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Inflammatory ultrasound features show independent associations with progression of structural damage after over two years of follow-up in patients with hand osteoarthritis

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ABSTRACT

Objective

To study the development of inflammatory features and it's relation to structural damage over a 2.3 year period in patients with hand osteoarthritis (HOA).

Methods

Synovial thickening, effusion and power Doppler signal (PDS) in distal interphalangeal (DIP), proximal interphalangeal (PIP), 1st carpometacarpal (CMC), metacarpal phalangeal (MCP) and 1st interphalangeal (IP) joints were assessed using ultrasonography in 56 consecutive HOA patients (mean age 61.2 years, 85.7% female) fulfilling American College of Rheumatology (ACR) classification criteria, at baseline and follow-up. Radiographic progression of osteophytes and joint space narrowing (JSN) was scored using the OARSI atlas.

With generalized estimating equations (GEE) OR with 95% CIs were calculated for the associations between inflammatory ultrasound features and radiographic progression taking in account patient effect, age, gender, Body Mass Index, baseline osteophytes and JSN scores, and other inflammatory ultrasound features.

Results

Of 1680 joints, 8.4%, 8.7%, and 19.8% had synovial thickening, PDS or effusion at baseline, respectively. 7.1% and 5.7% of joints had progression of osteophytes and JSN, respectively. Independent associations were found between synovial thickening, effusion and PDS (grade 2-3 versus 0), and progression of osteophytes (OR (95%CI): 2.6 (1.02 to 6.5), 3.5 (1.7 to 7.4) and 5.7 (1.5 to 21.1)) and of JSN (OR (95%CI): 3.4 (1.3 to 8.4), 3.3 (1.5 to 7.6) and 3.1 (1.01 to 9.2)). Persistent inflammatory features at baseline and follow-up showed stronger associations with radiographic progression than fluctuating inflammatory features in comparison to no inflammatory features.

Conclusions

Inflammatory features, especially when persistently present, are independently associated with radiological progression in HOA after 2.3 years, indicating a role of inflammation in the aetiology of structural damage in HOA.

INTRODUCTION

Hand osteoarthritis (OA) is a highly prevalent musculoskeletal disorder leading to pain, disability and structural damage of the hand joints.[1] Which are the underlying pathogenic processes that play a role in disease development and progression are far from understood. MRI and ultrasound have shown that inflammatory features are frequently found in hand OA and are associated with pain.[2,3] After short-term follow-up of 3 months, the total inflammatory burden in the hand joints as assessed by ultrasound remain stable, although on joint level fluctuation can be seen.[4] However, it is unknown how these inflammatory features behave over long-term follow-up and what the clinical implication of their presence is. In knee OA, inflammatory ultrasound features, such as effusion, have been shown to be involved in progression of structural progression as assessed by replacement of a joint prosthesis.[5] Whether inflammation is involved in structural progression in hand OA, has not been studied before.

The objectives of the present study are to investigate whether inflammatory ultrasound features are associated with structural radiological damage after long-term follow-up of 2 to 3 years and to investigate the course of inflammatory ultrasound features over long-term follow-up.

Patients and methods

Patient population and OA diagnosis

In this prospective longitudinal observational study, consecutive patients were recruited from the rheumatology outpatient clinic of the Leiden University Medical Centre, a secondary consultation centre for the Leiden region, The Netherlands, from May/June 2008 until January 2010. Follow-up visits were performed between January 2011 and April 2012. Patients were included after informed consent; the local medical ethics committee of the Leiden University Medical Centre gave approval.

All patients met the American College of Rheumatology classification criteria for hand OA and were at least 45 years of age.[6] Exclusion criteria were: trauma or operation of the hands within 6 months, or an intra-articular injection within 3 months prior to inclusion, oral corticosteroids one month prior to inclusion, positive rheumatoid factor, carpal tunnel syndrome or another inflammatory joint disease (i.e. crystal arthropathy, such as gout or chondrocalcinosis with clinical symptoms, rheumatoid arthritis, psoriatic arthritis).

Clinical assessment

Demographic characteristics were collected by standardised questionnaires at baseline and follow-up. Global hand pain was assessed by a 100 mm visual analogue scale (VAS).

No analgesics were allowed during 72 h preceding the clinical and ultrasound assessment.

Ultrasound procedure

Ultrasound was performed on the same day as the clinical assessment by one experienced ultrasonographer (MCK), scoring together in consensus in the presence of a second ultrasonographer (WYK) at all visits, always using the same machine: a Toshiba Applio scanner (Toshiba Medical systems, Tustin, California) with a 10-14 MHz linear array transducer. Both ultrasonographers were blinded to clinical findings. Ultrasound assessment was performed of all distal interphalangeal joints (DIPJs), proximal interphalangeal joints (PIPJs), 1st interphalangeal joints (IPJs), 1st carpometacarpal joints (CMCJs) and metacarpal phalangeal joints (MCPJs); 30 joints in total.

Power Doppler signal (PDS) was assessed with a pulse repetition frequency (PRF) of 13.2 kHz and a medium wall filter. Gain was adjusted until background signal was removed. Settings were optimised by an application specialist of the manufacturer of the machine.

Hand joints were scanned on the dorsal side in longitudinal and transverse planes. Features had to be present in both planes. Each joint was scored for PDS, synovial thickening and effusion as described before. All ultrasound features were scored using a semi-quantitative scale: 0=none, 1=mild, 2=moderate and 3=severe.[3] For the progression analyses, due to low numbers of joints with ultrasound features grade 2 and 3, these grades were analysed together (grade 2+3).

Intraobserver reliability was tested by performing a second ultrasound in 10% (randomly chosen) of patients on the same day after at least 5 h. In between, at least one other ultrasound assessment was performed.

The intraobserver reliability, taking in account the severity of the score, depicted by the intraclass correlation coefficient (ICC), was 0.62 for PDS, 0.93 for synovial thickening, and 0.84 for effusion.

We defined joints with fluctuating and persistent inflammation as follows: reference joints that showed no inflammatory features at baseline nor at follow-up, joints that showed inflammatory features either at baseline or follow-up (fluctuating inflammation), and joints with inflammatory features at both time points (persistent inflammation).

Radiographs

Dorso-volar radiographs of both hands were obtained at baseline and follow-up. The 30 hand joints (being DIPJs, PIPJs, 1st IPJs, 1st CMCJs, MCPJs) were scored for joint space narrowing (JSN) and osteophytes following the OARSI atlas; per joint a grade of 0 to 3 was given.[7] Baseline and follow-up radiographs were scored paired in known order by MCK. Films were blinded for patients' characteristics and clinical data.

The intrareader reliability based on randomly selected radiographs from 10 (18%) patients depicted by the ICC was 0.86 for osteophytes and 0.76 for JSN.

Progression of osteophytes and JSN for each joint was defined as an increase of at least 1 grade of the OARSI score at follow-up.

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 between ultrasound inflammatory and structural features at baseline and follow-up were analysed using the Wilcoxon signed rank test.

The association between inflammatory ultrasound features and radiographic progression in separate hand joints was studied using generalised estimating equations (GEE), where radiographic progression was the outcome and inflammatory ultrasound features were the determinant. Since a joint with an osteophyte or JSN score of grade 3 cannot further progress, these joints were not included in the analyses for the radiographic feature under study.

Relative risks were presented as OR with 95% CIs. In the present analyses, ORs approximate relative risks since the presence of the outcome (progressive structural damage) was rare (around 6%). Adjustments were made for patient effects, age, gender, Body Mass Index, baseline JSN and osteophytes scores, and the other inflammatory ultrasound features.

Data were analysed using SPSS for Windows, V.20.0 (IBM SPSS statistics, New York, USA).

RESULTS

Study population

Sixty-three patients were included in the study and 56 completed the follow-up (89%). Baseline patient characteristics are depicted in table 6.1. Seven patients discontinued the study: five patients lost interest in the study, one moved away without leaving an address, and one patient was excluded because she was diagnosed with polymyalgia rheumatica for which she was treated with prednisolone. The mean (SD) follow-up duration was 28 (2.7) months.

At follow-up, eight joints of the left hand of one patient were impossible to score on the radiograph due to a positioning problem. Also, four 1st CMCJs were excluded at follow-up due to the fact that prostheses were placed in these joints.

All 56 patients had hand joints with osteophytes. Only one patient had no joints with JSN. All other patients had JSN in at least four joints.

There were no statistically significant differences between baseline characteristics of the studied patient group and the total patient group.

Table 6.1 Baseline characteristics of 56 patients with hand osteoarthritis.

Baseline characteristics	Number=56 patients
Women; number (%)	48 (85.7)
Age; mean, years (SD)	61.2 (8.9)
BMI; mean, kg/m^2 (SD)	27.6 (4.6)
VAS; median, mm (range)	49 (0-99)
Median number of involved joints per patient (range)	
- Nodes	10 (1-22)
- Soft tissue swelling	2 (0-15)
- Osteophytes	14 (3-29)
- JSN	16 (0-27)

BMI, body mass index; VAS, visual analogue scale; JSN, joint space narrowing

Prevalence of inflammatory ultrasound and radiological features at baseline and follow-up.

At baseline and follow-up, the majority of the patients had hand joints with inflammatory ultrasound features. At baseline, 49 patients had joints with PDS, 41 with synovial thickening and 51 with effusion. At follow-up, 49 patients had joints with PDS, and all had synovial thickening and effusion.

The number of joints that showed inflammatory ultrasound signs increased between baseline and follow-up, especially for synovial thickening and effusion. At baseline PDS, synovial thickening and effusion were found in 146 (8.7%), 141 (8.4%) and 332 (19.8%) of 1680 joints, respectively. At follow-up 177 (10.5%), 736 (43.8%) and 768 (45.7%) of 1676 joints showed PDS, synovial thickening and effusion, respectively. These differences were statistically significant ($p=0.006$, $p<0.001$, $p<0.001$).

Osteophytes and JSN were seen at baseline in 890 (53%) and 762 (45%) joints, and at follow-up in 941 (56%) and 798 (48%) joints, respectively. At baseline, 108 joints had an osteophyte score of grade 3, and 88 joints a JSN score grade 3; these joints were omitted in the progression analysis. Radiological progression was seen in 120 (7.1%) joints in 42 patients for osteophytes and in 96 (5.7%) joints in 22 patients for JSN.

Association between baseline inflammatory ultrasound features and radiological progression

Strong associations were found between inflammatory US features at baseline and progression of osteophytes and JSN, as depicted in table 6.2. PDS was dose-dependently and independently of baseline radiological features and other inflammatory features associated with radiological progression.

Synovial thickening was independently associated with radiological progression, but only the association between synovial thickening and JSN progression showed a clear dose-response relationship. Effusion grade 2+3 was associated with radiological

progression, independently from baseline radiological features and other inflammatory features, whereas grade 1 showed no association.

Association between fluctuating and persistent inflammatory ultrasound features and radiological progression

At baseline and follow-up, PDS, synovial thickening and effusion were present at both time points in 40 (2%), 118 (7%) and 232 (14%) joints respectively. Features were present either at baseline or follow-up in 243 (14%), 641 (38%) and 636 (38%) joints, respectively.

The persistent presence, hence present at baseline and follow-up, of all inflammatory ultrasound features was strongly associated with progression of both osteophytes and JSN (table 6.3), even independently of the presence of other inflammatory features at baseline. Only the fluctuating presence, hence the presence at only one time point, of PDS was associated with radiological progression. Synovial thickening and effusion were not. The fluctuating presence of PDS was also associated with osteophytes progression independent of the presence of synovial thickening and effusion at baseline.

Table 6.2 Association of inflammatory US features at baseline and progression of osteophytes and joint space narrowing in hand joints at risk for progression (max. 30 joints per patient) in 56 hand osteoarthritis patients over 2.3 years of follow-up

Ultrasound feature	Number of joints with/without progression	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
		Osteophyte progression		
PDS				
Grade 2+3	13/13	14.8 (5.7-38.8)	11.6 (4.1-32.6)	5.7 (1.5-21.1)
Grade 1	16/81	2.9 (1.7-5.0)	3.4 (2.0-5.9)	2.4 (1.3-4.7)
Grade 0	91/1348	1	1	1
Synovial thickening				
Grade 2+3	15/30	8.1 (4.3-15.1)	6.1 (2.9-12.7)	2.6 (1.02-6.5)
Grade 1	21/56	6.0 (3.1-11.8)	9.1 (4.3-18.9)	5.5 (2.5-12.2)
Grade 0	84/1356	1	1	1
Effusion				
Grade 2+3	24/47	8.3 (4.7-14.8)	7.0 (3.5-14.3)	3.5 (1.7-7.4)
Grade 1	22/188	1.9 (1.09-3.3)	1.5 (0.8-3.0)	0.9 (0.4-1.9)
Grade 0	74/1207	1	1	1
		Joint space narrowing progression		
PDS				
Grade 2+3	8/16	11.1 (4.1-29.8)	6.3 (2.1-19.0)	3.1 (1.01-9.2)
Grade 1	14/90	3.0 (1.6-5.8)	2.4 (1.3-4.3)	2.0 (1.1-3.7)
Grade 0	74/1378	1	1	1
Synovial thickening				
Grade 2+3	12/27	9.5 (3.9-23.1)	6.9 (2.8-17.3)	3.4 (1.3-8.4)
Grade 1	10/69	3.0 (1.4-6.4)	2.3 (1.03-5.4)	1.2 (0.5-3.2)
Grade 0	74/1388	1	1	1
Effusion				
Grade 2+3	16/52	7.5 (3.6-15.6)	4.3 (2.0-9.6)	3.3 (1.5-7.6)
Grade 1	25/193	2.9 (1.6-5.4)	1.9 (0.98-3.5)	1.4 (0.7-2.9)
Grade 0	55/1239	1	1	1

*Model adjusted for age, gender, Body Mass Index (BMI), baseline joint space narrowing score and baseline osteophyte score.

**Model adjusted for age, gender, BMI, baseline osteophyte and baseline joint space narrowing score, and other baseline inflammatory features.

PDS, power Doppler signal

Table 6.3 The natural course of inflammatory ultrasound features and its association with progression of osteophytes and joint space narrowing in hand joints at risk for progression (max. 30 joints per patient) in 56 hand osteoarthritis patients over 2.3 years of follow-up.

US feature	Number of joints with/without progression	Crude OR (95% CI)	Adjusted OR (95% CI)*	Adjusted OR (95% CI)**
		Osteophyte progression		
PDS				
Persistent§	14/19	16.4 (7.9-34.0)	13.6 (6.0-30.7)	4.6 (1.8-12.0)
Fluctuating§	33/177	3.2 (2.0-5.2)	3.0 (1.8-5.1)	2.2 (1.3-3.7)
Absent	73/1246	1	1	1
Synovial thickening				
Persistent	34/68	11.8 (6.5-21.4)	11.3 (5.5-23.0)	4.6 (2.0-10.3)
Fluctuating	45/559	1.6 (1.01-2.4)	1.3 (0.8-2.3)	NP
Absent	41/815	1	1	1
Effusion				
Persistent	40/165	5.7 (3.6-9.1)	4.6 (2.7-7.9)	2.2 (1.1-4.5)
Fluctuating	44/538	1.7 (1.05-2.8)	1.3 (0.8-2.2)	NP
Absent	36/739	1	1	1
		Joint space narrowing progression		
PDS				
Persistent	10/21	11.7 (5.1-27.0)	6.6 (2.5-17.8)	3.1 (1.2-8.0)
Fluctuating	24/198	2.6 (1.6-4.0)	1.7 (1.09-2.8)	1.3 (0.8-2.3)
Absent	62/1265	1	1	1
Synovial thickening				
Persistent	21/77	8.2 (4.0-17.0)	5.6 (2.6-12.1)	2.7 (1.1-6.3)
Fluctuating	44/570	2.2 (1.2-3.9)	1.5 (0.8-2.8)	NP
Absent	31/837	1	1	1
Effusion				
Persistent	36/172	6.9 (3.9-12.1)	3.6 (2.0-6.5)	2.3 (1.1-4.5)
Fluctuating	35/555	2.0 (1.2-3.3)	1.3 (0.8-2.1)	NP
Absent	25/757	1	1	1

*Model adjusted for age, gender, Body Mass Index (BMI), baseline joint space narrowing score and baseline osteophyte score.

**Model adjusted for age, gender, BMI, baseline osteophyte and baseline joint space narrowing score, and other baseline inflammatory ultrasound features.

§ Persistent = present both at baseline and follow-up, fluctuating = present either at baseline or at follow-up

PDS, power Doppler signal; NP, not performed.

DISCUSSION

In the present prospective 2.3-year follow-up study in patients with OA of the hand, it was shown that inflammatory ultrasound features, such as PDS, synovial thickening and effusion, are frequently seen in hand joints. Baseline inflammatory ultrasound features in hand joints are strongly associated with radiological progression in these joints, independently of each other and also independent of baseline radiological features. Repeated measurements of inflammatory ultrasound features revealed that the prevalence of joints with synovial thickening and effusion increased with 35 and 26%, respectively, after 2.3 years, while only a slight increase (2%) of joints with PDS was seen. The minority of joints showed persistent inflammatory ultrasound features at baseline and follow-up -2, 7 and 14% respectively for PDS, synovial thickening and effusion- while 14, 38 and 38% of joints showed fluctuating features. Especially persistent inflammatory ultrasound features were associated with radiological progression after 2.3 years. Joints with persistent and fluctuating PDS had an increased risk to progress radiologically over 2.3 years.

This is the first prospective longitudinal study that investigated whether inflammatory ultrasound features associate with structural damage in OA of the hand over time. Earlier, cross-sectional studies have been done showing associations between inflammatory features as assessed by ultrasound or MRI and structural damage[8,2] which support the observations of this study. Risk factors for structural damage have been more widely investigated in patients with OA of the knee. Although, only a few longitudinal studies in OA of the knee have been performed that studied the relationship of inflammatory features and structural damage, using MRI and ultrasound. Three studies with a follow-up duration of 30 months showed that baseline synovitis/ effusion were associated with incident and progressive cartilage loss.[9,10,11] Two longitudinal studies found only an association of effusion with structural damage, but not with synovial thickening.[5,12] One of these studies used ultrasonography to assess inflammation. Visualisation of the whole knee joint could be more difficult using ultrasonography due to the presence of the patella in front of the tibio-femoral joint. Therefore, synovial thickening might be more difficult to capture. The second study used MRI to assess inflammation, but the follow-up period was only 6 months and, therefore, structural progression was only limited. This might explain why no association with synovial thickening in these studies was found. Another possibility is that aetiology of cartilage loss in OA of the knee is different from that in OA of the hand. In OA of the knee, local mechanical forces are thought to be of great importance in the development and progression of OA.[13,14,15] In OA of the hand, systemic factors seem to be involved.[16,17] This might implicate that different underlying pathogenic processes are present and, therefore, that different risk factors for progression are of importance at different OA joint sites.

In the present study, the presence of PDS appears to be a strong predictor of radiological progression. Synovial thickening, and to a lesser extent effusion, are also of importance, but these features are especially associated with radiological progression when they persist over time. In our earlier study, where patients with OA of the hand were followed for 3 months, we already showed that in some joints inflammatory ultrasound features are variable and persistent in others.[4] Further studies are warranted in order to confirm these findings, as well as further elucidating the aetiology and implication of fluctuating and persistent inflammatory features.

After 2.3 years, a large increase of inflammatory features was seen for effusion and synovial thickening. It is possible that this is the natural course of the disease. Since OA of the hand has not been studied longitudinal with ultrasound or MRI up till now, the natural course on the long term of inflammatory features is not known. The study population consisted of patients with severe OA of the hand, as supported by the presence of 18 patients with erosive OA of the hand at baseline, and with a fairly high VAS hand pain. More longitudinal studies in different patient populations are warranted to understand the natural course of these inflammatory features. We do not expect that the increase in inflammatory ultrasound features is an artifact. The ultrasonographers were the same during the whole study period, as was the ultrasound machine, the machine settings and the scoring method.

In an earlier study, performed by the same ultrasonographers and using the same ultrasound machine, we followed patients for 3 months. In this study we did not see an increase in the total amount of inflammatory ultrasound features,[4] which support the truth of our observations.

In conclusion, the present study shows that inflammatory features are strongly and independently associated with radiological progression after 2.3 years in patients with OA of the hand. These findings are of importance to understand the underlying pathogenic processes in radiological progression in OA of the hand. Further research is warranted to confirm these findings.

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