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EXTENDED REPORT

The relation between progressive osteoarthritis of the knee and long term progression of osteoarthritis of the hand, hip, and lumbar spine

G Hassett, D J Hart, D V Doyle, L March, T D Spector

Background: The association between progression of knee osteoarthritis and progression of osteoarthritis at sites distant from the knee is unclear because of a lack of multisite longitudinal progression data.

Objective: To examine the association between radiological progression of knee osteoarthritis and osteoarthritis of the hands, hips, and lumbar spine in a population based cohort.

Methods: 914 women had knee x rays taken 10 years apart, which were read for the presence of osteophytes and joint space narrowing (JSN). Progression status was available for hand, hip, and lumbar spine x rays over the same 8 to 10 year period. The association between progression of knee osteoarthritis and osteoarthritis at other sites was analysed using odds ratios (OR) and 95% confidence intervals (CI) in logistic regression models.

Results: 89 of 133 women had progression of knee osteoarthritis based on osteophytes, and 51 of 148 based on JSN definition. Progression of JSN in the knee was predicted by progression in lumbar spine disc space narrowing (OR = 2.9 (95% CI 1.2 to 7.5)) and hip JSN (OR = 2.0 (1.0 to 4.2)). No consistent effects were seen for hand osteoarthritis. The associations remained after adjustment for age and body mass index.

Conclusions: Progression of knee osteoarthritis is associated with progression of lumbar spine and hip osteoarthritis. This may have implications for trial methodology, the selection of patients for osteoarthritis research, and advice for patients on prognosis of osteoarthritis.

Radiographic assessment

At baseline, all women had an anteroposterior (AP) radiograph of the hands, a weight bearing AP radiograph of the knee, a supine radiograph of the lateral lumbar spine, and an AP supine radiograph of the hip. Follow up x rays were taken at variable time points (year of the Chingford Study) and intervals for each anatomical site (table 1).

Radiographs of the knees were standardised with the back of the knees in contact with the cassette, the patella centralised over the lower end of the femur, and the beam centred 2.5 cm below the apex of the patella, with a tube to film distance of 100 cm. Repeat AP extended view weight bearing knee radiographs were taken 10 years later by the same technician using the same equipment and methods as at baseline in order to maximise standardisation. Paired films were read side by side by a trained examiner (DH) for the presence of knee osteophytes and JSN for each compartment, using a validated atlas on a 0–3 scale of severity.

Radiographs of the hands were graded 0–3 for the presence of osteophytes and JSN using the same validated atlas at the carpometacarpal joint (CMC), distal interphalangeal joint; DIP, and proximal interphalangeal joint; DIP. Disease modifying antirheumatic drug; DMOAD, joint space narrowing; JSN, joint space narrowing; JSW, joint space width

Abbreviations: AO, anterior osteophyte; BMI, body mass index; CMC, carpometacarpal joint; DIP, distal interphalangeal joint; DMOAD, disease modifying antirheumatic drug; DSN, disc space narrowing; JSN, joint space narrowing; JSW, joint space width
Progression was defined as an increased grade ≥1 from baseline or developing a grade 1+ osteophyte or JSN in the contralateral hip. Analysis of our intraobserver limits of agreement for hip JSN measurement in millimetres at the site of maximum JSN was 0.23 to 0.25 mm, and therefore we defined progression as at least twice this value (>0.5 mm decrease in joint space width (JSW)) at that site from baseline. Lumbar spine osteoarthritis was defined using thresholds of AO or DSN grade 1+ in at least one or more vertebrae (L1 to L5) within a subject. Progression was defined as an increase in grade in an affected year 1 vertebra or developing an AO or DSN grade 1+ affected vertebra.15 For all anatomical sites a subject was defined as having osteoarthritis on the basis of either osteophytes or JSN as mutually exclusive case definitions.

Reproducibility of grading
Reproducibility for change in longitudinal knee radiographs in the Chingford cohort has yielded intraobserver agreement of $k = 0.79$ for osteophytes and $k = 0.70$ for joint space narrowing.13 The within observer reproducibility ($k$) of radiographic assessment of the hip and hand x rays was $>0.70$, and 0.78 to 0.89 for the lumbar spine.14,15 Fewer than 3% of subjects appeared to regress radiographically and these were excluded from the analysis.

Statistical analysis
Odds ratios (OR) and 95% confidence intervals (CI) were derived for the radiographic progression at other sites on the progression of knee osteoarthritis, adjusting for age and BMI within subjects, using logistic regression models. The statistical package (STATA) was used for all analyses.

RESULTS
Paired radiographs were available for analysis in 796 women for the lumbar spine, 704 for the hands, 800 for the hips, and 914 for the knees (table 1). The numbers of films available varied owing to losses at follow up and a recruitment drive during the 10th year to recontact all those women who had previously dropped out. Of the women with paired knee x rays, 133 (14.6%) had baseline knee osteoarthritis defined by osteophytes and 148 (16.2%) defined by JSN; these were therefore studied for analysis of progression.

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**Table 1**

<table>
<thead>
<tr>
<th>Site of x ray</th>
<th>Reader</th>
<th>No of x rays</th>
<th>Year of study</th>
<th>Duration of follow up (y)</th>
<th>Score</th>
<th>$k$ Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>GH*</td>
<td>796</td>
<td>1, 9</td>
<td>9</td>
<td>OS, DSN</td>
<td>$k = 0.89$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$k = 0.78$</td>
</tr>
<tr>
<td>Hand</td>
<td>GH*</td>
<td>704</td>
<td>1, 11</td>
<td>11</td>
<td>OS, JSN</td>
<td>$k = 0.70$</td>
</tr>
<tr>
<td>Hip</td>
<td>GH*</td>
<td>800</td>
<td>2, 8</td>
<td>7</td>
<td>OS, JSN</td>
<td>$k = 0.70$</td>
</tr>
<tr>
<td>Knee</td>
<td>DH†</td>
<td>914</td>
<td>1, 10</td>
<td>10</td>
<td>OS, JSN</td>
<td>$k = 0.79$</td>
</tr>
</tbody>
</table>

*G Hassett; †D J Hart.

DSN, disc space narrowing; JSN, joint space narrowing; OS, osteophytes; y, years.

---

**Table 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 914)</th>
<th>Knee OA: OS progressors (n = 89)</th>
<th>Knee OA: OS non-progressors (n = 44)</th>
<th>Knee OA: JSN progressors (n = 51)</th>
<th>Knee OA: JSN non-progressors (n = 97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.1 (6.0)</td>
<td>57.6 (5.3)</td>
<td>56.1 (6.2)</td>
<td>55.2 (5.5)</td>
<td>53.9 (6.5)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (4.2)</td>
<td>27.7 (4.2)</td>
<td>27.8 (5.5)</td>
<td>26.4 (4.6)</td>
<td>26.0 (4.2)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

BMI, body mass index; JSN, joint space narrowing; OA, osteoarthritis; OS, osteophytes.
Baseline characteristics
Table 2 shows the baseline characteristics of the 914 women with paired radiographs available, and those with knee osteoarthritis based on osteophyte and JSN progressor status.

The mean (SD) age of the group at baseline was 54.1 (6.0) years; after the 10 year follow up it was 64.1 (6.0) years. Women with knee osteoarthritis progression defined by osteophytes were older than the non-progressors, but had...
similar BMI values. Women with progression of knee osteoarthritis defined by JSN were younger than non-progressors but had non-significant differences in BMI.

Rates of progression

Tables 3 and 4 show the frequency of baseline osteoarthritis at all sites and progression of knee osteoarthritis defined by osteophytes or JSN, respectively, by progression of osteoarthritis at the hip, lumbar spine, and hand. Of the women with baseline knee osteoarthritis, 67% (89 of 133) progressed by an osteophyte definition and 35% (51 of 148) progressed by a worsening of JSN grade over a 10 year period. Progression rates per year can be calculated from the tables 3 and 4. For knee and hand osteoarthritis progression rates ranged from 3.5% to 6.7% a year according to the definition of osteoarthritis, with similar rates of osteophyte progression seen at both sites. Lumbar spine osteoarthritis progression rates were 3.9% for anterior osteophytes and 3.2% for DSN, while at the hip the rates were 4.5% and 7.4% for osteophyte and JSN progression. Progression in the knee and hand occurred in 58.9% of women (30 of 51) with baseline osteophytes at the two anatomical sites, and in 23.8% (15 of 63) of those with baseline JSN. Progression in the knee and lumbar spine occurred in 31.6% of women (30 of 95) with baseline osteophytes at the two anatomical sites, and in 19.5% (17 of 87) of those with baseline JSN and DSN, respectively. In the Chingford cohort the prevalence of radiographic hip osteoarthritis defined by semiquantitative JSN grade at baseline is low (n = 29) and therefore there were only a few women with JSN at the hip and knee at baseline (n = 7); this meant that progression data in this subgroup were difficult to interpret and univariate and multivariate analysis could not be done. Hip osteoarthritis JSN progression defined by a >0.5 mm decrease in JSW from baseline resulted in larger numbers of affected women and the data was therefore available for subgroup analysis.

Osteophytosis of the hip, although less diagnostic, was more common. Progression in the knee and hip occurred in 40% of women (14 of 35) with baseline osteophytes at the two anatomical sites.

Risk of knee progression by alternate joint site

For knee osteophyte progression, there was an approximately fourfold increased risk of progression if DSN progression occurred at the lumbar spine (OR = 4.5 (95% CI, 1.3 to 15.5)) (table 5), with non-significantly increased risks for lumbar spine osteophytosis alone (OR = 1.4 (0.6 to 3.3)), for hand osteophytic osteoarthritis (OR = 2.5 (0.6 to 10.0)), or for hand JSN osteoarthritis (OR = 1.8 (0.4 to 7.7)), and no difference with radiographic hip osteoarthritis.

There was a two- to threefold increased risk of knee JSN progression if there was DSN progression (OR = 2.9 (95% CI, 1.2 to 7.5)) or anterior osteophyte progression (OR = 1.7 (0.8 to 4.0)). Hip progression defined by a >0.5 mm change in JSW increased the risk twofold (OR = 2.0 (1.0 to 4.2)). While a similar increase in risk was seen with progression of hip osteophytes (OR = 2.5 (0.6 to 10.0)), the number of women was small (n = 14) and the confidence intervals wide. A non-significant risk reduction of 40–60% for progression was shown for progression of hand osteophytes (OR = 0.6 (0.1 to 2.6)) and JSN (OR = 0.4 (0.1 to 1.2)).

Table 6 shows the adjusted odds ratios for knee osteoarthritis progression risk by progression of osteoarthritis at the hip, lumbar spine, and hand. We adjusted for age and BMI, two well established risk factors for knee osteoarthritis. Estimates of the magnitude of risk for progression of knee osteoarthritis stratified for progression of osteoarthritis at other anatomical sites were not altered by adjustment for age or BMI, except for the odds ratio for knee JSN progressors which increased for those women who were also hip JSN progressors.

### Table 5  Univariate analysis of the association of knee osteoarthritis progression and progression of osteoarthritis at other anatomical sites

<table>
<thead>
<tr>
<th>Anatomical Site of Progression</th>
<th>Knee OA</th>
<th>Knee JSN</th>
<th>Knee OS non-progressors OR (95% CI)</th>
<th>Knee JSN non-progressors OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand osteophytes</td>
<td>30</td>
<td>10</td>
<td>2.5 (0.6 to 10.0)</td>
<td>0.6 (0.1 to 2.6)</td>
</tr>
<tr>
<td>Hand JSN</td>
<td>25</td>
<td>7</td>
<td>1.8 (0.4 to 7.7)</td>
<td>1.2 (0.1 to 12)</td>
</tr>
<tr>
<td>Hip osteophytes</td>
<td>14</td>
<td>7</td>
<td>0.8 (0.2 to 3.5)</td>
<td>2.5 (0.6 to 10.0)</td>
</tr>
<tr>
<td>Hip JSN (mm)</td>
<td>33</td>
<td>16</td>
<td>0.9 (0.4 to 2.1)</td>
<td>2.0 (1.0 to 4.2)</td>
</tr>
<tr>
<td>Lumbar spine AO</td>
<td>30</td>
<td>11</td>
<td>1.4 (0.6 to 3.3)</td>
<td>1.7 (0.8 to 4.0)</td>
</tr>
<tr>
<td>Lumbar spine DSN</td>
<td>29</td>
<td>4</td>
<td>4.5 (1.3 to 15.5)</td>
<td>2.9 (1.2 to 7.5)</td>
</tr>
</tbody>
</table>

*Except where otherwise indicated, values are numbers of patients.

AO, anterior osteophytes; BMI, body mass index; CI, confidence interval; DSN, disc space narrowing; JSN, joint space narrowing; OA, osteoarthritis; OR, odds ratio; OS, osteophytes.

### Table 6  Multivariate analysis of the association of knee osteoarthritis progression and progression of osteoarthritis at other anatomical sites

<table>
<thead>
<tr>
<th>Anatomical Site of Progression</th>
<th>Knee OA</th>
<th>Knee JSN</th>
<th>Knee OS non-progressors OR (95% CI)</th>
<th>Knee JSN non-progressors OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand osteophytes</td>
<td>2.0</td>
<td>0.5</td>
<td>0.5 (0.1 to 2.5)</td>
<td>0.4 (0.1 to 1.4)</td>
</tr>
<tr>
<td>Hand JSN</td>
<td>1.6</td>
<td>0.4</td>
<td>2.1 (0.4 to 9.7)</td>
<td>2.7 (1.2 to 6.3)</td>
</tr>
<tr>
<td>Hip osteophytes</td>
<td>0.9</td>
<td>0.4</td>
<td>1.5 (0.6 to 3.7)</td>
<td>3.7 (1.2 to 11.1)</td>
</tr>
<tr>
<td>Hip JSN (mm)</td>
<td>0.9</td>
<td>0.4</td>
<td>1.3 (0.3 to 2.3)</td>
<td>1.5 (0.6 to 6.3)</td>
</tr>
<tr>
<td>Lumbar spine AO</td>
<td>1.3</td>
<td>0.5</td>
<td>2.8 (0.5 to 15.1)</td>
<td>7.0 (1.2 to 37.7)</td>
</tr>
<tr>
<td>Lumbar spine DSN</td>
<td>6.8</td>
<td>1.8</td>
<td>5.4 (1.3 to 22.7)</td>
<td>3.1 (0.6 to 15.7)</td>
</tr>
</tbody>
</table>

*All odds ratios are adjusted for age (years) and BMI (kg/m²).

AO, anterior osteophytes; BMI, body mass index; CI, confidence interval; DSN, disc space narrowing; JSN, joint space narrowing; OA, osteoarthritis; OR, odds ratio; OS, osteophytes.
DISCUSSION

Clinicians are often asked by their patients about the risk of their knee osteoarthritis progressing, or about the risks of development and progression of osteoarthritis at distant anatomical sites. Up to now we have not had the prospective longitudinal x-ray data to answer questions about the progression of multisite osteoarthritis. Thus the association between knee osteoarthritis progression and the progression of osteoarthritis at anatomically distant sites is important to establish. In addition, if osteoarthritis progression is correlated between anatomical sites, then perhaps the results of recent DMOAD trials in knee osteoarthritis can be extrapolated to other sites. However, it is still to be established whether the same biological processes determine progression at each site, and the generalisability of DMOAD trial results for knee osteoarthritis would need to be tested and confirmed in the context of prospective osteoarthritis intervention studies.

Progression of disc space narrowing in the lumbar spine was associated with progression of knee osteoarthritis on the basis of either osteophytes or JSN, although the relation was stronger for JSN progression, with a fourfold increase in risk. The association of knee osteoarthritis with lumbar spine osteoarthritis may suggest a common mechanism through obesity or mechanical forces (for example, occupation or physical activity), although it remained after adjustment for BMI. Occupational activity and physical activity have, however, previously not been shown to be risk factors for progression of lumbar spine osteoarthritis in the Chingford cohort. A recent family-based study suggested a genetic relation between generalised osteoarthritis and disc degeneration, which may in part explain the correlation of progression between lumbar spine and knee osteoarthritis. Anterior osteophytes of the lumbar spine did not show a significant association with progression of knee osteoarthritis, which may in part reflect the high prevalence of anterior osteophytes by the age of 50 (60–80%), with onset and progression of these osteophytes occurring in subjects at a younger age than that for knee osteoarthritis.

Progression of radiographic hand osteoarthritis showed inconsistent and non-significant results, with similar findings when we analysed radiographic progression at the CMC and the DIP joints separately (data not shown). This may in part be because JSN at the hand is not a useful predictor. Our study tentatively suggests an association between hand osteophytes and knee osteoarthritis, although not with knee JSN, which may indicate that JSN at the knee is not a good indicator of multisite osteoarthritis, or that the mechanisms driving osteophyte production are different from those involved in the loss of cartilage and JSW in the knee.

Hip JSN (mm) and osteophyte progression were associated with a twofold increase in the risk of knee JSN progression, although the results were not significant for osteophytes (which may reflect the small numbers of women in this subgroup analysis). Given the low prevalence of hip osteoarthritis—as defined by semiquantitative measures for osteophytes and JSN because of the older age of onset of hip osteoarthritis and the relatively young age of the women in the Chingford cohort—we cannot draw any firm conclusions about the association between hip and knee osteoarthritis progression in the younger age group. However, the relation should be explored in an older population group, given our findings using a JSN (mm) definition of hip osteoarthritis progression which detected an association in the younger subjects of the study. We acknowledge that a threshold change in hip JSW of ≥0.5 mm could represent an age related change rather than progression in a pre-osteoarthritic hip. Nevertheless given the low prevalence of hip JSN ≤2.5 mm we felt it was a marker of more rapid change and could have validity in some cases where hip osteoarthritis occurred early.

The likelihood of progression of knee osteoarthritis has previously been shown to be increased in those subjects with prevalent osteoarthritis at other sites. To our knowledge no previous studies have examined the longitudinal relations at different sites. Previously the cross-sectional prevalence of lumbar spine disc degeneration has been reported to be higher in patients with generalised osteoarthritis at other sites, and in women with Heberden’s nodes. Thus we included lumbar spine disc degeneration as one of the three potential anatomical sites of radiographic osteoarthritis progression. Several non-population-based studies have examined subjects with end stage lower limb osteoarthritis and the relation in these subjects to the presence of osteoarthritis in other joints. Thus we included lumbar spine disc degeneration as one of the three potential anatomical sites of radiographic osteoarthritis progression. Several non-population-based studies have examined subjects with end stage lower limb osteoarthritis and the relation in these subjects to the presence of osteoarthritis in other joints.

Limitations of the study need to be discussed. Obesity is reported to be a risk factor for progression of knee osteoarthritis, but even after adjusting for BMI our results did not change except for hip JSN expressed in mm. Biomechanical factors, including abnormal static and dynamic joint loading, may play a role in the progression of lower limb osteoarthritis, and this may explain in part the relation between the hip and the knee. However, we did not have any data on alignment or mechanical forces through the knee or hip to explore this.

Racial variations in osteoarthritis prevalence exist. Thus, although there are no data on racial differences in osteoarthritis progression, our data may not be applicable to other races, or to men.

To assess progression, we used a grade 1+ definition for the presence of baseline osteoarthritis at all four anatomical sites and a change in grade of ≥1 or a new grade 1+ in an unreported joint of a joint or disc site remaining in keeping with traditional definitions of progression. The definitions of progression are, however, problematic given lack of standard accepted or validated definitions and the multicompartment joint and disc space levels of the knee, hand, and lumbar spine, respectively. Moreover, it is not possible to have a standardised system for each joint site that
can be combined and which reflects similar sensitivity, similar relation to symptoms, and similar observer error. In general, however, these factors would act against us finding associations, and indeed some of the non-significant trends found may be underestimates of the true association.

Precise minimum joint space measurements for the knee were not possible because of the use in the Chingford cohort of the traditional fully extended knee view as opposed to the current semiflexed views of the knee, which make this measurement and semiquantitative assessment easier, although still with methodological concerns.

Although most subjects had mild disease, we could make no allowance for osteoarthritis treatment or treatment of diseases that may influence the progression of osteoarthritis. The time to follow up for the x rays ranged from a minimum of seven years to a maximum of 11 years. The long time intervals and the absence of intermediate measures means that we may have missed important time points or intervals at which progression occurs, but radiation doses make more intensive study impossible.

Lumbar facet joints were not examined as they are not easily or consistently visualised on lateral lumbar spine x rays. DSN may, however, be a surrogate for associated facet joint osteoarthritis, for when DSN occurs there is posterior displacement of the vertebral body and subsequent subluxation of the apophyseal joint which may lead to osteoarthritis at this site.

Our study has potential implications for clinicians managing and discussing prognosis with patients with osteoarthritis, research workers involved in basic science and epidemiological studies of osteoarthritis, and investigators of DMOADs in clinical trials. The value of biochemical markers may be in separating patients with generalised progression from non-progressors, rather than as markers of progression in individual joints. DMOADs may have a greater impact on the burden of osteoarthritis disease if progressors with knee osteoarthritis are likely to progress at other anatomical sites. Clinicians may also encourage patients with known osteoarthritis progression at the lumbar spine, hip, or knee to protect their joints at other anatomical sites and use potential DMOAD drugs.

In conclusion, this is the first population based longitudinal multisite study to examine the relation of knee osteoarthritis progression to longitudinal progression of hand, hip, and lumbar spine osteoarthritis. We have shown that in subjects with knee osteoarthritis, progression in the knee is not an isolated phenomenon but is often associated with progression of osteoarthritis in the lumbar spine, hand, or hip in the same individual.

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We thank the Arthritis Research Campaign for their support of this project and the staff and patients of Highams Park Medical Partnership and Chingford Hospital. We also thank Maxine Daniels and Tina Worthy for assistance with data collection. GH was supported by an Australian NHMRC scholarship

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