8

Inflammation is associated with erosive development in patients with hand osteoarthritis: a prospective ultrasonography study

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Submitted to Arthritis and Rheumatology

ABSTRACT

Objective

To study associations between inflammatory ultrasound (US) features and erosive development over 2.3 years follow-up in hand osteoarthritis (OA).

Methods

In 56 consecutive hand OA patients (mean age 61 years, 86% female), fulfilling ACR criteria, effusion, synovial thickening and Power Doppler signal (PDS) were assessed in all interphalangeal joints (IPJs) with US using standardized methods at baseline and follow-up. Radiographs were scored at both time-points for osteophytes/JSN (OARSI method) and for erosive disease, defined as E- and R-phase (Verbruggen-Veys method). Erosive development was defined as a non-erosive joint becoming erosive. E- and R-phases at baseline were excluded. Associations were analysed using GEE logistic regression, adjusting for age, gender, BMI and baseline structural abnormalities.

Results

At baseline 51 IPJs (18 patients) and at follow-up 89 IPJs (26 patients) were erosive, hence 38 IPJs showed erosive development. Moderate/severe synovial thickening and PDS at baseline were associated with erosive development: adjusted odds ratio (95% confidence interval) 8.8 (2.4-32.3) and 7.1 (1.9-26.9), respectively. Especially persistent inflammation was associated with the development of erosions.

Conclusions

Inflammatory US features are associated with the development of erosions in hand OA, implicating that inflammation plays a role in its pathogenesis and could be a therapeutic target.

INTRODUCTION

Erosive hand osteoarthritis (OA) is a subset of hand OA, defined radiographically by subchondral central erosions, cortical destruction and subsequent reparative change, which may include bony ankylosis.[1] Currently, its pathogenesis is not understood and it is unclear whether it is a separate disease entity or reflects a severe disease stage. What we do know is that erosive OA has a high clinical burden and can progress relatively fast[2]. Few studies looked into underlying mechanisms or risk factors that associate with development of erosions. A sib-pair study in hand OA patients reported that erosive development clusters in patients and families.[3] Especially, painful joints, that have soft tissue swelling or joint space narrowing (JSN) on radiographs, seem to be at risk.[3,4] These findings suggest that underlying systemic processes, such as inflammation, play a role in erosive development. Inflammation is often seen in erosive OA.[5,6] An earlier study showed that inflammatory features are more frequently present in erosive OA as compared to non-erosive hand OA,[6,7] not only in joints with erosions, but also in joints without.[7]

Therefore, the objective of the present study is to investigate the association of erosive development with inflammatory US features in patients with hand OA.

Patients and methods

Patient population and OA diagnosis

Consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre from May 2008 until January 2010. Follow-up visits took place between January 2011 and April 2012. Patients were included after informed consent; the local medical ethics committee gave approval.

Patients with primary hand OA following the American College of Rheumatology criteria and ≥ 45 years were included.[8] Exclusion criteria were: trauma/operation of the hands, treatment with corticosteroids or the presence of another inflammatory joint disease, as described in more detail elsewhere.[7]

Clinical assessment

Demographic characteristics as assessed by standardized questionnaires, and 100 mm visual analogue scale were obtained at baseline and follow-up. Patients were not allowed to use any analgesics during 72 hours preceding the assessments.

Ultrasound procedure

US was performed on the same day as the clinical assessment at baseline and follow-up by one experienced ultrasonographer (MCK) in the presence of a second ultrasonographer (WYK) scoring together in consensus, always using the same Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear

array transducer. Settings were optimized. Both ultrasonographers were blinded to clinical findings.

All 1st interphalangeal joints (1st IPJs), distal IPJs (DIPJs), proximal IPJs (PIPJs), (total 18 joints) were scored for power Doppler signal (PDS), synovial thickening and effusion with US as described[9], using a semi-quantitative scale: 0=none, 1=mild, 2=moderate and 3=severe[9]. Due to the limited amount of joints with grade 2 /3, these were combined in generalized estimating equations (GEE) analyses.

To study associations between the course of inflammatory US features and development of erosions, inflammatory US features were defined as "persistent" (present both at baseline and follow-up), "fluctuating" (present only at baseline or follow-up), or "absent" (absent at both time-points).

Intra-observer reliability was good, as reported elsewhere[7].

Radiographs

Radiographs were obtained at baseline and follow-up and scored paired in known order by MCK. IPJs of both hands were scored for JSN (grade 0-3) and osteophytes (grade 0-3) using the OARSI atlas.[10] Films were blinded for patient characteristics and clinical data.

Erosions were scored in the IPJs using the Verbruggen-Veys method[11], which comprises of five anatomical phases: normal (N), stationary (S), joint space loss (J), erosive (E) and remodeled (R) phase. The sequence of evolution from N to S to J to E to R phases is presumed to reflect the natural history of erosive OA. A joint in E- or R-phase has been defined as erosive. Erosive OA has been defined as having at least one erosive joint. Erosive development has been defined as transition of N-, S- or J-phase into E- or R-phase. Since joints in E- and R-phase at baseline were not at risk to develop into an erosive joint anymore during follow-up, these joints were removed from the analyses.

8

Intra-reader reliability based on 18% randomly selected radiographs depicted by the ICC was 0.86 for osteophytes and 0.76 for JSN, and 0.80 for the anatomical phases.

Statistical analysis

Differences between the original population, and the study population were calculated using Mann-Whitney U test.

Reliability was determined by estimating intra-class correlation coefficients (ICC) using generalizability theory, a random factor model ANOVA approach that estimates the components of variance within each model. Using this method is more suitable compared to traditional ICC analyses or kappa analyses due to the separate outcomes on joint level, with unique joints clustered within a patient. Interpretation of the correlations is: 0-0.20 slight, 0.21-0.40 fair, 0.41-0.60 moderate, 0.61-0.80 good and 0.81-1.00 excellent.

Associations between inflammatory US features and erosive development were estimated using logistic regression. To correct for within patient correlations between joints, GEE approach was followed with an exchangeable working correlation model. Associations were presented as odds ratios (OR) with 95% confidence intervals (CI). OR can be interpreted as relative risks since the outcome (erosive development) was rare (4%). Adjustments were made for age, gender, body mass index and structural abnormalities at baseline.

Structural abnormalities were assessed in this study by individual features (osteophytes and JSN) as well as anatomical phases. We aimed to adjust for all possible structural features at baseline, and therefore wanted to include all assessments, but we expected overlap between the scoring of the individual features and the anatomical phases. Therefore, the frequency of anatomical phases and osteophytes/JSN was evaluated using cross tables. Osteophyte scores did not overlap with the anatomical phases and therefore adjustments were performed for both variables separately. JSN and the anatomical phases did overlap, except for the S-phase. (supplementary table S8.1). Therefore, no adjustments were made for JSN, but in order to include the variance of JSN in the S-phase, structural abnormalities at baseline were defined by a variable consisting of 6 categories, being the anatomical phases N, J, E and R, and in addition the categories “S-phase-JSN grade 0/1” and “S-phase-JSN grade 2/3”. No joints at baseline in N-phase showed erosive development. Therefore, N- and S-phase-JSN0/1 were combined in the analyses. Data were analysed using SPSS 20 for Windows/Apple, version 20.0 (IBM SPSS).

RESULTS

Study population:

Sixty-three patients were included, 56 completed follow-up (89%). Five patients lost interest in the study, one moved away without leaving an address and one patient developed polymyalgia rheumatica and was excluded. At follow-up radiographic scoring of 8 joints of a patient’s left hand was impossible due to a positioning problem, and were therefore excluded.

The follow-up duration was 2.3 years (mean (SD): 28 (2.7) months).

There were no statistical differences between baseline characteristics of the studied patient group and the original patient group.

Table 8.1 Baseline characteristics of 56 hand osteoarthritis patients.

Baseline characteristics	**N=56**
Age, yrs; mean (SD)	61.2 (8.9)
Female; %	48 (85.7)
BMI, kg/m^2; median (range)	27.6 (4.6)
VAS, mm; median (range)	49 (0-99)
Imaging features, no. of joints per patient (0-18); median (range)	
Ultrasonography:	
- Synovial thickening	1 (0-10)
- Effusion	5 (0-12)
- PDS	1 (0-5)
Radiography	13 (3-18)
- Osteophytes	12 (0-18)
- JSN	

yrs=years, SD=standard deviation, BMI=body mass index, VAS= visual analogue scale, mm=millimeter, no.=number, PDS = power Doppler signal, JSN= joint space narrowing.

Table 8.2 Evolution of anatomical phases of 1008 joints in 56 hand osteoarthritis patients over 2.3 years follow-up.

Anatomical phases	**Baseline; no. of joints (%)**	**Transition from baseline to follow-up; no. of joints***		**Follow up; no. of joints (%)**
N-phase;	158 (15%)	N-N =147 N-S =8	Missing: 3	148 (15%)
S-phase	773 (77%)	S-N =1 S-S =733 S-J =15 **S-E =17** **S-R =2**	Missing: 5	741 (74%)
J-phase	J =26 (3%)	J-J =7 **J-E =15** **J-R =4**		22 (2%)
E-phase	E =26 (3%)	E-E =15 E-R =11		47 (5%)
R-phase	R =25 (3%)	R-R=25		42 (4%)

*Numbers displayed in bold were joints that developed an erosion at follow-up.

Erosive development

Of 56 hand OA patients, 18 (32%) were erosive at baseline. During follow-up 8 patients developed erosions, hence 26 patients were erosive (47%). 51 (5%) of 1008 joints at baseline, and 89 (9%) of 1000 joints (8 missing joints) at follow-up showed erosive disease; thus 38 (4%) joints developed an erosion.

Table 8.2 shows the evolution of the anatomical phases during follow-up. No joints in N-phase progressed to E- or R-phase. Of 51 erosive joints at baseline, 25 were in the R-phase and 26 joints in the E-phase. The baseline joints in the E-phase were potentially at risk to progress to an R-phase: 11 of 26 joints (42%) progressed.

Association of inflammatory US features and erosive development.

Table 8.3 shows the association of inflammatory US features at baseline and erosive development on joint level. Synovial thickening, effusion and PDS were associated with erosive development, however after adjustment for baseline structural abnormalities only synovial thickening and PDS remained associated.

All inflammatory US features -synovial thickening, effusion and PDS- were strongly associated with erosive development when persistently present both at baseline and follow-up.

Inflammatory features also seem to play a role in baseline joints that progress from E- to R-phase. Since just 26 joints were in E phase at baseline of which 11 progressed to follow up, only descriptive analyses were performed. Of the joints that progressed to R-phase after 2.3 years of follow up, synovitis, effusion and PDS was seen in 3 (27%), 6 (55%) and 1 (9%) joints respectively versus 2 (13%), 3 (20%) and 3 (20%) joints that remained in E-phase. The joint with PDS in the group of joints that progressed to R phase had a PDS score of 3. The joints with PDS in the group of joints that remained in E phase, all had a PDS score of 1.

Table 8.3 Association of inflammatory US features at baseline, and in addition the course of inflammatory US features, and erosive development in 949 interphalangeal joints in 56 hand osteoarthritis patients at approximately 2.3 years of follow-up analysed using generalized estimating equations.

Imaging feature (grades)	Total joints* (No. of joints without / with development of erosion)	Adjusted OR (95% CI)**	Adjusted OR (95% CI)***
Syn. thick.			
2+3	38 (27/11)	14.5 (5.4-39.1)	8.8 (2.4-32.3)
1	60 (56/4)	2.7 (0.8-9.3)	4.1 (0.7-23.7)
0	851 (828/23)	1	1
Effusion			
2+3	69 (57/12)	7.3 (2.9-18.2)	2.5 (0.7-9.1)
1	191 (182/9)	1.6 (0.8-3.6)	0.7 (0.3-1.9)
0	644 (627/17)	1	1
PDS			
2+3	20 (13/7)	13.1 (3.5-48.5)	7.1 (1.9-26.9)
1	61 (57/4)	2.1 (0.6-7.0)	1.4 (0.2-9.9)
0	868 (841/27)	1	1
Imaging feature course**	**Total joints* (No. of joints without / with development of erosion)**	**Adjusted OR (95% CI)****	**Adjusted OR (95% CI)*****
Syn. thick.			
Persistent	88 (73/15)	10.7 (3.6-31.5)	9.6 (3.2-29.2)
Fluctuating	502 (486/16)	1.7 (0.6-4.4)	1.5 (0.5-4.5)
Absent	359 (352/7)	1	1
Effusion			
Persistent	188 (171/17)	4.6 (1.6-13.2)	3.7 (1.1-12.0)
Fluctuating	476 (460/16)	1.8 (0.7-4.4)	2.3 (0.8-6.7)
Absent	279 (274/5)	1	1
PDS			
Persistent	22 (16/6)	13.5 (4.6-40.0)	11.4 (2.7-49.1)
Fluctuating	136 (119/17)	5.7 (2.7-12.1)	4.9 (2.1-11.6)
Absent	791 (776/15)	1	1

Abbreviations: US=ultrasound, OR=odds ratio, CI= confidence interval, syn. thick.=synovial thickening, PDS= power Doppler signal.
*Joints that could not progress at baseline (E- and R-phase, being 51 joints) were excluded.
**Adjusted for age, gender and body mass index.
*** Adjusted for age, gender, body mass index and baseline structural abnormalities (osteophytes and joint space narrowing/anatomical phases).
**** Persistent defined as: feature present at baseline and follow-up, fluctuating: feature present at baseline or follow-up and absent: features absent both at baseline and follow-up.

DISCUSSION

In this longitudinal US study in patients with hand OA the association of inflammatory US features and erosive development was investigated. It shows that non-erosive hand joints have an increased risk to develop erosions when moderate to severe synovial thickening or PDS is present at baseline in the same joints, independent of cartilage and bone abnormalities at baseline. No statistical significantly association was seen between moderate to severe effusion at baseline and erosive development. All inflammatory US features were associated with erosive development when the inflammatory feature was present both at baseline and follow-up. These observations implicate a role for inflammation in the pathogenesis of erosive OA and it might render new therapeutic options that can halt erosive development.

Few studies investigated risk factors associated with erosive development. In an earlier randomized control trial of 12 months in 60 erosive OA patients,[4] an association of soft tissue swelling and erosive development on joint level was found, suggesting that inflammation might be of importance. However, no adjustments for confounders were made. In an observational study in 236 hand OA patients erosive development after 6 years was associated with self-reported pain at baseline, but also with JSN at baseline.[3] The latter observation stresses the need for adjustment for structural abnormalities at baseline. Inflammation was not assessed, but possibly self-reported pain could reflect signs of inflammation.

Recently, Haugen and colleagues examined associations of baseline MRI features and erosive development after 5 years.[12] Of 209 recruited patients with hand OA eventually 74 were included in the study. Of these only joints of female participants were included in the analyses concerning erosive development. Associations adjusted for age, BMI and duration of follow-up, were found between erosive development and moderate/severe synovitis. No adjustments were made for structural abnormalities at baseline in this study. The authors comment that synovitis could be an intermediate variable in between structural damage and the development of erosions. This could be the case. However, some pathways have been described that could induce synovitis of the joints independent of structural damage, such as aging, presence of crystals and adipokines, whereas via other pathways inflammation could induce structural damage by itself.[13] In order to investigate whether synovitis could be an independent risk factor, we performed additional adjustments for structural damage at baseline as well. When synovitis would have been only an intermediate variable, it is expected that the association would disappear after adjustment. In the present analyses, the strength of the association weakened but remained statistically significant, suggesting that synovitis is independently associated with erosive development.

The present study confirms the hypothesis that inflammation plays a role in the pathogenesis of erosive OA, suggesting a systemic process. Earlier studies in erosive OA patients observed higher CRP levels than in non-erosive hand OA, and synovitis indistinguishable from rheumatoid arthritis in biopsies from erosive IPJs.[2,14]
Studies aiming at suppression of inflammation in erosive OA, however, have shown inconclusive results.[15] Further research is warranted to investigate the efficacy of an anti-inflammatory drug, such as prednisolone, in erosive OA to understand more of the role of inflammation.

In the present study, 4% of IPJs showed erosive development, which is in line with an earlier study reporting 5.7% progression after 3 years,[11] and the study by Haugen et al. reporting 9% progression after 5 years. Bijsterbosch et al. found progression in only 4.4% of IPJs after 6 years.[3,12] This difference could be explained by the more severely affected patients in the present study. No joints with N-phase at baseline showed erosive development, whereas only a limited number of joints in S-phase did (2.5%). Joints in J-phase progressed in 73%; E-phase progressed to R-phase in 40%. This is in line with earlier results[3,11].

The present study has limitations. Patients were selected from a rheumatology outpatient clinic and were severely affected, as reflected by the high percentage of erosive OA at baseline. Further studies are warranted to investigate whether these results are reproducible in other hand OA populations.

Contributor statement

Substantial contributions to the conception or design of the work (MCK, MK), or the acquisition (MCK, WYK, MR), analysis or interpretation of data. MCK, MK, TS

Drafting the work or revising it critically for important intellectual content. MCK, MR, WYK, TS, MK

Final approval of the version published. MCK, MK

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. MCK, MK

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Supplement

Table S8.1 Crosstabulation comparing the anatomical phases of the Verbruggen-Veys score with joints space narrowing, and with osteophytes.

Anatomical phases		**Baseline JSN score**				**Total**
		none	**mild**	**moderate**	**severe**	
	N fase	156	1	1	0	158
	S fase	209	409	137	18	773
	J fase	0	0	2	24	26
	E fase	0	0	1	25	26
Total		365	410	141	67	983
		Baseline osteophytes score				**Total**
		none	**mild**	**moderate**	**severe**	
	N fase	157	0	1	0	158
	S fase	162	453	121	37	773
	J fase	2	5	6	13	26
	E fase	0	1	5	20	26
Total		321	459	133	70	983

Abbreviations: JSN=joint space narrowing