Clinical and radiological factors associated with erosive radiographic progression in hand osteoarthritis

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INTRODUCTION

Erosive osteoarthritis (OA) is a subset of hand OA: whether it is a separate disease entity or reflects a severe phase in the course of hand OA is still under debate. Its more aggressive course compared to non-erosive OA is well known: patients with erosive joints experience a higher level of pain and more functional impairment

Moreover, radiographic damage seems to have the largest contribution to this functional impairment.

Prognostic factors of radiographic progression could play a role in the approach of erosive OA, by identifying patients with a high risk of radiographic progression. These patients could be a potential target population for treatment with disease modifying osteoarthritis drugs (DMOADs).

In hand OA, a high level of self-reported pain and pain intensity are associated with radiographic progression. Furthermore self-reported pain predicts the development and progression of erosions. In another study, the number of tender joints and joints with soft tissue swelling were associated with radiographic progression in erosive OA. In prospective cohorts, the identification of prognostic factors of radiographic progression in erosive OA is limited.
The aim of this study is to confirm the existing and identify new prognostic factors of erosive progression in a prospective cohort of hand OA patients.

Method

Study population

Patients were selected from a multicenter cohort of 270 patients who met the American College of Rheumatology criteria for hand OA, recruited from May 2007 through January 2010. Details of this cohort are described elsewhere. Patients recruited from the Ghent University Hospital (n = 249) were contacted and invited for a follow-up visit. Five patients died and 20 had inaccurate contact details. Fifty-one dropped out. Finally, 173 patients agreed with the follow-up visit that took place between January and March 2014. The Medical Ethics Committee of the Ghent University Hospital approved the study and written informed consent from all participants was already present.

Radiographic assessment

Patients underwent radiographs if the last was performed more than a year ago. Sixteen patients refused. After revision of the data, three patients were additionally excluded. Two patients were too young at baseline (<45 years), one was not compliant with the follow-up protocol. Radiographs of 154 patients were assessed. All 18 interphalangeal (IP) joints were scored according to the anatomical scoring system for hand OA. Six anatomical phases are described through which a joint can progress: from ‘N’, normal; to ‘S’, stationary joint, showing minimal signs of OA; to ‘J’, complete or partial loss of joint space; to ‘E’, characterized by manifest erosions and destruction of the subchondral plate; and eventually to ‘R’, characterized by reappearance of joint space and extensive remodeling of the subchondral plate. In rare cases, ‘E’ progresses to ‘F’, which corresponds with ankylosis. Joints with prosthesis or an inconclusive score due to e.g., superposition were recorded as missing. One trained (RW) and two newly trained readers (CV and PM), scored the radiographs independently. These scores were mutually compared and a consensus score was made. Reliability was determined using a random factor ANOVA approach. Inter- and intra-observer reliability, determined by intraclass correlation coefficients (ICC) were excellent: respectively 0.84 (CV-RW-PM) and 0.95 (RW) and 0.83 (PM).

Clinical assessment and patient reported outcomes

Similar clinical assessments and patient reported outcomes were performed at baseline.

Patients were asked to indicate the level of pain experienced during the last 48 h on a Visual Analogue Scale (VAS pain, 0–100) and to complete the Functional Index for Hand osteoarthritis (FIHOA) and AUStalian CANazian Osteoarthritis index (AUSCAN). Painful IP joints during the last 48 h were assessed. All IP joints were examined for soft tissue swelling and tenderness upon pressure. Grip strength of both hands was measured (My-Gripper, Yamasa, Tokei, Japan; in kg). The best of three attempts was registered.

Statistical analysis

Descriptive analysis was performed on data of the hand OA patients. Mean and standard deviation (SD) were calculated for continuous variables, frequencies and percentages for categorical variables.

To exclude potential attrition bias, differences in disease duration, pain (by VAS) and functional impairment (by FIHOA and AUSCAN) between the dropouts and participants were calculated using the Student’s t-test.

A generalized estimating equation (GEE) model with a binary logistic function was used to identify prognostic factors of radiographic progression of the 154 hand OA patients on joint level. Progression (present or absent) was defined as a joint progressing from at least one anatomical phase from baseline to follow-up, excluding progression from ‘N’ to ‘S’. Joints with ‘F’ phase at baseline were excluded from the analysis. Disease duration (<5 or >5 years), joints in the dominant hand, presence of a painful joint, a tender joint, and a joint with soft tissue swelling at baseline were selected as clinical variables. Presence of a joint in ‘J’ and a joint in ‘E’ phase at baseline were selected as radiographic variables. All variables were dichotomous variables. Taking into account the clustering of IP joints within one patient, an exchangeable correlation structure matrix was chosen on joint level.

A GEE model with a Poisson loglinear function was used on hand and patient level. Progression was defined as an increase in progressive joints per hand, respectively per patient. On hand level, the potential prognostic factors ‘pain’, ‘tenderness’, ‘soft tissue swelling’, ‘J’ and ‘E phase’ were recollected as the number of the present variable per hand. Disease duration and joints in the dominant hand were dichotomous variables. The potential prognostic factors on patient level were similar as on hand level. The numerical variables on hand level were recalculated on patient level by taking the sum of the right and left hand. ‘Joints in the dominant hand’ was not selected, because of the accumulation of the non-dominant and dominant hand. Furthermore, an independent correlation structure matrix was chosen on patient level.

An adjustment for the follow-up interval in all GEE analyses was made.

During the follow-up period, 56 patients were treated with a biological (adalimumab or etanercept). To correct for the potential confounding effect of this treatment, a subgroup analysis was performed by excluding these patients.

IBM SPSS Statistics 22 was used for the statistical analyses. Odds ratios (OR) were presented with 95% confidence intervals (CI). The level of significance (α) is 0.05. P-values ≤0.05 determined statistical significance.

Results

Comparison between participants and dropouts

No statistically significant difference was seen between the participants and dropouts for disease duration, VAS pain, FIHOA and AUSCAN (Supplementary file 1).

Study population

Demographics and clinical data of the hand OA patients are shown in Table I. The mean follow-up interval was 5.8 years. The distribution of the anatomical phases at baseline and follow-up are shown in Supplementary file 2.

Prognostic factors of erosive progression in hand OA

Joint level

In total, 2750 joints were analyzed from 154 patients. Seven joints were missing: five with a prosthesis and two with an inconclusive score. Fifteen joints were in ‘F’ phase at baseline.
Progression, including 'N' to 'S' phase, was present in 1014 joints (36.9%). Even 26 normal joints progressed to 'E' or following phases.

From the three significant clinical variables, a joint with soft tissue swelling showed the strongest association (Table II). Disease duration and joints in the dominant hand were not associated with radiographic progression.

Two radiographic prognostic factors were identified (OR [95% CI]), a joint in 'I' [16.74 [9.09–30.83]] and a joint in 'E' phase [76.34 [42.17–138.23]], the latter having the strongest association with radiographic progression.

Hand level
Two clinical prognostic factors were identified on hand level (Table II). Again, the same two radiographic variables were statistically significant associated with progression.

Table I
Demographic and clinical data of the hand OA patients (n = 154)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hand OA (n = 154)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (F/M) (n [%])</td>
<td>133/21 (86.4%/13.6%)</td>
<td></td>
</tr>
<tr>
<td>Age (years) [range]</td>
<td>62.2 [45–84]</td>
<td>SD = 7.14</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.9</td>
<td>SD = 6.21</td>
</tr>
<tr>
<td>Daily activities (0/1/2) (n [%])</td>
<td>3/126/25 (2.0%/81.8%/16.2%)</td>
<td>7/120/27 (4.6%/77.9%/17.5%)</td>
</tr>
<tr>
<td>Clinical data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nr of painful joints [%]</td>
<td>3.4</td>
<td>SD = 3.27</td>
</tr>
<tr>
<td>Nr of tender joints [%]</td>
<td>3.0</td>
<td>SD = 3.06</td>
</tr>
<tr>
<td>Nr of joints with soft tissue swelling</td>
<td>1.4</td>
<td>SD = 1.83</td>
</tr>
<tr>
<td>Maximal grip strength dominant hand (kg)</td>
<td>11.4</td>
<td>SD = 1.70</td>
</tr>
<tr>
<td>Maximal functioning non-dominant hand (kg)</td>
<td>18.6</td>
<td>SD = 3.05</td>
</tr>
<tr>
<td>VAS pain (mm) (range: 0–100)</td>
<td>41.6</td>
<td>SD = 25.02</td>
</tr>
<tr>
<td>FIHOA (range: 0–30)</td>
<td>8.7</td>
<td>SD = 6.36</td>
</tr>
<tr>
<td>AUSCAN pain (range: 5–50)</td>
<td>20.5</td>
<td>SD = 10.48</td>
</tr>
<tr>
<td>AUSCAN stiffness (range: 1–10)</td>
<td>4.9</td>
<td>SD = 2.56</td>
</tr>
<tr>
<td>AUSCAN function (range: 0–90)</td>
<td>39.5</td>
<td>SD = 21.04</td>
</tr>
</tbody>
</table>

F/M = Female/Male; VAS = Visual Analogue Scale.

Except where indicated otherwise, data shown are mean values.

1 Sum of the 18 IP joints in a patient.

2 Painful defined as pain during the last 48 h indicated by the patient.

3 Tender defined as tenderness upon pressure.

Table II
Exploration of potential prognostic factors of radiographic progression in hand OA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Joint level (n = 2750)</th>
<th>Hand level (n = 308)</th>
<th>Patient level (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GEE-OR (95% CI)[a]</td>
<td>P-value[b]</td>
<td>GEE-OR (95% CI)[a]</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (≤5 years, &gt;5 years)</td>
<td>1.40 (0.85–2.30)</td>
<td>0.185</td>
<td>1.22 (0.90–1.65)</td>
</tr>
<tr>
<td>Joints in the dominant hand</td>
<td>0.94 (0.75–1.17)</td>
<td>0.585</td>
<td>0.99 (0.86–1.14)</td>
</tr>
<tr>
<td>Pain</td>
<td>1.48 (1.01–2.15)</td>
<td>0.044</td>
<td>1.03 (0.97–1.10)</td>
</tr>
<tr>
<td>Tenderness</td>
<td>2.18 (1.56–3.05)</td>
<td>&lt;0.001</td>
<td>1.07 (1.01–1.13)</td>
</tr>
<tr>
<td>Soft tissue swelling</td>
<td>2.56 (1.54–4.24)</td>
<td>&lt;0.001</td>
<td>1.10 (1.00–1.20)</td>
</tr>
<tr>
<td>Radiographic variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'I' phase</td>
<td>16.74 (9.09–30.83)</td>
<td>&lt;0.001</td>
<td>1.29 (1.13–1.48)</td>
</tr>
<tr>
<td>'E' phase</td>
<td>76.34 (42.17–138.23)</td>
<td>&lt;0.001</td>
<td>1.42 (1.32–1.54)</td>
</tr>
<tr>
<td>Subanalysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint level (n=154)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>'I' phase</td>
<td>42.06 (16.90–104.66)</td>
<td>&lt;0.001</td>
<td>1.52 (1.20–1.94)</td>
</tr>
<tr>
<td>'E' phase</td>
<td>87.99 (41.53–186.44)</td>
<td>&lt;0.001</td>
<td>1.51 (1.29–1.78)</td>
</tr>
</tbody>
</table>

'a' Joint space loss; 'E' = erosive; OR= Odds Ratio; CI= Confidence Interval; N.A. = Not Applicable.

All significant p-values, i.e, p-values lower than 0.05, are represented in bold.

[b] GEE-OR (95% CI): OR and 95 CI obtained by GEE modeling.

[c] P-values calculated by GEE modeling.

1 Variables are dichotomous on joint level (present or absent) and continuous on hand and patient level (sum of present variable per hand and per patient).

2 Subgroup analysis performed after exclusion of patients who received biologicals (n = 98) during follow-up demonstrated similar ORs for all clinical variables (data not shown). The radiographic variables 'I' and 'E' phase were even more strongly associated with erosive progression (Table II).

Discussion
Potential prognostic factors of erosive progression were studied in this prospective cohort of hand OA patients. These factors could
help us with the identification of patients at high risk of further radiographic progression. Consequently, high-risk patients could be a potential target population for therapeutic trials with potential DMOADs.

This study confirmed soft tissue swelling as the only clinical variable associated with radiographic progression in hand OA on all levels. The smaller number of cases on hand and patient level and the different definitions of the outcome variable ‘progression’ are a likely explanation for the non-significance of pain and tenderness on respectively hand and patient level. Disease duration was not associated with radiographic progression, nor were joints belonging to the dominant hand. Two radiographic variables, ‘J’ and ‘E’ phase, were associated with radiographic progression on all levels. Not surprisingly, the radiographic variables showed stronger associations than the clinical ones. The anatomical scoring system detects significant progression over a 1–3 year follow-up interval \(^{11,12}\). The mean follow-up interval of this study was 5.8 years. As a result, the identification of significant progression of ‘J’ and ‘E’ phases was expected. Similar reasons as for the non-significance of tenderness and pain, explain the lower ORs of all identified prognostic factors on hand and patient level. Nevertheless, the identification of prognostic factors was comparable on all levels.

In a previous study the odds for progression were higher when patients had shorter disease duration, but the definition of radiographic progression was different: defined as ‘N’, ‘S’ or ‘J’ phase becoming an ‘E’ phase.\(^3\) Not surprisingly, this progression occurs more in the first years from onset. Our study defined radiographic progression differently: further progression towards remodeling was also included. This probably explains the discrepancy. Our study could confirm the previously identified prognostic factor ‘pain’.\(^3\) In literature, conflicting results concerning ‘tenderness’ as prognostic factor were present.\(^1,4\) However, our study reinforces the association of tenderness with radiographic progression.

One of the strengths of this study was the prospective design. Additionally, the definition of radiographic progression made detection of radiographic progression possibly more sensitive.

Unfortunately, some limitations need to be acknowledged. First, the dropout rate was high. Second, progression in the early phase of hand OA was missed due to the already longer disease duration at baseline.\(^1\) Third, few joints were at ‘J’ phase in our baseline sample. Despite this low number, we observed significant ORs indicating that a strong association with ‘J’ phase is present. Fourth, the treatment effect could be a potential confounder: fifty-six patients did participate into a randomized clinical trial with biologicals during the time of follow-up. However, subgroup analysis, after excluding these patients, showed even stronger associations. This reinforces the previous results.\(^5\) Fifth, new imaging techniques were not used, despite their potentials. Synovitis, joint space narrowing and bone marrow lesions on magnetic resonance imaging (MRI)\(^1)\) and Power Doppler signal and effusion on ultrasound\(^2)\) were previously found to be associated with radiographic progression in hand OA.

In future research, larger prospective studies should be performed when redefining radiographic progression into subcategories (limited, average and much progression). New factors associated with limited and severe progression should be discovered. Furthermore, annual follow-up of newly diagnosed patients might reveal more sensitive prognostic factors. Additionally, the association of MRI and ultrasound with radiographic progression in hand OA should be further investigated. Finally, the impact of radiographic progression on the clinical manifestation needs to be further identified.

In conclusion, three clinical and two radiographic variables were associated with radiographic progression. Soft tissue swelling was the only clinical prognostic factor identified on all levels. The radiographic prognostic factors (‘J’ and ‘E’ phase) showed the strongest association. Moreover, a ‘J’ phase predicts radiographic progression to an erosive joint. The identified factors should be confirmed in further studies, and probably considered when selecting patients for therapeutic trials with potential DMOADs.

**Contributions**

All authors have made substantial contributions to all three of sections below:

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content
3. Final approval of the version to be submitted

Paulien Meersseman (paulien.meersseman@ugent.be) and Ruth Wittoek (ruth.wittoek@ugent.be) take responsibility for the integrity of the work as a whole, from inception to finished article.

**Ethics approval**

This study was conducted with the approval of the local ethics committee, University Hospital Ghent, De Pintelaan 185, 9000 Ghent, Belgium. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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**Competing interests**

All authors declare that there is no conflict of interest.

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**Supplementary data**

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2015.06.008.

**References**


