

## EXTENDED REPORT

# Clustering of hand osteoarthritis progression and its relationship to progression of osteoarthritis at the knee

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**ABSTRACT**

**Objective** To investigate patterns of osteoarthritis (OA) progression within hand joints and the relationship between hand OA progression and progression of OA at the knee.

**Methods** Radiographic progression over 6 years, defined as change in osteophytes or joint space narrowing above the smallest detectable change, was assessed on hand and knee radiographs of 236 hand OA patients participating in the Genetics, Arthrosis and Progression (GARP) sibling pair cohort study using OARS atlas. Clustering of radiographic progression between hand joint groups (DIP, PIP, IP-1 and CMC-1) was assessed using  $\chi^2$  test. Symmetry, clustering by row and ray and familial aggregation in sibling pairs were also evaluated. The association between hand OA progression and progression of OA at the knee was assessed using generalised estimating equation analysis.

**Results** There was clustering of OA progression between hand joint groups, the strongest relationship among DIP, PIP and IP-1 joints. Other patterns were symmetry (OR 4.7 (95% CI 3.3 to 6.5)) and clustering by row (OR 2.9 (95% CI 1.9 to 4.6)) but not by ray (OR 1.3 (95% CI 0.7 to 2.4)). There was familial aggregation of hand OA progression. Patients with progression of hand OA had a higher risk for radiographic change at the knee than those without hand OA progression (OR 2.3 (95% CI 1.3 to 4.0)).

**Conclusions** Progression of hand OA clusters between hand joint groups, especially between IP joints, and within sibling pairs. It is associated with OA change at the knee. These findings contribute to defining hand OA subsets and suggest a role for systemic factors.

**INTRODUCTION**

Hand osteoarthritis (OA) is a common musculoskeletal disorder characterised by degradation of cartilage and abnormalities in subchondral bone leading to pain and disability.<sup>1</sup> It is a heterogeneous disease depicted by, for example, the involvement of multiple hand joints, the presence of several subsets and the variable course over time with some patients experiencing rapid progression and others remaining relatively stable over time.<sup>2</sup>

Hand OA often affects multiple hand joints, and several studies have shown symmetry as the strongest pattern of joint involvement (ie, involvement of the same joint from the left and right hands), followed by clustering by row (ie, involvement of several distal interphalangeal (DIP) or proximal

interphalangeal (PIP) joints) and by ray (ie, DIP/PIP joint involvement of the same digit).<sup>3–5</sup> This has been found for radiographic as well as symptomatic hand OA. These patterns of joint involvement teach us about the aetiology of hand OA. In the studies mentioned, symmetry was the strongest pattern, and it is therefore suggested that systemic factors may play a more important role than mechanical factors. All data on this topic are cross-sectional, and it is unclear whether these patterns are also involved in the course of OA in hand joints over time.

Apart from clustering of OA within the hand, hand OA occurs with OA at other joint sites.<sup>6–9</sup> The strongest and most consistent association has been found between the presence of hand OA and the presence or future occurrence of knee OA. To allow for better identification of individuals at risk of OA progression, the association between progression at the two joint sites is of interest. It has implications for conducting clinical trials as well as for clinical practice. The relationship between progression at the hand and the knee, conducted in the general population, is assessed in only one study.<sup>10</sup>

Knowledge on the patterns of OA progression within hand joints and progression of hand OA in relation to progression of OA at other joint sites gives insight in the complex aetiology of hand OA. This has implications for hand OA treatment. Therefore, we investigated the patterns of OA progression within hand joints as well as the relationship between hand OA progression and progression of OA at the knee in a cohort of hand OA patients followed for 6 years. Because the population comprises sibling pairs, it was possible to assess the role of familial factors in hand OA progression.

**PATIENTS AND METHODS****Study design and patient population**

The Genetics, Arthrosis and Progression (GARP) study is a cohort study aimed at identifying determinants of OA susceptibility and progression. The study population comprises 192 Caucasian sibling pairs with symptomatic OA at multiple sites in the hand or in at least two of the following sites: hand, knee, hip or spine. Details about the recruitment and inclusion have been published elsewhere.<sup>11</sup> The GARP study was approved by the Medical Ethics Committee of the Leiden University Medical Center. Written informed consent was obtained.

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## Clinical and epidemiological research

Patients were included for baseline assessment between August 2000 and March 2003. From April 2007 to June 2008, participants who consented for a follow-up evaluation were assessed. All consenters completed questionnaires, and most of them visited the outpatient clinic for physical examination and radiographic evaluation.

Patients were eligible for the present study if they had hand OA, defined according to the American College of Rheumatology criteria for clinical hand OA,<sup>12</sup> or if structural abnormalities were present. Structural abnormalities were defined as the presence of radiographic hand OA based on a Kellgren–Lawrence score of  $\geq 2$  in at least one IP or first carpometacarpal (CMC-1) joint or the presence of at least two joints with Heberden or Bouchard nodes. Knee OA was defined as a Kellgren–Lawrence score of  $\geq 2$  in the tibiofemoral joints.

### Radiographic assessment

Standardised radiographs of the hands (dorsal–volar) and knees (posterior–anterior weight bearing, non-fluoroscopic fixed-flexion protocol) were obtained at baseline and followed up by a single radiographer, employing a standard protocol to ensure consistent joint positioning with fixed film focus distance (1.15 m (hands)).

Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB and IW) scoring together to obtain one score. To avoid bias, radiographs for hand and knee were scored on separate occasions. Osteophytes and joint space narrowing (JSN) were graded 0–3 using the Osteoarthritis Research Society International (OARSI) atlas in the DIP, PIP, first IP (IP-1), CMC-1, metacarpophalangeal and scaphotrapeziotrapezoidal joints and medial and lateral compartments of the tibiofemoral joints.<sup>13</sup> Reproducibility based on 25 randomly selected pairs of radiographs was good with intraclass correlation coefficients (ICCs) for osteophytes and JSN of 0.94 and 0.87 in the hands and 0.99 and 0.98 in the knees, respectively (see online supplementary appendix 1 for ICCs for separate hand joint groups).

### Definition of radiographic progression

For osteophytes and JSN, the smallest detectable change (SDC), calculated as  $1.96 \times SD_{\Delta(\text{change scores})} / \sqrt{2}$ , was used to assess change above measurement error.<sup>14</sup> Radiographic progression was assessed in all hand joints together, separate hand joint groups (DIP, PIP, IP-1 and CMC-1) and the knees and was defined as a change in total score for osteophytes or JSN above the SDC (see online supplementary appendix 1 for SDCs). Patients without radiographic end-stage disease at baseline who received knee prosthesis during follow-up were considered to have radiographic progression in that joint.

### Statistical analysis

Data were analysed using SPSS V.17.0 (SPSS Inc, Chicago, Illinois, USA). The number of patients with radiographic progression of hand OA was assessed, as well as the number of patients with radiographic progression at hand joint groups (patient level) and the number of joints with radiographic progression within each hand joint group (joint level).

We tested whether progression of hand OA clusters in hand joint groups (DIP, PIP, IP-1 and CMC-1) within a patient. If clustering is present, this means that progression between the hand joint groups is more likely to occur than expected just by chance. To test for clustering, we first obtained the prevalence of progression for each joint group by dividing the number of joints with

progression within one group by the total number of joints in that group. Using these prevalences, the number of patients expected to have progression in 0, 1, 2 or at least 3 joint groups was calculated, assuming that progression between the different joint groups is independent. These were compared with the observed frequencies using the  $\chi^2$  test. We assessed the relationship between the specific hand joint groups using generalised estimating equation (GEE) models with robust variance estimators to account for family effects within sibling pairs with adjustment for age, sex and body mass index (BMI). Other patterns of progression we assessed using GEE models were symmetry and clustering by row and ray. We defined symmetry as the same joint on the left and right hands. We defined row as DIP or PIP joints in different digits of the same hand and ray as DIP and PIP joints on the same digit. Clustering by row or ray means evaluating whether the progression is more present in that row or ray compared with the other joints. Adjustments were made for age, sex and BMI.

In addition, we assessed whether familial factors play a role in hand OA progression by comparing siblings of probands with and without progression of hand OA. This analysis requires availability of follow-up data for proband and sibling. ORs were estimated for hand OA progression in the siblings, given hand OA progression in probands, using logistic regression analyses with adjustment for age, sex and BMI.

The risk of radiographic progression at the knee, given progression of OA in the hand, was assessed using GEE analysis with corrections for age, sex and BMI, in the total hand OA population as well as in hand OA patients with and without knee OA at baseline separately.

## RESULTS

### Study population

Of the 357 patients fulfilling the hand OA criteria at baseline, 300 (84%) consented for the follow-up study, of which 242 visited the outpatient clinic and 58 completed questionnaires only. Consent was not given by 43 (12%) patients, 12 (3.3%) were deceased and 2 (0.6%) were lost to follow-up. Reasons for non-consent are listed elsewhere.<sup>2</sup> Of the 242 eligible patients, 236 had complete radiographic data and were included in the present study. The mean follow-up time was 6.1 years (range 5.0–7.8 years). There were 87 sibling pairs with follow-up data for proband and sibling for the analysis on familial aggregation.

Baseline characteristics are shown in table 1. The 87 sibling pairs did not differ from the whole-patient group, and there were no differences between probands and siblings. Patients not included in the present study were somewhat older. Other parameters did not differ between consenters and non-consenters.

**Table 1** Baseline characteristics of 236 hand OA patients

Age, years, mean (SD)	58.9 (7.1)
Women, n (%)	196 (83)
Postmenopausal women, n (%)	176 (90)
Body mass index (kg/m <sup>2</sup> ), mean (SD)	27.1 (5.0)
ACR criteria hand OA, n (%)	183 (78)
Knee OA*	90 (38)
Osteophytes hand (0–96), mean (SD)	10.7 (8.2)
Joint space narrowing hand (0–96), mean (SD)	19.1 (11.3)

\*Defined as Kellgren–Lawrence score  $\geq 2$ .  
ACR, American College of Rheumatology; OA, osteoarthritis.

**Table 2** Distribution of progression of hand osteoarthritis (OA) in hand joint groups over 6 years in 236 hand OA patients

	Radiographic progression, n (%)	Osteophyte progression, n (%)	Joint space narrowing progression, n (%)
Patient level			
DIP joints	98 (41.5)	73 (30.9)	53 (22.5)
PIP joints	69 (29.2)	67 (28.4)	24 (10.2)
IP-1 joints	66 (28.0)	49 (20.9)	29 (12.3)
CMC-1 joints	84 (35.6)	66 (28.0)	42 (17.8)
MCP joints	31 (13.1)	19 (8.1)	16 (6.8)
STT joints	30 (12.8)	6 (2.6)	27 (11.5)
Total	124 (52.5)	106 (44.9)	61 (25.8)
Joint level			
DIP joints (n=1886)	184 (9.8)	128 (6.8)	86 (4.6)
PIP joints (n=1881)	120 (6.4)	102 (5.4)	41 (2.2)
IP-1 joints (n=471)	77 (16.3)	52 (11.0)	36 (7.6)
CMC-1 joints (n=466)	103 (22.1)	77 (16.5)	49 (10.5)
MCP joints (n=2359)	44 (1.9)	25 (1.1)	26 (1.1)
STT joints (n=471)	32 (6.8)	7 (1.5)	29 (6.2)
Total (n=7534)	560 (7.4)	391 (5.2)	267 (3.5)

CMC-1, first carpometacarpal; DIP, distal interphalangeal; IP-1, first interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; STT, scaphotrapezotrapezoidal.

### Patterns of radiographic progression of hand OA

Over 6 years, radiographic progression in the hand was present in 124 (52.5%) patients. Progression of osteophytes and JSN was present in 106 (44.9%) and 61 (25.8%) patients, respectively. Table 2 shows that at the patient level, progression was most frequent in DIP joints followed by the CMC-1 and PIP joints. However, at the joint level, progression was most frequent in CMC-1 and IP-1 joints (table 3). Baseline osteophytes and JSN scores and their distribution among hand joint groups are provided in online supplementary appendix 2.

There was clustering of progression between hand joint groups. Table 4 shows the distribution of the observed and the expected number of patients with radiographic progression for the number of hand joint groups ( $p < 0.001$ ). Especially in the 2 and  $\geq 3$  hand joint groups involved category, the observed number of patients is higher than expected. The relationship between specific hand joint groups shows that all joint groups contributed to this clustering (table 5). The strongest relationship was between the IP joint groups.

Another pattern for progression of hand OA was symmetry with an overall OR of 4.7 (95% CI 3.3 to 6.5). There was also clustering by row with an OR of 2.9 (95% CI 1.9 to 4.6) but not by ray (OR 1.3 (95% CI 0.7 to 2.4)).

The adjusted OR for a sibling having hand OA progression if the proband had progression of hand OA was 3.0 (95% CI 1.2 to 7.5).

### Radiographic progression of hand OA in relation to knee OA

Among the 90 patients with knee OA at baseline, 67 (74.4%) had radiographic progression and among the 146 patients without knee OA at baseline, radiographic change was present in 42 (28.8%) patients, giving a total of 109 patients with progression at the knee.

The relationship between hand OA progression and progression of OA in the knee is shown in table 6. Overall, patients with progression of hand OA had a higher risk for radiographic change at the knee than patients without hand OA progression (OR 2.3 (95% CI 1.3 to 4.0)). For the patients with knee OA at

**Table 3** Distribution of changes in osteophytes and joint space narrowing of the hand over 6 years in 236 hand osteoarthritis patients

	$\geq -1$	0	1	2	3
Osteophytes					
DIP joints	3 (0.2)	1755 (93.1)	112 (5.9)	16 (0.8)	
PIP joints	2 (0.1)	1777 (94.5)	85 (4.5)	16 (0.8)	1 (0.1)
IP-1 joints	1 (0.2)	418 (88.7)	50 (10.6)	2 (0.4)	
CMC-1 joints		389 (83.5)	69 (14.8)	8 (1.7)	
MCP joints	2 (0.1)	2332 (98.9)	23 (1.0)	2 (0.1)	
STT joints	2 (0.4)	462 (98.1)	7 (1.5)		
Joint space narrowing					
DIP joints	29 (1.5)	1771 (93.9)	68 (3.6)	17 (0.9)	1 (0.1)
PIP joints	12 (0.7)	1828 (97.2)	27 (1.4)	14 (0.7)	
IP-1 joints	3 (0.6)	432 (91.7)	32 (6.8)	4 (0.8)	
CMC-1 joints	11 (2.3)	406 (87.1)	46 (9.9)	3 (0.6)	
MCP joints	1 (0.0)	2332 (98.9)	21 (0.9)	5 (0.2)	
STT joints	1 (0.4)	462 (98.1)	7 (1.5)		

The numbers in the table represent the number of joints with corresponding change (ranging from  $-1$  or more to 3) for each hand joint group.

CMC-1, first carpometacarpal; DIP, distal interphalangeal; IP-1, first interphalangeal; MCP, metacarpophalangeal; PIP, proximal interphalangeal; STT, scaphotrapezotrapezoidal.

## Clinical and epidemiological research

**Table 4** Observed and expected number of patients with radiographic progression in hand joint groups over 6 years in 236 hand osteoarthritis patients

Number of hand joint groups*	Observed	Expected
0	112	130
1	33	58
2	49	37
≥3	42	11
$\chi^2$	104.52	
p Value	<0.001	

\*Hand joint groups: DIP, PIP, IP-1 and CMC-1 joints. CMC-1, first carpometacarpal; DIP, distal interphalangeal; IP-1, first interphalangeal; PIP, proximal interphalangeal.

baseline, a similar OR was found. In the patients without knee OA at baseline, those with progression of hand OA had a higher risk for the development of radiographic OA in the knee than those without hand OA progression (OR 2.7 (95% CI 1.3 to 5.9)).

The presence of knee OA at baseline was not associated with progression of hand OA (OR 1.1 (95% CI 0.6 to 1.9)).

## DISCUSSION

This study shows that progression of hand OA clusters between hand joint groups as well as in a symmetrical pattern and in rows but not in rays. Also, there was clustering of hand OA progression within sibling pairs. Patients with progression of hand OA over 6 years had a higher risk for radiographic change at the knee compared with those without hand OA progression. Separate analysis in those with and without knee OA at baseline showed similar results. These findings give insight in the complex aetiology of hand OA, suggesting that systemic rather than mechanical factors play a role.

Radiographic progression of hand OA was present in half of the patients. At the patient level, progression was most frequent in the DIP joints followed by the PIP and CMC-1 joints. However, at the joint level, progression was by far the most prevalent in the CMC-1 followed by the IP-1 joints. This difference is explained by the higher number of joints and thus higher chance of progression in the DIP and PIP joints. This may imply that progression at joint level is a better reflection of the true progression. Our findings are in line with the Framingham OA Study on progression of hand OA over a period of 9 years, showing that the most radiographic progression was present at the CMC-1 joint.<sup>15</sup> These findings suggest that thumb base OA is more progressive than IP OA and may

**Table 6** Relationship between progression of hand OA and knee OA

	OR (95% CI)	
	Crude	Adjusted*
All hand OA patients (n=236)	2.0 (1.2 to 3.3)	2.3 (1.3 to 4.0)
Hand OA patients with knee OA at baseline (n=90)	2.0 (0.8 to 5.3)	2.5 (0.9 to 6.9)
Hand OA patients without knee OA at baseline (n=146)	2.4 (1.1 to 5.0)	2.7 (1.3 to 5.9)

ORs relate to radiographic change at the knee for patients with hand OA progression versus those without hand OA progression.

\*Adjusted for age, sex, BMI and family effects within sibling pairs. OA, osteoarthritis.

represent a subset of hand OA with worse outcome. This contributes to the characterisation of hand OA subsets.<sup>16 17</sup>

A number of cross-sectional studies assessed the clustering of hand OA in both radiographic and symptomatic hand OA.<sup>3-5</sup> They all showed that symmetry was the strongest pattern of joint involvement, followed by clustering by row and ray. This is in line with our findings on clustering of hand OA change over time. In the Framingham OA Study mentioned above, it was found that the incidence of hand OA occurred in a symmetrical way.<sup>15</sup> These findings suggest that systemic factors are involved in the progression of hand OA and are more important than mechanical factors. It is known that systemic factors play a role in the development of hand OA,<sup>18 19</sup> and evidence for the involvement in hand OA progression is growing. In the GARP study, for example, we showed that accelerated localised bone mineral density loss, indicating inflammatory activity, was related to progression of hand OA<sup>20</sup> as well as the adipokine adiponectin.<sup>21</sup>

We found the strongest clustering among the DIP, PIP and IP-1 joints, suggesting that the IP-1 joint can be regarded as IP joint instead as part of the thumb. This is in line with Egger *et al*<sup>3</sup> who found that the association between OA presence at the DIP/PIP and the IP-1 joints was stronger than that at the CMC-1 and IP-1 joints. However, principal component analysis by Marshall *et al*<sup>22</sup> showed that the IP-1 joint grouped with the CMC-1 joint. Although there is inconsistent evidence, we think the IP-1 joint should be regarded as an IP joint.

We also found that familial factors play a role in hand OA progression, although we did not specifically assess familial factors in relation to the patterns of hand OA progression. This familial aggregation suggests involvement of genetic factors in OA progression. It is well known that genetic factors influence OA susceptibility.<sup>23 24</sup> However, their role in the disease course is still unclear.

**Table 5** Association between radiographic progression at specific hand joint groups over 6 years in 236 hand osteoarthritis patients

Joint groups	Radiographic progression OR (95% CI)*	Osteophyte progression OR (95% CI)*	JSN progression OR (95% CI)*
DIP-PIP	5.4 (2.9 to 10.3)	4.5 (2.4 to 8.3)	4.4 (1.5 to 13.0)
DIP-IP1	5.1 (2.6 to 9.9)	2.6 (1.2 to 5.4)	7.1 (2.8 to 17.7)
DIP-CMC-1	4.4 (2.4 to 8.0)	4.2 (2.1 to 8.3)	6.3 (2.4 to 16.5)
PIP-IP-1	5.5 (2.8 to 10.7)	6.3 (3.2 to 12.8)	4.5 (1.5 to 13.6)
PIP-CMC-1	4.6 (2.5 to 8.6)	3.0 (1.5 to 6.0)	12.8 (4.2 to 38.6)
IP-1-CMC-1	3.9 (2.0 to 7.7)	3.1 (1.4 to 6.6)	3.8 (1.4 to 10.8)

\*Adjusted for age, sex, BMI and family effects within sibling pairs.

CMC-1, first carpometacarpal; DIP, distal interphalangeal; IP-1, first interphalangeal; JSN, joint space narrowing; PIP, proximal interphalangeal.

We showed that patients with progression of hand OA over 6 years had a higher risk for radiographic change at the knee than those without hand OA progression, independent of BMI. This again indicates that systemic factors may play a role in hand OA, because in active disease, there is progression of OA signs not only at the hand but also at another joint site. To our knowledge, there is only one other study that assessed the relationship between progression of OA at the hand and at the knee.<sup>10</sup> This study by Hassett *et al*, over a period of 10 years, showed that progression of knee osteophytes or JSN was not related to progression of hand osteophytes or JSN. The effect sizes for osteophyte progression were similar to our results. A general population study by Dahaghin *et al*<sup>9</sup> showed that the presence of hand OA at baseline was a risk factor for the future occurrence of knee OA. A number of cross-sectional studies found an association between the presence of hand and knee OA, with the strongest relationship in women.<sup>6–8</sup> Since we had a study population selected on the presence of hand OA, it was not possible to evaluate this cross-sectional relationship.

JSN is a widely accepted measure of articular cartilage loss. However, for osteophytes, it is shown that in the absence of other structural abnormalities on radiographs, they may reflect the sole effect of ageing.<sup>25</sup> In our study, all patients with progression of osteophytes also had progression of JSN or JSN present at baseline. This implies that in our study, osteophytes can be regarded as OA feature and not only the effect of ageing.

For clinical practice, these findings imply that hand OA patients with progression are at risk for OA changes at the knee and maybe other joints as well. Thus, not only hand joints but also other joint sites, in particular the knee, should be evaluated at baseline and follow-up visits. Furthermore, the contribution of our study to the emerging evidence of the role for systemic and metabolic factors in the pathogenesis of hand OA may contribute to the development of new treatment strategies.

There are a number of potential limitations to this study. First, the possibility of bias due to differences between consenters and non-consenters. However, only age was different between these groups and the baseline radiographic scores did not differ so we expect no effect on study outcome. Radiographic follow-up data were not available in all patients since only a proportion of patients completed questionnaires. Baseline radiographic scores did not differ between those with and without complete data, indicating that selection bias is probably absent. Second, we investigated patients with familial OA at multiple sites. Although we corrected part of our analysis for familial effects, this is a specific phenotype with probably stronger genetic influences. Whether the results can be generalised to patients with other hand OA phenotypes have to be investigated. Although the hand OA patients had other sites involved, we only assessed the relationship with knee OA. Hip OA was present in around 20% of the patients, and therefore patient numbers were too small to draw meaningful conclusions. Third, almost all women were postmenopausal, making it impossible to assess hormonal influences. Finally, apart from genetic factors, shared environmental influences may also explain the familial aggregation we found. By including only one sibling per proband, we minimised this effect.

In conclusion, this study gives insight in the complex aetiology of hand OA by showing that its progression clusters between hand joint groups, especially the IP joints, as well as with change of OA at the knee, and that familial factors are involved, suggesting a role for systemic factors and genetic influence. Further research on the progression of hand OA in relation to OA changes at other joint sites is needed to confirm and

extend our findings. These findings contribute to unravelling the pathogenesis of hand OA and to the defining hand OA subsets, which is of importance when development of new treatment strategies is concerned.

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## Clustering of hand osteoarthritis progression and its relationship to progression of osteoarthritis at the knee

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