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## **Hand osteoarthritis : natural course and determinants of outcome**

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## CLUSTERING OF HAND OSTEOARTHRITIS PROGRESSION AND ITS RELATIONSHIP TO PROGRESSION OF OSTEOARTHRITIS AT THE KNEE

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## **ABSTRACT**

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

**Methods.** Osteophytes and joint space narrowing (JSN) were scored at baseline and after 6 years on hand and knee radiographs of 236 hand OA patients (mean age 59 years, 83% women) participating in the Genetics ARthrosis and Progression (GARP) sibling pair study. Radiographic progression was defined as change in osteophytes or JSN above the smallest detectable change. Clustering of radiographic progression between hand joint groups was assessed using a chi-squared 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 equations analysis.

**Results.** There was clustering of OA progression between hand joint groups. Other patterns were symmetry (OR (95%CI) 4.7 (3.3 to 6.5)) and clustering by row (OR (95%CI) 2.9 (1.9 to 4.6)), but not by ray (OR (95%CI) 1.3 (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 (95%CI) 2.3 (1.3 to 4.0)), which was also found in separate analyses in those with and without knee OA at baseline.

**Conclusion.** Progression of hand OA clusters between hand joint groups, within sibling pairs and is associated with change of OA at the knee, suggesting 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 as we showed previously.<sup>2</sup>

Hand OA often affects multiple hand joints with symmetry as the strongest pattern of joint involvement, followed by clustering by row and clustering by ray.<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. Symmetry was the strongest pattern suggesting that systemic factors may play a more important role than mechanical factors. All data on this topic are cross-sectional and it is unclear if 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 hand OA and the presence and future occurrence of knee OA. Only one study, conducted in the general population, assessed the relationship between progression at the two joint sites.<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, particularly the role of systemic factors. From a clinical point of view 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> In brief, probands were recruited from rheumatologists, orthopaedic surgeons and general practitioners. Subsequently, affected siblings were recruited via the probands. Both proband and sibling were required to have OA at multiple sites. The GARP study was approved by the medical ethics committee.

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 some 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 interphalangeal (IP) or first carpometacarpal (CMC-1) joint, or the presence of at least two joints with Heberden's or Bouchard's nodes. Knee OA was defined as a Kellgren-Lawrence score of  $\geq 2$ .

### **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 follow-up by a single radiographer, employing a standard protocol with fixed film focus distance.

Radiographs were scored paired in chronological order blinded for patient characteristics by consensus opinion of two experienced readers (JB, IW). 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 distal interphalangeal (DIP), proximal interphalangeal (PIP), first interphalangeal (IP-1), CMC-1, metacarpophalangeal (MCP) and scaphotrapezotrapezoidal (STT) 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 (ICC) for osteophytes and JSN of 0.94 and 0.87 in the hands and 0.99 and 0.98 in the knees, respectively.

### **Definition of radiographic progression**

For osteophytes and JSN the smallest detectable change (SDC) was used to assess change above measurement error.<sup>14</sup> Progression was assessed in all hand joints together, separate hand joint groups (DIP, PIP, IP-1 and CMC-1 joints) and the knees. Radiographic progression for each of these joint sites was defined as a change in total score for osteophytes or JSN above the SDC. 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, version 17.0 (SPSS, 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 and the number of joints with radiographic progression within each hand joint group.

To test whether progression of hand OA is likely to cluster in multiple hand joint groups of the same patient, we used the prevalence of progression for each hand joint group to calculate the numbers of patients expected to have progression in 0, 1, 2 or at least 3 joint groups, assuming that the occurrence of progression in different joints is independent. Observed frequencies were compared to the expected distribution using the chi-squared test. We assessed the relationship between the specific hand joint groups using generalised estimating equations (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. 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 both proband and sibling. Odds ratios (ORs) were estimated for hand OA progression in 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. We assessed change in osteophytes and JSN at the knee in the total hand OA population as well as in hand OA patients with and without knee OA at baseline, separately.

For all analyses odds ratios (ORs) are reported with 95% confidence intervals (95%CI).

## 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 both 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 (data not shown). Patients not included in the present study were somewhat older. Other clinical and radiographic baseline parameters did not differ between consenters and non-consenters (data not shown).

**Table 1.** Baseline characteristics of 236 patients with hand osteoarthritis (OA).

Age, mean (SD), years	58.9 (7.1)
Women, no (%)	196 (83)
Postmenopausal women, no (%)	176 (90)
Body mass index, mean (SD), kg/m <sup>2</sup>	27.1 (5.0)
ACR criteria hand OA, no (%)	183 (78)
Knee OA*	76 (32)

\*Defined as Kellgren-Lawrence score  $\geq 2$

ACR: American College of Rheumatology

## Patterns of radiographic progression of hand OA

Over 6 years radiographic progression in the hand, defined as a change in osteophytes or JSN above the SDC, 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 joint level progression was most frequent in CMC-1 and IP-1 joints. This difference may be due to the higher number of DIP and PIP joints compared to the CMC-1 and IP-1 joints. The distribution of changes at joint level is shown in table 3.

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

	Radiographic progression, n (%)	Osteophyte progression, n (%)	Joint space narrowing progression, n (%)
<b>Patient level</b>			
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)
<b>Joint level</b>			
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)

Abbreviations: DIP: distal interphalangeal, PIP: proximal interphalangeal, IP-1: first interphalangeal, CMC-1: first carpometacarpal.

**Table 3.** Distribution of changes in osteophytes and joint space narrowing of the hand over 6 years in 236 patients with hand osteoarthritis. The numbers represent the number of joints (%) with corresponding change for each hand joint group.

	≥ -1	0	1	2	3
<b>Osteophytes</b>					
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)	
<b>Joint space narrowing</b>					
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)	

Abbreviations: see table 2.



There was clear evidence for clustering of progression between hand joint groups (table 4). There were 42 patients with progression in at least three hand joint groups, compared with 11 patients expected in this category. The relationship between specific hand joint groups shows that all joint groups contributed to this clustering (table 5). The strongest relationship was between the interphalangeal joint groups.

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

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

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

In total 109 (46.2%) patients had a change in osteophytes or JSN of the knee above the SDC. Of these patients 90 had knee OA at baseline of whom 67 (74.4%) had radiographic progression. Of the 146 patients without knee OA at baseline radiographic change was present in 42 (28.8%) patients.

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

Number of hand joint groups*	Observed	Expected
0	114	130
1	31	58
2	49	37
≥3	42	11
Chi-square	105.79	
p-value	<0.001	

\*Hand joint groups: DIP, PIP, IP-1 and CMC-1 joints.  
Abbreviations see table 2.

**Table 5.** Association between radiographic progression at specific hand joint groups over 6 years expressed as OR (95%CI) in 236 patients with hand osteoarthritis.

Joint groups	Radiographic progression*	Osteophyte progression*	Joint space narrowing progression*
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.  
Abbreviations see table 2.

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 (95%CI) 2.3 (1.3 to 4.0)). For the patients with knee OA at baseline, a similar effect size 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 (95%CI) 2.7 (1.3 to 5.9)).

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

**DISCUSSION**

This study is the first to show 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 to 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 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 joint groups. 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 most radiographic progression was present at the CMC-1 joint.<sup>15</sup> The findings at the joint level suggest that thumb

**Table 6.** Relationship between progression of hand osteoarthritis (OA) and progression of knee osteoarthritis.

Knee OA progression	OR (95%CI)	
	Crude	Adjusted*
<b>All hand OA patients (n=236)</b>		
Absent (n=127)	1	1
Present (n=109)	2.0 (1.2 to 3.3)	2.3 (1.3 to 4.0)
<b>Hand OA patients with knee OA at baseline (n=90)</b>		
Absent (n=23)	1	1
Present (n=67)	2.0 (0.8 to 5.3)	2.5 (0.9 to 6.9)
<b>Hand OA patients without knee OA at baseline (n=146)</b>		
Absent (n=104)	1	1
Present (n=42)	2.4 (1.1 to 5.0)	2.7 (1.3 to 5.9)

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

base OA is more progressive than interphalangeal OA and may represent a subset of hand OA with worse outcome. This contributes to the emerging evidence proposing hand OA subsets based on differences in risk factors, associations and outcomes.<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 clustering by 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 that 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. If mechanical factors would be more important, we would expect clustering by ray to have more influence than symmetry and clustering by row.

It is known that systemic factors play a role in the development of hand OA.<sup>18,19</sup> However, risk factors for the progression of hand OA are less clear and they may differ from those associated with OA susceptibility.<sup>20</sup> Evidence for the involvement of systemic factors in hand OA progression is growing. In the GARP study we showed that over 2 years accelerated localised bone mineral density loss was related to progression of hand OA.<sup>21</sup> Since localised bone mineral density loss in rheumatoid arthritis is associated with progression of joint damage, indicating inflammatory activity, this indicates a role for inflammation in active, progressive hand OA.<sup>22,23</sup> Adipokines are thought to contribute to inflammatory and metabolic processes, although the precise nature of their actions remains unclear.<sup>24</sup> The adipokine adiponectin was associated with progression of hand OA over 6 years in the GARP study.<sup>25</sup> In a systematic review Yusuf et al. found that obesity was associated with the development of hand OA.<sup>26</sup>

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. It is well known that genetic factors influence OA susceptibility.<sup>27,28</sup> However, their role in the disease course is still unclear. We made a first step in assessing this question concerning hand OA by providing evidence for transmission of the progression trait in families. A next step would be to assess specific genetic loci in the progression of hand OA.

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, since in active disease there is not only progression of OA signs 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 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 osteophytes or JSN at the hand. The effect sizes found for progression of osteophytes were similar to our results. A general population study by Dahaghin et al. showed that the presence of hand OA at baseline was a risk factor for the future occurrence of knee OA.<sup>9</sup> 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.

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 a proportion only completed questionnaires. Baseline radiographic scores did not differ between those with and without complete data indicating that selection bias is probably absent. Secondly, we investigated patients with familial OA at multiple sites. Whether the results can be generalised to patients with other hand OA phenotypes has 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. 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 as well as with change of OA at the knee and that familial factors are involved, suggesting a role for systemic or metabolic factors. 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 unraveling the pathogenesis of hand OA which is of importance when development of new treatment strategies is concerned.

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