7

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 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 ultrasound on a 4-point scale. Generalized estimating equation analyses were used to compare ultrasound features between EOA and HOA, and to associate ultrasound features with anatomical phases; OR with 95% confidence intervals were calculated with adjustments for patient 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. Summated scores of PDS and effusion were higher in EOA than in non-EOA. Effusion and synovial thickening were more frequent in S, J, E and R-phases compared to N-phases. 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 (IPJ). 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 (GS) synovitis, synovial thickening and effusion, are frequently seen in both HOA and EOA.[6-10] Two studies, examining the frequency of inflammatory ultrasound 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 hypothesised that inflammatory signs are implicated in erosive evolution. We therefore investigated the presence of inflammatory signs assessed by ultrasound in erosive and non-erosive IPJ in patients with EOA in comparison to IPJ 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 IPJ 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 osteoarthritis 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 the subchondral plate. EOA was defined by the presence of at least one joint in the 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

US 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 IPJ 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 ultrasound for HOA.[13] Features had to be present in both planes.

Each joint was scored for PDS, effusion and 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 four-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 h. 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 in account the severity of the score, depicted by the intra-class coefficient (ICC) 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 standardised questionnaires. All patients filled in a 100-mm visual analogue scale (VAS) to assess hand pain over the last 48 h. In addition, hand pain and function were assessed over the last 48 h by the subscales of the Australian Canadian osteoarthritis hand index (AUSCAN).[16] AUSCAN responses are rated on a five-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 IPJ, proximal IPJ and distal IPJ 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 h before the clinical and ultrasound assessments.

Statistical analysis

Data were summarised using the mean 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 X^2 test.

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

Generalised estimating 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 variable).

Data were analysed using SPSS for Windows, V.17.0.

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 7.1). Their mean age was 61 years, 86% were women. Median symptom duration was 5 years. Median VAS and AUSCAN pain were 51 and 9.1, respectively. Patients that were excluded did not differ significantly from patients who 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 E phase and 82 joints were in 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 7.1).

Table 7.1 Demography of 55 patients with osteoarthritis of the hands and separately for patients with EOA and non-EOA

	All patients	**EOA[a] patients (n=28)**	**Non-EOA patients (n=27)**
Age, yrs; mean (SD)	61.4 (9.3)	65 (8.5)	58 (8.9)
Female, %	47 (85.5)	89.3	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 (0-99)	54 (22-99)	47 (0-79)
Tender joints[b]			
Summated score, median (range)	8.0 (0-31)	12 (0-31)	5 (0-18)
No. of joints, median (range)	6.0 (0-13)	8 (0-18)	4 (0-12)
Soft tissue swelling, no.; median (range)	1 (0-9)	2 (0-9)	0 (0-5)

[a]EOA defined as at least one interphalangeal joint with erosion

[b]Tender joints at physical examination as assessed by the Doyle index for hands

EOA, erosive hand osteoarthritis; BMI, body mass index; AUSCAN, Australian Canadian osteoarthritis hand index ; VAS = visual analogue scale

Also IPJ 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 ultrasound in EOA and non-EOA

The 94 erosive joints in particular showed inflammation. Ultrasound inflammatory signs in erosive and non-erosive joints are depicted in table 7.2.

Table 7.2 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 (X^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.

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 higher than in patients with non-EOA (table 7.3). 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).

Table 7.3 Signs of inflammation and osteophytes as assessed by ultrasound in IPJ of patients with EOA[a] and non-EOA.

	EOA patients (n=28)[b]	Non-EOA patients (n=27)[b]	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
Syn 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

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

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 7.4). Synovial thickening showed the highest association with 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 R phase. PDS was more frequent in the J phase and significantly more often found in E phase; the highest association was seen with the E phase.

Table 7.4 Association analysed by generalized estimating equations of Verbruggen-Veijs anatomical phases and ultrasound inflammatory signs in IPJ of 55 patients with HOA.

	Synovial thickening[a]	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)

[a]Depicted are OR (95% CI), adjusted for age, gender and body mass index.
HOA, hand osteoarthritis; IPJ, interphalangeal joints; PDS, power Doppler signal

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 IPJ 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 IPJ of patients with non-EOA (table 7.5).

Therefore, we concluded that effusion and PDS are independently more frequent in IPJ 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 7.5 Comparison between ultrasound features in non-erosive IPJ in 28 patients with EOA versus 27 patients with non-EOA analysed by generalised estimating equations.

Ultrasound features	Adjusted OR (95% CI)[a]
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)

[a]Adjusted for age, gender and body mass index.
EOA, erosive hand osteoarthritis; IPJ, interphalangeal joints; PDS = power Doppler signal.

DISCUSSION

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

This study demonstrates for the first time that non-erosive IPJ of patients with EOA have more inflammation, as reflected by PDS and effusion, than IPJ 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 IPJ 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 to develop 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, since 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 anticyclic citrullinated peptide antibodies could not participate from the 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 IPJ [21] The number of erosive IPJ necessary to diagnose EOA is not clear. Often it is stated that more than one erosive interphalangeal joint is needed,[21] but we showed earlier that already one erosive IPJ increases the clinical burden of HOA.[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 having 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 radiography, 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 good detection of erosions using ultrasound.[10,2]

Also, in the present study the pulse repetition frequency 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 IPJ that are not erosive. This is already true when EOA is defined as the presence of one erosive IPJ. Whether inflammation in EOA are 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 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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