination, as soft tissue swelling was present during physical examination in EOA. These results underscore the earlier observations of EOA as inflammatory HOA[4,5]. In contrast, synovial thickening, which is frequently found in HOA[6-10], does not distinguish between the different HOA subsets. The non-discriminating nature of synovial thickening was also described in an ultrasound study evaluating the effect of methylprednisolone in hand OA; in the latter study no effect of methylprednisolone on synovial thickening was seen[18]. So whether synovial thickening reflects any inflammation in HOA is not clear and should be studied further. The latter can be done by performing MRI studies with contrast enhancement.

The prevalence of EOA was estimated to be 2.8% in the general population, rising to 15.5% in those with symptomatic HOA[19]. In the present study in consecutive patients with HOA, a high prevalence (51%) of EOA was found, which is in accordance with prevalences of EOA in other rheumatology clinics[20]. An explanation for this high prevalence could be the source of patients, being a rheumatology outpatient clinic. Often patients were referred by their general practitioner because of suspicion of an inflammatory rheumatic disease. This might have caused a selection of patients with more severe HOA. To make sure that the included patients had HOA and not an inflammatory rheumatic disease, patients were carefully examined for rheumatic diseases and psoriasis. Patients with presence of rheumatoid factor or anti-citrulllinated peptide antibodies could not participate in the present study. Another explanation for the high prevalence of EOA in the present study population could be the use of the ACR criteria for HOA requesting signs of OA in multiple hand joints.

The diagnosis of EOA is based on subchondral erosions on radiographs in interphalangeal joints[21]. The number of erosive IPJs necessary to diagnose EOA is not clear. Often it is stated that more than one erosive IPJ is needed[21], but we showed earlier that already one erosive interphalangeal joint increases the clinical burden of hand OA[19]. Therefore, in the present study we investigated both EOA as defined by at least one or by more than one erosive IPJ. The results were the same for both definitions, confirming that one erosive IPJ is enough to define a patient as EOA.

The present study has limitations. Erosive features were not studied by ultrasound but only by radiography. In earlier articles it was found that erosions are better detected by radiographs, because the ultrasone beam is unable to penetrate the cortex and visualise structures beneath it[22]. Bony abnormalities such as osteophytes can overly erosions which can therefore be undetected on ultrasound. However, recent studies performed on ultrasound showed very good detection of erosions using ultrasound[10,23].

Also, in the present study the pulse repetition frequency (PRF) was 13.2 kHz. The machine was tested for optimal settings by a technical engineer from the manufacturer of the machine before the study was started and this was the lowest available PRF at that time. We do not know what the optimal values for PRF are. Lower values give higher

sensitivity, but on the other hand, it is not known whether such low PRF values still give clinically relevant information. In the present study, an age difference between patients with and without EOA was present. For this reason all analyses were adjusted for age.

In conclusion, this study shows that EOA demonstrates more inflammatory signs compared to non-EOA, even in IPJs that are not erosive. This is already true when EOA is defined as the presence of one erosive IPJ. Whether inflammation in EOA is a cause of erosive evolution or a result of extensive destruction in particular joints is not known; the finding that inflammatory signs are also demonstrated more often in non-erosive joints in EOA suggests that inflammation is a cause. Further longitudinal studies are needed to further elucidate the role of inflammation in the development of erosiveness. In case inflammation is a cause of erosive evolution inflammation could be a therapeutic target.

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