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ORIGINAL RESEARCH

Factors associated with radiographic progression of hand osteoarthritis over 2 years

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ABSTRACT

Purpose To characterise radiographic progression over 2 years and associated characteristics in patients with hand osteoarthritis.

Methods Baseline and year 2 data from the Hand OSTeoArthritis in Secondary (HOSTAS) care cohort were used, including patients from a rheumatology outpatient clinic.

We collected demographics, disease and patient characteristics and MRI scans of the right hand. Erosive disease was classified using the Verbruggen-Veys system. Dorso-volar hand radiographs were scored blinded, paired, in chronological order, with the Osteoarthritis Research Society International system (osteophytes and joint space narrowing (JSN), scored 0–3/0–1, depending on the joint) per joint (sum score 0–88), with high to excellent reliability. We used the smallest detectable changes to classify progressors (all joints, thumb-base joints and IP joints). Associations between progression and characteristics were analysed with logistic regression.

Results Among 417 patients (mean age 61 years, 86% female), 272 (65%) showed osteophyte progression (median sum score (IQR) change 1 (0–2)) and 135 (32%) JSN progression (median sum score (IQR) change 1 (0–2)). Both osteophyte and JSN progressors had more radiographic damage at baseline. Associations were found between baseline erosive disease or bone marrow lesions and osteophyte progression in IP joints, and between female sex and osteophyte progression in thumb-base joints. The association of baseline osteophytes with change in osteophytes was strongest in younger females.

Conclusion Over 2 years, a considerable proportion of patients demonstrated radiographic progression. Progressors were especially those with erosive disease, more radiographic damage (most pronounced in younger females) and bone marrow lesions at baseline.

INTRODUCTION

Hand osteoarthritis (OA) causes hand symptoms such as pain, stiffness and loss of function. It can be further divided into interphalangeal (IP) and thumb-base OA, as described in the 2023 European Alliance of Associations for Rheumatology (EULAR) criteria. These subgroups are associated with

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Structural damage in hand osteoarthritis (OA) is one of the core features and is commonly investigated over time using radiography.
- ⇒ Few studies have investigated radiographic progression on the short term, or radiographic progression for hand OA subtypes.

WHAT THIS STUDY ADDS

- ⇒ Radiographic damage at baseline is associated with progression of radiographic damage, especially in younger females in our cohort.
- ⇒ Furthermore, erosive disease was specifically associated with progression in interphalangeal joints.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ This information may be used to guide patient selection for future trials investigating potential disease-modifying anti-osteoarthritis drugs.

separate outcomes and risk factors.^{1 2} Hand OA can be diagnosed clinically or radiographically. Radiographic hand OA is highly prevalent and was detected in 67% of females and 55% of males in participants of a population-based cohort with a mean age of 66.6 years,³ and is expected to grow even more common in the future.⁴

Structural damage in hand OA is commonly investigated by radiography, where it is predominantly characterised by osteophytes (OP) and joint space narrowing (JSN).^{5–7} Periodic radiographs allow investigators to track progression of the disease. Previous studies have shown the slow but inexorable nature of structural progression in hand OA, with progression seen in up to 94% over an average of 12 years.^{8–12} To our knowledge, only a few studies on short-term follow-up of 2 years in hand OA have been done, leaving a knowledge gap.^{8 13} The previous studies that have been done only investigated

progression in both hands as a whole, whereas IP OA and thumb-base OA need not share the same pattern and risk profile for progression as the entire hand, or each other. The need to distinguish these subtypes can be seen from the separate EULAR diagnostic criteria published recently.¹

Patients showing progression over such a short term may represent a group with rapid progression. This group might not be representative of the entire hand OA population, but may be of particular interest for clinical trials. It could allow treatments to be studied more efficiently, particularly for disease-modifying anti-osteoarthritic drug (DMOAD) capacity.¹⁴ With faster progression, the effect of treatment compared with placebo will show earlier. This allows for shorter follow-up time, or larger differences between the groups when longer follow-up is possible, with subsequent increases in power and lower requirements for sample size. Imagine a trial is studying a drug that is expected to prevent progression of structural damage in 50% of patients over 2 years. In the hypothetical situation where 20% of patients would experience progression without intervention, 199 patients would be needed per arm to detect this difference. Should we enrich the sample to the point where 50% of patients are expected to experience progression, this number would drop to 116 per arm. A potential downside is that groups enriched for progression may be less representative of the overall hand OA population, limiting generalisability. However, this approach could still yield valuable information. Unfortunately, information on risk factors that can be used to identify progressors remains scarce. A recently published attempt to collect a cohort enriched for progression of knee OA showed the difficulty of identifying patients experiencing rapid progression.¹⁵

As such, more information on factors associated with rapid progression in hand OA is required. One of the factors that has been implicated in OA progression is the perimenopause.⁸ Observational studies have indicated that hand OA incidence rises in the perimenopausal age.^{16–22} As such, the perimenopausal period may also be a risk factor for rapid progression. Other factors that have been described include female sex, age (although the direction of the effect of age differs between studies), the number of affected joints, existing radiographic damage at baseline and presence of erosive disease.²³ Diabetes has also been associated with radiographic progression.²⁴ Earlier observational work also showed an association between synovitis and bone marrow lesions (BMLs) in the finger joints on the joint level and the patient level with radiographic progression after 2 years and 5 years.^{13 25}

More information is needed on patients experiencing rapid radiographic progression of hand OA. Therefore, we aimed to investigate which patients show radiographic progression over 2 years and to characterise these patients.

METHODS

Population

Data of the first 2 years from the Hand OSTeoArthritis in Secondary care (HOSTAS) cohort were used. HOSTAS consists of consecutively referred patients with primary hand OA diagnosed according to the clinical judgement of their treating rheumatologist at the Leiden University Medical Center Rheumatology outpatient clinic. Patients were included from 2009 to 2015. Patients with secondary hand OA (due to metabolic, inflammatory, endocrine or developmental diseases, or due to other major local factors such as hypermobility or gout) or hand symptoms caused by other illnesses (eg, tendinitis, carpal tunnel syndrome, strain, fibromyalgia or arthritis due to other rheumatic diseases) were excluded. During follow-up, patients filled in yearly questionnaires, underwent physical examinations by trained research nurses and hand radiographs were performed at baseline and year 2. Furthermore, 313 patients underwent an MRI scan of the right hand at baseline.²⁶ Full details on the cohort, including detailed descriptions of exclusion criteria, have been published previously.²⁷

For the current analysis, we included all patients who had a hand radiograph assessed for OP and JSN at both baseline and year 2, provided OP and JSN scores were available for all joints of interest.

Measurements

Questionnaires regarding demographics (age in years, sex), patient characteristics (body mass index (BMI) in kg/m², years since menopause and symptom duration) were collected, as were the pain (0–20) and function (0–36) domains of the Australian Canadian Osteoarthritis Hand Index (AUSCAN).²⁸ Higher scores indicate worse pain or function. Comorbidities, including presence of diabetes, were collected using a modified version of the Charlson Index.²⁹ Given the distribution of the data on comorbidities (with most participants having 0 or 1, a few having 2 or more), we dichotomised this variable to presence or absence of comorbidities.

Physical examination included collection of patient-reported joint tenderness on palpation in the proximal interphalangeal (PIP), distal interphalangeal (DIP), IP, metacarpophalangeal (MCP) joints and the thumb-base. This was scored as no tenderness (0), patient indicating pain (1), patient grimacing (2) or patient pulling away the examined joint (3). For this analysis, we dichotomised the scores to present (1) or absent (0) and summed the scores over both hands (range 0–30). Presence of knee or hip OA was established based on the American College of Rheumatology (ACR) clinical criteria.^{30 31} Presence of a prosthesis in a knee or hip was also regarded as presence of OA in that joint. We categorised co-occurrence of at least one hip or knee with OA or a prosthesis as having concomitant knee/hip OA.

Radiographic scoring

Bilateral dorso-volar hand radiographs were scored blinded, paired, in chronological order, using the OARSI

system (OP and JSN scored 0–3 per joint, 0–1 in the IP-1 and scaphotrapeziotrapezoidal (STT) joints, total 0–88) by one reader (SvB).⁶ The bilateral PIP, DIP, IP-1, MCP, first carpometacarpal (CMC-I) and STT joints were scored. A random sample of 45 patients was drawn and scored twice at both time points to assess reliability. Intra-observer reliability for sum scores was excellent (single measures intra-class correlation (ICC) 0.99 and 1.00 at baseline for OP and JSN, respectively). Reliability for change scores was high (single measures ICC 0.80 and 0.85, for OP and JSN, respectively).

Baseline radiographs were scored using the Kellgren-Lawrence (KL) system (score per joint (DIP, PIP, IP-1, MPC and CMC-I joints) 0–4, total score 0–120).⁵ Erosive disease was defined as ≥ 1 joint of the DIP and PIP joints in the Verbruggen-Veys erosive or remodelling phase.³² Both KL and Verbruggen-Veys scoring was performed blinded for clinical and demographic data, with good intra-observer reliability (ICC >0.9 for all scores).²⁷

Magnetic resonance imaging

At baseline, MRI scans of the DIP and PIP joints of the right hand were performed in a subset ($n=313$) between 2011 and 2015. T1-weighted and T2-weighted fat-saturated MRI images in the axial and coronal plane were obtained using a 1.5 T MRI extremity scanner, and were scored blinded for patient characteristics using the Hand OsteoArthritis MRI Scoring system for synovitis/effusion and BMLs (0–3, total score 0–24).³³ Reliability of scoring was excellent, with an ICC of 0.93 for synovitis and >0.95 for BMLs, based on 25 scans rescored after 3 weeks, blinded to scores of the first assessment. Scoring was performed by one well-trained reader (SEST), supervised by a musculoskeletal radiologist with extensive experience (MR). Most patients had a sum score of 0, some had a score of 1 or 2, with very few having scores ranging from 3 to 10. To prevent undue extrapolation, we dichotomised these variables to presence/absence of synovitis or BMLs on MRI.

Statistical analysis

The scores per joint at baseline and year 2, as well as numbers and percentages of joints showing an increase of at least one point, are presented for JSN and OP separately. We made a heatmap with the percentage of joints showing an increase, for each joint separately, and per subset of joints (DIP, PIP, MCP, STT, CMC-I and IP-1 joints), per hand.

We calculated sum scores for the bilateral hand joints (range 0–88), the bilateral IP joints (PIP, DIP and IP-1 joints, range 0–50) and the bilateral thumb-base joints (STT and CMC-I joints, range 0–8) at baseline and year 2, as well as their respective change scores, for OP and JSN separately. These are presented as median and IQR.

The smallest detectable changes (SDC) for the sum score of all joints in the hands were 0.92 for OP (cut-off 1) and 1.32 for JSN (cut-off 2), based on the formula by Bruynesteyn *et al.*³⁴ SDCs were also calculated separately

for the joints of both thumb-bases, and for the bilateral IP joints. For the thumb-base joints, SDCs were 0.40 and 0.29 for OP and JSN, respectively. For the IP joints, SDCs were 0.52 and 0.72 for OP and JSN, respectively. As such, we determined all cut-offs to be 1 for these joint

Table 1 Population characteristics

Number of participants	N=417
Patient characteristics	
Female sex; n (%)	360 (86)
Age, years; mean (SD)	60.8 (8.2)
BMI, kg/m ² ; mean (SD)	26.9 (4.8)
Comorbidities present (yes); n (%)	178 (44)
Diabetes present (yes); n (%)	31 (8)
Perimenopausal state; n (%)	121 (48)
Radiographic outcomes	
KL sum score; median (IQR)	
All joints (range 0–120)	17 (9–29)
Interphalangeal joints* (range 0–72)	13 (6–25)
Thumb-base joints† (range 0–8)	2 (1–4)
Baseline OP; median (IQR)	
All joints (range 0–88)	9 (5–18)
Interphalangeal joints (range 0–50)*	7 (3–14)
Thumb-base joints (range 0–8)†	1 (0–3)
Baseline JSN; median (IQR)	
All joints (range 0–92)	9 (4–20)
Interphalangeal joints (range 0–50)*	7 (2–18)
Thumb-base joints (range 0–8)‡	1 (0–2)
Disease characteristics	
Symptom duration, years; median (IQR)	5.4 (2.0–12.6)
Tender joint count; median (IQR) (range 0–30)	3 (1–6)
Erosive disease; n (%)	118 (28)
Presence of synovitis on MRI; n (%)	63 (26)
Presence of bone marrow lesions on MRI; n (%)	78 (32)
ACR criteria fulfilled; n (%)	379 (91)
Concomitant knee/hip OA; n (%)	117 (28)
Patient-reported outcome measures	
AUSCAN	
Pain; mean (SD) (range 0–20)	9.2 (4.3)
Function; mean (SD) (range 0–36)	15.4 (8.3)
Missingness was lower than 5% unless indicated otherwise. BMI $n=394$, symptom duration $n=387$, synovitis on MRI $n=240$, bone marrow lesions on MRI $n=243$, perimenopausal state $n=252$. For tertile groupings of baseline radiographic score, see online supplemental table A1. *Bilateral proximal interphalangeal joints, distal interphalangeal joints and interphalangeal joints. †Bilateral first carpometacarpal joints and scaphotrapeziotrapezoidal joints. ‡Bilateral first carpometacarpal joints. ACR, American College of Rheumatology; AUSCAN, Australian Canadian Osteoarthritis Hand Index; BMI, body mass index; JSN, joint space narrowing; KL, Kellgren-Lawrence; OA, osteoarthritis; OP, osteophytes.	

Table 2 Changes in OP and JSN over 2 years of follow-up

	Median (IQR) sum at baseline	Median (IQR) sum at year 2	Median (IQR) progression	N (%) patients with progression
Bilateral hands				
OP	9 (5–18)	11 (5–21)	1 (0–2)	272 (65)
JSN	9 (4–20)	10 (4–21)	1 (0–2)	135 (32)
Interphalangeal joints				
OP	7 (3–14)	8 (4–17)	1 (0–2)	224 (54)
JSN	7 (2–18)	7 (3–19)	0 (0–1)	169 (41)
Thumb-base joints				
OP	1 (0–3)	1 (0–3)	0 (0–0)	88 (21)
JSN	1 (0–2)	1 (0–3)	0 (0–0)	97 (23)

Progression of OP and JSN over 2 years. N=417 patients.
JSN, joint space narrowing; OP, osteophytes.

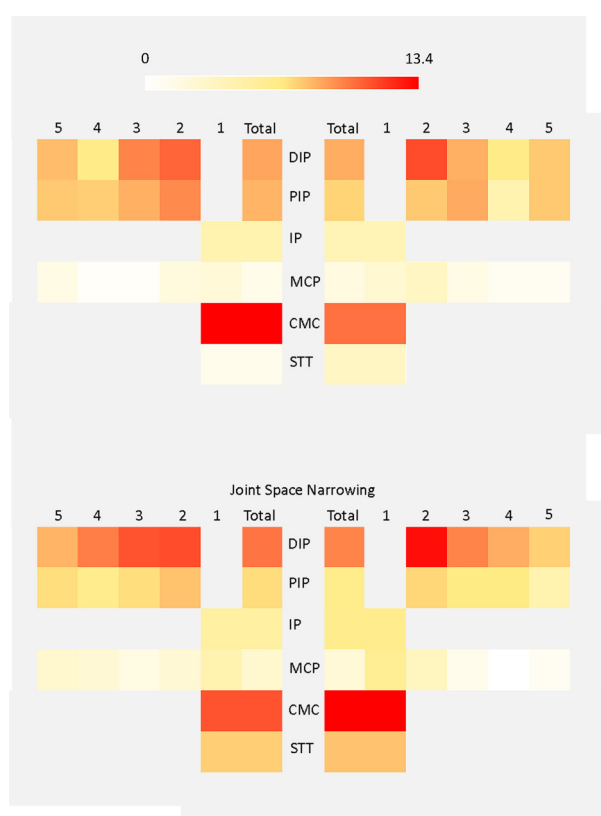


Figure 1 Percentage of joints with progression in either joint space narrowing or osteophytes. Darker colour indicates a higher percentage of joints with progression. Percentage calculated as a percentage of joints at baseline that progressed over 2 years. Total columns indicate the percentage of joints within that joint group (DIP, PIP, MCP, IP or CMC) that progressed, indicating an average over the rows. CMC, carpometacarpal; DIP, distal interphalangeal; IP, interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; STT, scaphotrapezotrapezoidal.

subgroups. A patient with a change in the sum score (in OP or JSN, for the whole hand or joint group) larger than the cut-off was classified as a progressor. Non-progressors encompassed both stable and decreasing scores.

We analysed progressor and non-progressor groups for associating variables by logistic regression. We used separate models for each variable, adjusting all models for baseline radiographic score, age, sex and BMI. Variables were demographics, comorbidities, disease characteristics, MRI-measured BMLs and synovitis and radiographic damage at baseline. The outcomes should be interpreted as the change in odds induced by one unit change in the independent variable, all other variables being equal. We performed all analyses separately for the bilateral hands, thumb-base and IP joints. In the thumb-base and IP joints analysis, variables were restricted to the joints under investigation where possible. For the thumb-base, the KL score was based on the CMC-I joint, and the OP and JSN scores on the STT and CMC-I joints. For the IP joints, KL sum score, OP and JSN scores were based on the PIP, DIP and IP-I joints. The linearity assumption of the logistic regression models was tested through inspection of visual plots and a curvature test (Tukey's one-degree-of-freedom test for non-additivity, with a quadratic component as the added variable). Baseline radiographic scores were found to violate the assumption and thus categorised into quartiles (IP and total scores) or tertiles (thumb-base scores). Symptom duration similarly violated the assumption and was categorised into quartiles.

To further investigate the association of (peri) menopausal state with radiographic progression, we performed analyses in females only. We dichotomised age since reaching the menopause into perimenopausal (10 or less years since starting the menopause) or postmenopausal (>10 years since starting the menopause) to facilitate comparison with an earlier study by our group,

Table 3 Associations with progression of osteophytes of the bilateral hands

Osteophytes	OR (95% CI)		
	Bilateral hands	Bilateral IP joints	Bilateral thumb-base joints
	Increase (n=272)	Increase (n=224)	Increase (n=88)
Patient characteristics			
Female sex*	1.52 (0.83 to 2.79)	1.40 (0.74 to 2.64)	2.30 (1.00 to 6.26)
Age†	0.96 (0.93 to 1.00)	0.94 (0.91 to 0.97)	0.98 (0.94 to 1.01)
BMI‡	0.97 (0.92 to 1.01)	0.96 (0.92 to 1.01)	0.99 (0.94 to 1.01)
Presence of any comorbidities	0.77 (0.49 to 1.21)	0.69 (0.44 to 1.09)	1.17 (0.70 to 1.95)
Diabetes	1.12 (0.49 to 2.71)	1.64 (0.69 to 4.00)	1.42 (0.48 to 3.69)
Perimenopausal state*§	1.02 (0.45 to 2.31)	2.01 (0.93 to 4.39)	0.60 (0.27 to 1.33)
Radiographic characteristics			
KL sum score	1.02 (0.99 to 1.05)	1.05 (1.02 to 1.09)	1.12 (0.93 to 1.35)
Group 1	1	1	1
Group 2	3.93 (1.95 to 8.20)	3.12 (1.40 to 7.28)	3.08 (1.19 to 8.73)
Group 3	8.15 (3.09 to 22.5)	9.98 (3.52 to 29.8)	7.62 (2.44 to 25.6)
Group 4	3.70 (0.91 to 15.2)	9.39 (2.14 to 42.3)	–
Baseline osteophytes¶			
Group 1	1	1	1
Group 2	1.57 (0.84 to 2.95)	2.59 (1.36 to 5.07)	2.52 (1.33 to 4.91)
Group 3	4.22 (2.18 to 8.37)	8.75 (4.38 to 18.1)	3.06 (1.58 to 6.10)
Group 4	4.70 (2.30 to 9.85)	10.6 (5.00 to 23.7)	–
Baseline joint space narrowing			
Group 1	1	1	1
Group 2	1.40 (0.76 to 2.62)	1.73 (0.90 to 3.37)	2.08 (1.10 to 4.00)
Group 3	2.09 (1.06 to 4.21)	1.88 (0.91 to 3.92)	2.10 (0.95 to 4.68)
Group 4	6.33 (2.67 to 15.8)	9.59 (4.04 to 23.8)	–
Erosive disease	2.79 (1.51 to 5.33)	4.50 (2.36 to 8.82)	0.85 (0.47 to 1.49)
Presence of synovitis in IP joints of the right hand on MRI at baseline	1.81 (0.93 to 3.63)	1.85 (0.95 to 3.63)	1.72 (0.80 to 3.67)
Presence of bone marrow lesions in IP joints of the right hand on MRI at baseline	1.77 (0.92 to 3.46)	1.98 (1.02 to 3.89)	1.62 (0.78 to 3.35)
Disease characteristics			
Symptom duration (years)	0.96 (0.94 to 0.99)	0.98 (0.96 to 1.01)	0.97 (0.94 to 1.00)
<2	1	1	1
>1.99 and <5.40	0.53 (0.27 to 1.01)	0.49 (0.26 to 0.94)	1.68 (0.82 to 3.53)
>5.39 and <12.57	0.61 (0.30 to 1.22)	0.61 (0.31 to 1.19)	1.24 (0.59 to 2.63)
>12.56	0.29 (0.14 to 0.59)	0.43 (0.22 to 0.85)	0.66 (0.29 to 1.49)
Tender joint count	0.99 (0.94 to 1.03)	1.01 (0.96 to 1.05)	0.97 (0.91 to 1.02)
Concomitant knee/hip OA	0.73 (0.45 to 1.19)	0.86 (0.53 to 1.39)	0.80 (0.45 to 1.39)
Patient-reported outcome measures			
AUSCAN at baseline			
Pain	0.99 (0.94 to 1.05)	1.00 (0.95 to 1.05)	1.03 (0.98 to 1.10)
Function	1.00 (0.97 to 1.02)	1.00 (0.97 to 1.02)	1.01 (0.98 to 1.05)
Change in AUSCAN baseline–year 2			
Pain	0.97 (0.92 to 1.03)	0.96 (0.91 to 1.02)	1.03 (0.96 to 1.10)

Continued

Table 3 Continued

Osteophytes	OR (95% CI)		
	Bilateral hands	Bilateral IP joints	Bilateral thumb-base joints
	Increase (n=272)	Increase (n=224)	Increase (n=88)
Function	1.00 (0.96 to 1.04)	1.00 (0.96 to 1.04)	1.02 (0.98 to 1.06)

Associations with change in osteophyte sum score.

Groups defined according to smallest detectable change in osteophyte sum score, being one for all three groups. Index groups are the stable/decrease groups for the corresponding joint group.

Adjusted for age, sex, BMI and baseline osteophytes, unless stated otherwise.

*Adjusted for age, BMI and baseline osteophytes.

†Adjusted for sex, BMI and baseline osteophytes.

‡Adjusted for age, sex and baseline osteophytes.

§Only in females; perimenopausal state=10 or less years since start of the menopause.

¶Adjusted for age, sex and BMI.

AUSCAN, Australian Canadian Osteoarthritis Hand Index; BMI, body mass index; IP, interphalangeal; KL, Kellgren-Lawrence; OA, osteoarthritis.

and based on literature describing that 10% of women experience perimenopausal symptoms for >10 years. This cut-off would thus ensure a high certainty of excluding perimenopausal women from the postmenopausal group.^{8 35} The perimenopausal state was then investigated as a possible determinant of progression of OP and JSN, in the same way as described for other possible determinants. We also stratified the females in our study population by tertiles of age and plotted the change in OP versus baseline OP. The associated unadjusted linear regression models with baseline score as independent and change score as dependent were estimated. These analyses were performed for the bilateral hands, the thumb-base and the IP joints separately.

Missing data were not imputed.

ICC and SDC were calculated with SPSS V.29. All other analyses were performed in R Studio, running R V.4.2.1.

RESULTS

417 patients had radiographs assessed at baseline and year 2 and complete scores for both JSN and OP. The mean (SD) age was 60.8 (8.2) years, 86% of patients were female and 90% fulfilled the ACR criteria for hand OA. At baseline, 404 (93%) patients had at least one joint with an OP (OP sum score for both hands >1), with a median OP sum-score of 9 (IQR 5–18). 376 (87%) patients had at least one joint with JSN, with a median JSN sum score for both hands of 9 (IQR 4–20) (table 1). Of 360 females, 252 had entered the menopause and had data available on age, of whom 121 were perimenopausal.

Of 417 participants, 272 (65%) showed OP progression (median (IQR) change in sum score 1 (0–2)) and 135 (32%) participants showed JSN progression (median (IQR) change in sum score 1 (0–2)) (table 2). Four participants (1%) showed a decrease in OP sum score, 18 (4%) showed a decrease in JSN sum score. With regard to the IP joints, 54% of patients showed OP progression (1 (0–2)) and 41% showed JSN progression (0 (0–1)). With regard to the thumb-base, 21%

(0 (0–0)) showed OP progression and 23% (0 (0–0)) showed JSN progression.

Per joint, the percentage of OP progression ranged from 13.4% (left CMC-I joint) to 0.2% (left MCP-2 and MCP-3 joints) in single joints. Progression was most frequent in CMC-I joints. Progression was slightly more frequent in DIP joints than in PIP joints, with most progression seen in the bilateral DIP-2 joints. The MCP, IP-I and STT joints showed the least OP progression (figure 1). For JSN, progression ranged from 12.2% (right CMC-I joint) to 0% (right MCP-4 joint) in single joints. Progression was most frequent in the CMC-I joints, and DIP joints ranked second in progression, primarily in the bilateral DIP-2 joints. The STT joints showed the third highest progression of JSN, followed by the PIP joints. The MCP and IP-I joints showed the least progression (figure 1). For a detailed overview, see online supplemental tables A2,A3. Neither OP progression nor JSN progression was markedly different between the two hands (figure 1).

Associations with progression of osteophytes

Females tend to have OP progression more often than men (OR 1.52, 95% CI 0.83 to 2.79, table 3, 241/360 (67%) females compared with 31/57 (54%) males). Progression of OP was positively associated with baseline OP sum score after adjustment for age, sex and BMI. After adjustment for age, sex, BMI and baseline OP sum score, OP progression was positively associated with radiographic damage (measured as either KL or JSN sum scores) and erosive disease at baseline. A negative association was seen with symptom duration and with age. No associations were found with patient-reported outcomes measures, either at baseline or change in patient-reported outcome measures over 2 years (table 3).

In an analysis of the bilateral PIP, DIP and IP-1 joints, radiographic damage at baseline was also positively associated with OP progression. Erosive disease had a markedly stronger association with progression in the IP joints than for the association with hands as a whole. Presence

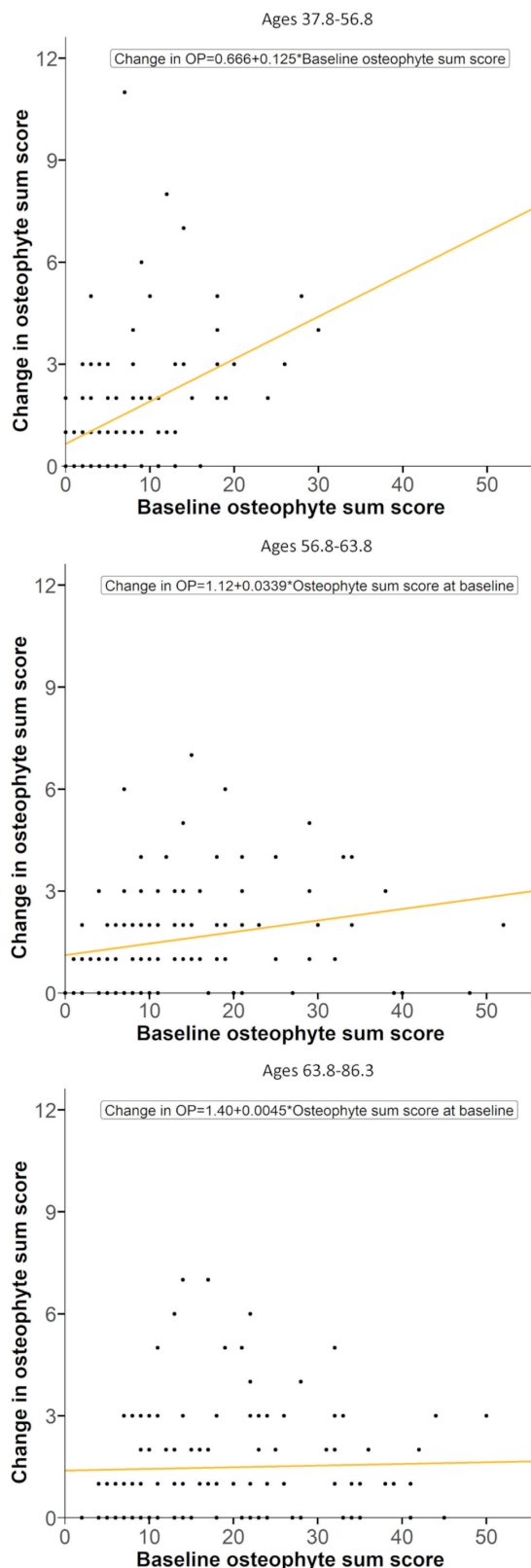


Figure 2 Distribution of change in osteophyte (OP) sum score versus baseline OP sum score, per age tertile. Scatter plots of change in OP sum score versus baseline OP sum score, per age tertile. Yellow lines indicate the corresponding unadjusted linear regression model, with the formulae shown in the boxes in the top of the graphs. Age groupings are similarly shown in the top of the graphs. Only female patients are included in these graphs.

of BMLs measured on MRI in the DIPs and PIPs of the right hand was also positively associated with OP progression in IP joints of both hands. In addition, a negative association was found with age (table 3).

Analysis of the thumb-base in isolation yielded different associations than for the whole hand. The associations with imaging outcomes attenuated, and an association with female sex (OR 2.30, 95% CI 1.00 to 6.26) was seen (table 3, online supplemental table A4).

Progression of osteophytes in younger females

Given the observed associations of OP progression with female sex (with a higher risk than men) and age (negative association), we further explored the relationship between perimenopausal stage, baseline OP scores and change in OP scores. These additional analyses were performed in females only.

Stratifying the patients in tertiles of age, we found that the association between baseline OP and change in OP differed per age tertile stratum. The association was strongest in the youngest group (37.8–56.8 years), attenuates in the middle group (56.8–63.8) and disappears in the oldest group (63.6–86.3) (figure 2). This was seen despite a lower median OP sum score in the younger age group (5, IQR 2–9) versus middle (10.5, IQR 3.6–17.8) and elder age groups (17, IQR 9–26.5). In separate analyses for IP joints and thumb-base joints, similar attenuation of the association between baseline OP and change in OP over tertiles of age was seen (table 4).

Association with progression of joint space narrowing

JSN progression was positively associated with radiographic damage in the hands at baseline, measured in JSN or OP sum scores as well as KL sum scores. A negative association was seen with symptom duration. No associations with patients-reported outcome measures at baseline were found, but JSN progression showed a positive association with development of AUSCAN function and pain scores over 2 years (table 5, online supplemental table A5).

Investigations of the bilateral IP joints yielded similar results, with somewhat attenuated effect sizes. The analyses of the thumb-base joints showed larger effect sizes in the associations of baseline radiographic damage measured as KL or OP score with JSN progression.

We performed similar exploratory stratified analyses for JSN as were done for OP. However, there were no associations between baseline JSN and change in JSN within the age strata if only investigating females.

DISCUSSION

Our aim was to investigate and characterise patients with radiographic progression of primary hand OA over a period of 2 years. A considerable proportion of patients showed radiographic progression, which was most prominent in the CMC-I and DIP2 joints and was symmetric between the hands. Progression of OP and JSN was associated with baseline radiographic damage. When

Table 4 Association of baseline osteophyte sum score with change in osteophyte sum score per joint group, stratified by tertiles of age

Age (years)	β (95% CI)		
	Whole hand	Interphalangeal joints	Thumb-base joints
<56.8	0.13 (0.08 to 0.17)	0.13 (0.08 to 0.18)	0.08 (0.00 to 0.15)
56.8–63.8	0.03 (0.01 to 0.06)	0.04 (0.01 to 0.07)	0.01 (–0.04 to 0.07)
>63.8	0.00 (–0.02 to 0.03)	0.02 (–0.01 to 0.05)	0.00 (–0.04 to 0.04)

Effect size β is derived from unadjusted linear regression within each age stratum.

the IP joints were analysed separately, a positive association between BMLs at baseline and OP progression was observed. The association of OP sum score at baseline with change in OP sum score was strongest in younger females (aged between 38 and 57 years). Progression of JSN was further associated with worsened pain and function.

We demonstrated progression of radiographic hand OA in the majority of our cohort after only 2 years, which was more than previously described in another study (65% and 32% vs 21.5% and 19.2%, for OP and JSN, respectively).⁸ Unlike the previous study, we scored the radiographs in known time order, which has been found to be more sensitive to change than scoring with an unknown time sequence.³⁶ The previous study concerned a population of siblings with hand OA, where genetics may have a more pronounced effect. Many participants not seeking medical care were identified and included through their sibling, and this could have led to less severe disease on average. These factors may help explain the differences observed.

We saw progression of OP more frequently than progression of JSN. This could be driven by differences in the reliability of scoring, shown by the cut-off of 1 for OP changes and 2 for JSN changes. JSN measurements assess the ‘empty’ space between the articulating bones on the radiograph, which consists of radio-translucent matter and includes synovial fluid and cartilage. As such, the increase (effusion) and decrease (loss of cartilage) in joint space width could both be pathological.³⁷ These factors could help explain the 4% of our population with a decrease in JSN over 2 years and could also explain the difference in reliability of scoring JSN compared with OP.

Our study adds to the existing body of evidence regarding factors associated with radiographic progression of hand OA. Most previous studies investigated longer time periods, up to 12 years. Our study adds valuable new data on the short term, which is closer to follow-up durations for trials. To our knowledge, our study is the first to investigate IP OA and thumb-base OA separately in addition to hand OA. Previous epidemiological studies have provided evidence that indicates age, female sex, menopausal changes, BML, synovitis, pain, erosive disease, baseline radiographic damage and BMLs, smoking and diabetes mellitus as potential risk factors.^{8–10 13 16 23–25 38–43} Not all these factors were found

to be associated with progression in our analyses, but we reaffirmed associations with baseline damage (both OP and JSN progression), erosive disease (OP progression, stronger in the IP joints), BMLs (OP progression in the IP joints), age (OP progression) and female sex (osteophyte progression in the thumb-base). We further found a negative association with symptom duration (both OP and JSN progression).

In the current study, MRI was used to assess the presence of synovitis and BMLs. If specific treatment for erosive hand OA (or other pathologies associated with specific MRI-detected lesions) becomes available, MRI could be of added value in the clinic, but currently its main use is in research.^{7 44} Especially smaller, handheld MRI scanners could provide benefits in this setting.

We took particular interest in the role of the perimenopausal period. There is substantial but circumstantial, cross-sectional evidence for an increase in OA development in the perimenopausal phase, with the biological mechanisms still unknown.^{17–22} A direct association between the perimenopausal state and progression of OP was not found in our study, unlike previous work in siblings with hereditary hand OA.⁸ We used a cut-off of 10 years to allow for better comparison with previous work and to provide a high certainty of excluding most perimenopausal women from the postmenopausal group. Our data on menopausal state are based on recalled age of entering the menopause. With an average of 10 years since the start of the menopause, this may have obscured associations. We examined the association of baseline structural damage with change in structural damage in females stratified by tertiles of age. There was a clear attenuation of the association between baseline OP score and change in OP score with age, whether looking at all hand joints, the IP joints or the thumb-base joints. This could be due to changes occurring during that lowest tertile, ranging from ages 37 to 57 years. This age range overlaps with the median age at the start of perimenopause (45–55 years).⁴⁵ Alternatively, this could reflect that structural progression in hand OA has a natural upper limit, with progression slowing down in older patients or as the disease progresses. It might also represent a ceiling effect in the OP and/or JSN scoring systems used. Both of these reasons could also explain the negative associations seen with age and symptom duration for OP and JSN progression. It is in accordance with previous studies

Table 5 Associations with progression of joint space narrowing of all joints in both hands

	OR (95% CI)		
	Bilateral hands	Bilateral IP joints	Bilateral thumb-base joints
	Increase (n=135)	Increase (n=169)	Increase (n=97)
Patient characteristics			
Female sex*	0.99 (0.53 to 1.91)	1.25 (0.67 to 2.36)	0.80 (0.42 to 1.60)
Age†	1.01 (0.98 to 1.04)	1.01 (0.99 to 1.04)	1.02 (0.99 to 1.05)
BMI‡	0.97 (0.92 to 1.02)	0.98 (0.93 to 1.02)	0.99 (0.94 to 1.04)
Presence of any comorbidities	0.95 (0.60 to 1.51)	0.94 (0.60 to 1.46)	1.20 (0.73 to 1.97)
Diabetes	1.63 (0.69 to 3.81)	1.42 (0.62 to 3.28)	0.93 (0.31 to 2.43)
Perimenopausal state*§	1.34 (0.61 to 3.02)	1.24 (0.59 to 2.64)	0.64 (0.28 to 1.47)
Radiographic characteristics			
KL sum score	1.02 (1.00 to 1.04)	1.02 (1.00 to 1.05)	1.24 (1.06 to 1.46)
Group 1	1	1	1
Group 2	1.62 (0.76 to 3.56)	1.79 (0.91 to 3.60)	2.17 (0.91 to 5.81)
Group 3	2.14 (0.98 to 4.82)	1.53 (0.74 to 3.22)	6.48 (2.56 to 18.3)
Group 4	2.32 (0.97 to 5.70)	2.34 (1.00 to 5.62)	–
Baseline osteophytes¶			
Group 1	1	1	1
Group 2	1.12 (0.51 to 2.47)	1.45 (0.71 to 2.99)	3.29 (1.56 to 7.38)
Group 3	1.55 (0.73 to 3.34)	2.17 (1.04 to 4.62)	7.05 (3.12 to 17.0)
Group 4	1.72 (0.74 to 4.10)	2.30 (0.98 to 5.49)	–
Baseline joint space narrowing			
Group 1	1	1	1
Group 2	3.03 (1.40 to 7.04)	3.74 (1.83 to 8.21)	2.16 (1.45 to 4.79)
Group 3	6.33 (2.96 to 14.6)	6.73 (3.22 to 15.1)	3.80 (2.03 to 7.25)
Group 4	6.18 (2.82 to 14.6)	6.01 (2.84 to 13.6)	–
Erosive disease	1.14 (0.61 to 2.17)	1.68 (0.89 to 3.20)	1.41 (0.83 to 2.37)
Presence of synovitis in IP joints of the right hand on MRI at baseline	0.72 (0.34 to 1.47)	1.12 (0.58 to 2.14)	0.89 (0.40 to 1.88)
Presence of bone marrow lesions in IP joints of the right hand on MRI at baseline	0.79 (0.38 to 1.60)	1.01 (0.53 to 1.93)	1.12 (0.54 to 2.28)
Disease characteristics			
Symptom duration (years)	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.02)	1.01 (0.98 to 1.04)
<2.00	1	1	1
>1.99 and <5.40	0.49 (0.25 to 0.98)	0.62 (0.33 to 1.18)	0.98 (0.45 to 2.13)
>5.39 and <12.57	0.58 (0.29 to 1.11)	0.68 (0.36 to 1.28)	1.18 (0.56 to 2.50)
>12.56	0.63 (0.31 to 1.23)	0.63 (0.33 to 1.20)	1.30 (0.61 to 2.79)
Tender joint count	0.99 (0.95 to 1.04)	0.99 (0.95 to 1.04)	1.03 (0.98 to 1.08)
Concomitant knee/hip OA	1.14 (0.69 to 1.86)	1.04 (0.65 to 1.67)	0.98 (0.57 to 1.65)
Patient-reported outcome measures			
AUSCAN at baseline			
Pain	1.00 (0.94 to 1.05)	1.03 (0.98 to 1.08)	1.01 (0.95 to 1.07)
Function	1.00 (0.97 to 1.02)	1.01 (0.99 to 1.04)	1.00 (0.97 to 1.04)
Change in AUSCAN baseline-year 2			
Pain	1.06 (1.00 to 1.13)	1.03 (0.98 to 1.10)	1.03 (0.96 to 1.10)

Continued

Table 5 Continued

	OR (95% CI)		
	Bilateral hands	Bilateral IP joints	Bilateral thumb-base joints
	Increase (n=135)	Increase (n=169)	Increase (n=97)
Function	1.06 (1.02 to 1.11)	1.04 (1.01 to 1.08)	1.02 (0.98 to 1.07)

Associations with change in joint space narrowing.

Groups defined according to smallest detectable change in joint space narrowing sum score, being two for the whole hand and one for IP and thumb-base joints.

Index groups are the stable/decrease groups for the corresponding joint group.

Models are adjusted for age, sex, BMI and baseline osteophytes, unless stated otherwise.

For tertile groupings of baseline radiographic score, see online supplemental table A1.

*Adjusted for age, BMI and baseline joint space narrowing.

†Adjusted for sex, BMI and baseline joint space narrowing.

‡Adjusted for age, sex and baseline joint space narrowing.

§Only in females; perimenopausal state=10 or less years since start of the menopause.

¶Adjusted for age, sex and BMI.

AUSCAN, Australian Canadian Osteoarthritis Hand Index; BMI, body mass index; IP, interphalangeal; KL, Kellgren-Lawrence; OA, osteoarthritis.

describing low levels of progression in patients over 75 years and is further supported by the data on age and symptom duration presented here in our cohort, which contains younger patients.⁴³ The effect of the perimenopause on hand OA progression warrants further investigation, preferably combining epidemiological data with biological information including hormone levels.

We found a positive association between erosive disease and progression of OP, but not JSN. This may indicate that progression of OP and JSN may depend on different factors, representing different underlying processes or points in time. An association between erosive disease and OP progression, but not JSN progression, fits with the evolution of anatomic phases of OA as described by Verbruggen and Veys.³² In this model, erosive disease (possibly with the occurrence of BMLs) occurs after the loss of joint space and is followed by rapid development of large OP. Erosive disease would then be associated with an increase in OP, but not JSN. Pseudo-widening of the joint space has been described as part of the same anatomic phase, explaining the occasional finding of a decreased JSN score. Erosive OA is regarded as a disease of the IP joints, and a lack of associations with thumb-base OA has been described previously and was confirmed here.^{2,46} Inversely, the stronger association seen in IP OA also fits with this model and was shown in our data. To our knowledge, we are the first to confirm this for the joints groupings of the 2023 EULAR criteria.

In the thumb-base joints, we found a stronger association between female sex and progression of OP than in the other subtypes. Given the positive association between thumb-base OA and mechanical loading (which is usually higher in men due to their occupation), this was unexpected.⁴⁷ Further research into the effects of mechanical loading on thumb-base OA in females may be warranted.

We also found a positive association between changes in JSN and changes in pain and function. It has to be noted that this association should not be interpreted as a risk factor, as the change in structural damage and symptoms occurs simultaneously, as opposed to symptoms measured at baseline. Previous studies showed associations between the development of tenderness and progression of structural damage, cross-sectional associations between radiographic damage and symptoms on the patient level and an association between baseline pain and radiographic progression after 6 years.^{10,38} Together, these data indicate that symptoms are at least in part dependent on structural damage. With the large number of joints involved in hand OA, the association between radiographic findings and symptoms can be difficult to measure, as changes in one or two joints may not be reflected in changed symptoms. However, from the patient perspective, pain or function in the complete hand is most relevant. As such, this remains a highly relevant subject for further investigations.

Our study leveraged a large sample, selected only on the presence of primary hand OA, excluding other causes of pain in the hands. It should be noted that our sample was collected from a secondary/tertiary rheumatology outpatient clinic, meaning there may be an over-representation of patients with more severe or inflammatory hand OA who have been referred by their general practitioner. This may have led to a higher incidence of progression in this study. Furthermore, due to investigating progression of structural damage in the hand joints in a cohort of hand OA patients, which is essentially in part selected on having structural damage in the joints of the hand, collider stratification bias may have occurred. This could bias the associations towards null.^{48,49} We also lacked information (eg, hormonal status) to investigate the effects of

the perimenopause in more detail. The MR images used in this study were made without use of contrast fluid and only scored in the right PIP and DIP joints. Using contrast fluid may further enhance precision of scoring, and scoring both hands may lead to more precise effect estimates as opposed to extrapolating the findings in only the right hand. Another limitation lies in the sex distribution in our cohort, which consists of primarily women. Although this may provide a truthful representation of the entire hand OA patient population, this may have biased our results and limited generalisability to individual males. A similar limitation regarding generalisability may arise from our data on comorbidities. We found that fewer than 50% of participants had one or more comorbidities, which is lower than that observed in other cohorts.^{50 51} This may be due to differences in data collection, including which comorbidities are documented. Finally, these results require validation in other cohorts and cannot be interpreted causally due to potential residual confounding. For example, we could not take hand usage in labour and hand dominance into consideration.

It is essential to emphasise that it is unclear whether the associations between baseline radiographic damage and progression of radiographic damage (either OP or JSN) represent causal relationships. It may be that underlying factors that lead to rapid progression also lead to more damage at a given moment, with all other factors being equal between two patients. These underlying factors require further elucidation. Furthermore, an effect due to the mathematical properties of the change scores, which are in part derived from the baseline scores, cannot be excluded. We did try to correct for this by adjusting for the baseline scores in our models.

To conclude, we reaffirmed the association between baseline radiographic damage and progression of OP and JSN in a large cohort, to which we added that the same is seen in the different subtypes classified by the new EULAR criteria. New, subtype-specific associations were also found. The association of baseline OP and OP progression attenuated with age in females. The presence of erosive disease was associated with OP progression in the IP joints. This information may be used to guide patient selection for future trials investigating potential DMOADs.

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