Osteophytes and progression of knee osteoarthritis

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Objectives. Osteophytes are thought to stabilize an osteoarthritic joint, thereby preventing structural progression. Meagre longitudinal data suggest, however, that they are associated with an increased risk of structural progression. Our objective was to evaluate the effect of osteophyte size on radiographic progression in osteoarthritis (OA).

Methods. Using data from a natural history study of persons with symptomatic knee OA, we obtained fluoroscopically positioned postero-anterior (PA) radiographs at baseline, 15 and 30 months. Using an atlas, osteophyte size was scored on a scale of 0–3 at each of four sites on the PA film and, for each knee, both compartment-specific (i.e. medial; lateral) and overall osteophyte scores were computed. Progression was defined as an increase over follow-up in medial or lateral joint space narrowing, based on a semiquantitative grading. Mechanical alignment was assessed using long limb films at the 15 month examination. Logistic regression was used to evaluate the relation of osteophyte size with progression, adjusting for age, gender and body mass index, and with and without adjustment for alignment.

Results. Of 270 subjects who had 470 eligible knees with follow-up, 104 (22%) knees showed progression. Overall, osteophyte score modestly increased the risk of progression [odds ratio (OR) per s.d. increase of osteophyte score = 1.4 (95% CI 1.1, 1.8, \(P = 0.02\)], but this effect weakened and became non-significant after adjustment for limb alignment (OR = 1.3). Compartment osteophyte score was strongly associated with malalignment to the side of the osteophyte (e.g. medial osteophyte and varus). Compartment-specific osteophyte score markedly increased the risk of ipsilateral progression (e.g. medial osteophytes \(\rightarrow\) medial progression) [OR per s.d. = 1.9 (95% CI 1.5, 2.5, \(P < 0.001\))] and decreased the risk of contralateral progression [OR per s.d. = 0.6 (95% CI 0.5, 0.8, \(P = 0.002\)], but these associations diminished when we adjusted for limb alignment (OR = 1.5 and 0.7 respectively).

Conclusions. Large osteophytes do not affect the risk of structural progression. They are strongly associated with malalignment to the side of the osteophyte, and any relation they have with progression is partly explained by the association of malalignment with progression.

Key words: Knee osteoarthritis, Osteophyte, Natural history, Biomechanics, Alignment.

Osteophytes are so common as a radiographic feature of osteoarthritis (OA) that they have been used to define the presence of disease [1]. They most often appear at the margins of the joint, originally as outgrowths of cartilage and subsequently undergo endochondral ossification. Growth factors such as transforming growth factor beta (TGF\(\beta\)) potentiate their development [2, 3].

The teleological purpose of osteophytes is unclear. In hip osteoarthritis, reconstitution or recovery of the joint space has been linked to the development of large osteophytes [4, 5], which presumably stabilize the hip joint. In the knee, after a tear of the anterior cruciate ligament, osteophytes develop anteriorly and posteriorly and limit translocation of the femur on the tibia, stabilizing the joint in the sagittal plane. Pottenger et al. [6] reported, in knee osteoarthritis specimens, that removal of medial and lateral osteophytes increases varus–valgus motion. If, in knee OA, an increase in stability prevents structural progression, then knees with large osteophytes should experience less progression over time than those with smaller osteophytes.

While this may be the theoretical effect of osteophytes, two longitudinal studies of knee OA using non-fluoroscopic conventional radiography [7, 8] have reported that knees with large osteophytes, have, if anything, an increased risk of subsequent joint space loss, which suggests cartilage loss. No studies using fluoroscopic positioning techniques have examined this question, nor have studies examined whether the effect of osteophytes is specific to the side of the osteophyte or whether osteophytes are related to limb malalignment, which has been recently shown to be a potent risk factor for progression [9, 10].

If osteophyte size has little relation to disease progression, or even increases it, that might suggest that either osteophytes do not increase stability or that joint stability does not influence disease progression.

We evaluated the effect of osteophytes on disease progression in knee OA, recognizing that this might not be relevant to their effect in other joints. In a longitudinal study of patients with knee OA in which serial fluoroscopically positioned radiographs were obtained, we determined whether osteophytes affect the risk of disease progression, defined on radiographs as joint space loss. In addition, we evaluated the relation of osteophyte size to limb alignment and tested whether osteophytes on one side of the joint might be related to progression on the same or the other side of the joint, and whether any relation of osteophytes to progression might, in part, be explained by malalignment.

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Materials and methods

Subjects were recruited to participate in a natural history study of symptomatic knee osteoarthritis, called the Boston Osteoarthritis of the Knee Study (BOKS). Subjects in this study are a subset of subjects whose recruitment has been described in detail elsewhere [8]. Briefly, subjects were recruited from two prospective studies of the quality of life of veterans (one of men and one of women), from clinics at the Veterans Administration Boston Health Care System and from advertisements in local newspapers. Potential participants were asked two questions: ‘Do you have pain, aching or stiffness in one or both knees on most days?’ and ‘Has a doctor ever told you that you have knee arthritis?’ For subjects who answered positively to both questions, we conducted a follow-up interview in which we asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified, then the individual was eligible for recruitment. To determine whether subjects had radiographic osteoarthritis, they underwent a series of knee radiographs (see below under radiographic assessment). If the subject had a definite osteophyte on any view in the symptomatic knee, they were eligible for the study. By having frequent knee symptoms and radiographic OA, all subjects met ACR criteria for symptomatic knee OA [1]. For the natural history study, we enrolled subjects who were interested in participating and who could walk with or without a cane.

The study included a baseline examination and follow-ups at 15 and 30 months. At all examinations, subjects obtained knee radiographs. They also were weighed using a balance beam scale with their shoes off, and height was assessed. The baseline and follow-up examinations were approved by the Boston University Medical Center and the Veterans Administration Boston Healthcare System IRBs. Each subject’s written consent was obtained according to the Declaration of Helsinki.

Radiographs

Subjects underwent weight-bearing postero-anterior (PA) radiography using the protocol of Buckland-Wright [11]. Using fluoroscopic positioning, we aligned the beam relative to the centre of the knee, and the knee was flexed so that the anterior and posterior lips of the medial tibial plateau were superimposed. Feet were rotated until the tibial spines were centred in the notch and outlines of foot rotation were then made on foot maps, so, for subsequent films, the foot rotation was the same. Fluoroscopic positioning has been shown to produce more accurate assessments of the joint space relative to non-fluoroscopic acquisition and to improve reproducibility of joint space assessment.

For evaluation of progression, we focused on the joint space width of the medial and lateral compartments, as that has been found to correlate with cartilage thickness [12]. For reading of joint space we used the Osteoarthritis Research Society International Atlas [13] in which each of the medial and lateral tibiofemoral joint spaces is graded from 0 (normal) to 3 (bone on bone). We defined progression of joint space narrowing in a knee compartment as progression by 0.5 mm. We assessed the reproducibility of joint space measurement at the second visit using methods previously described [10]. Inter-observer agreement for reading each osteophyte’s score was $\kappa = 0.78$ ($P < 0.001$).

The overall osteophyte score for a knee consisted of the sum of the scores of the individual osteovertes (no more than one osteophyte at each site) and could range from 0 to 12 (0–3 at four sites). In addition to an overall osteophyte score, we evaluated medial and lateral osteophyte scores (hereafter called compartment-specific osteophyte scores) for each knee consisting of the sum of tibia and femur osteophytes on the medial and lateral sides, respectively (both ranged from 0–6).

Measure of alignment

Mechanical alignment was measured on a long limb film which was acquired at the second visit using methods previously described [10]. We measured alignment as the angle in degrees subtended by one line connecting the middle of the femoral head with the middle of the knee and the other line connecting the middle of the ankle with the middle of the knee. Inter-observer agreement for reading alignment was high [intra-class correlation coefficient $= 0.97$ ($P < 0.001$)]. Unless otherwise specified, alignment was evaluated as a continuous measure.

Data analysis

We initially examined whether overall osteophyte score was related to the risk of subsequent radiographic progression. Because osteovertes are so closely tied to disease severity and to narrowing, we felt that adjusting for baseline narrowing in regression analyses would not be an adequate adjustment for this relation. We therefore used an analytical approach we have previously used to separate effects of two related predictors [15]. To separate the effect of osteovertes from baseline narrowing, we stratified knees by the worse joint space narrowing grade in the knee (0–3) at baseline and, within each grade of narrowing, calculated $z$ score using the knee’s overall osteophyte score. These $z$ scores were then used as the measure of osteophyte size in the analysis. We used the same $z$ score approach to compute a compartment-specific osteophyte score.

We examined mean compartment-specific osteophyte score by quartile of alignment and the correlation of osteophyte score by alignment.

To evaluate the relation of osteophyte score to progression, we used logistical regression with progression as the dependent variable. Generalized estimating equations were used to adjust for the correlation between knees. We performed these analyses before and after adjustment for limb alignment, which was defined continuously. To evaluate compartment-specific osteovertes and their effects, we started by examining each possible association (medial osteovertes → medial progression; lateral osteovertes → medial progression; medial osteovertes → lateral progression; lateral osteovertes → lateral progression) and, when we determined that medial and lateral osteovertes had similar effects on ipsilateral progression and also had similar effects on contralateral progression (e.g. effects of medial osteovertes → medial progression similar to lateral osteovertes → lateral progression), we combined all ipsilateral and contralateral analyses (e.g. combining medial → medial progression and lateral → lateral progression). We defined a weakening of an odds ratio (OR) linking osteovertes to progression as a 10% change in the OR toward the null [16].

We examined all knees eligible for progression, but our study also included knees with only patellofemoral disease. Therefore, we conducted secondary analyses in which knees without any

For Kellgren and Lawrence grade, we used the Atlas of Standard Radiographs [14].
tibiofemoral findings and only disease in the patellofemoral compartment were excluded.

All *P* values reported are two-tailed.

**Results**

Of 323 subjects entering the natural history study and obtaining radiographs at baseline, there were 547 knees eligible for progression (Fig. 1). Of these, 470 (86%) had at least one follow-up film. One hundred and four (22%) of these knees showed progression vs 366 knees that did not.

Subjects in the study had a mean age was 67 yr, and most subjects were men, given the origin of most subjects from the Veterans Administration. The median overall osteophyte score was 2 (range 1–12) and the median Kellgren and Lawrence score was 2. Some knees were affected only in the patellofemoral compartment, leaving a tibiofemoral Kellgren and Lawrence score of 0. Those subjects followed differed on several entry parameters (Table 1) from those lost to follow-up. Compared with those who participated in the follow-up, those lost to follow-up tended more often to be men and to have higher WOMAC pain scores at baseline.

When we examined the relation of overall osteophyte score with progression, we found that a higher osteophyte score modestly increased the risk of progression [OR of progression per S.D. of osteophyte score = 1.4 (95% CI 1.1, 1.8, *P* = 0.02)]. However, this effect was weakened and became non-significant when we adjusted for alignment [OR = 1.3; 95% CI 1.0,1.7, *P* = 0.06]. When we examined progression among knees in Kellgren and Lawrence grades 2 and 3 at baseline (the most prevalent grades where almost all progression cases occurred), this same effect was seen across levels of baseline disease severity (Table 2).

Medial osteophyte score was strongly related to varus alignment with a higher medial osteophyte score present in limbs that were most varus (Fig. 2a). The relation of lateral osteophyte score to valgus alignment was not as clear (Fig. 2b). Whereas there was an increase in lateral osteophyte score in the most valgus quartile of alignment, there was also an increase in the most varus limbs. There was no evidence of a linear trend in the relation of lateral osteophyte score to alignment (*r* = 0.01; *P* = 0.8).

We combined ipsilateral analyses, examining whether the size of osteophytes in one compartment affected the risk of progression in that compartment (Table 3) and found that an increase in osteophyte size markedly increased the risk of ipsilateral progression [OR per S.D. of increase in osteophyte = 1.9 (95% CI 1.5, 2.5, *P* < 0.0001)], whereas large osteophytes lowered the risk of progression on the other side of the joint [OR = 0.6 (95% CI 0.5, 0.8, *P* = 0.002)]. Both of these effects diminished substantially when we adjusted for alignment (Table 3)—for ipsilateral progression, OR fell to 1.5 and for contralateral progression, OR rose to 0.7. Not surprisingly, alignment had a large effect on the risk of progression [per degree, OR = 1.3 (95% CI 1.2, 1.4, *P* < 0.0001)]. We found similar results when we conducted analyses in which we excluded knees with only patellofemoral OA (Table 3).

**Fig. 1.** Number of subjects and their knees included in study.

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### Table 1. Description of subjects followed and those not followed at baseline

<table>
<thead>
<tr>
<th></th>
<th>Follow-up</th>
<th>No follow-up</th>
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<tbody>
<tr>
<td>No of subjects</td>
<td>270</td>
<td>39</td>
</tr>
<tr>
<td>Age (yr) (mean ± s.d.)</td>
<td>66.6 ± 9.2</td>
<td>69.0 ± 9.1</td>
</tr>
<tr>
<td>% women</td>
<td>40.4</td>
<td>20.5</td>
</tr>
<tr>
<td>BMI (mean ± s.d.)</td>
<td>31.3 ± 5.7</td>
<td>30.9 ± 5.7</td>
</tr>
<tr>
<td>WOMAC pain*a (mean ± s.d.)</td>
<td>7.2 ± 3.7</td>
<td>8.7 ± 4.3</td>
</tr>
<tr>
<td>No. of knees</td>
<td>470</td>
<td>77</td>
</tr>
<tr>
<td>Baseline overall osteophyte sum (mean ± s.d.)</td>
<td>2.2 ± 2.2</td>
<td>2.5 ± 2.4</td>
</tr>
<tr>
<td>Median osteophyte sum (range)</td>
<td>2 (1–12)</td>
<td></td>
</tr>
<tr>
<td>Maximum of baseline osteophyte sum in medial compartment and in lateral compartment (mean ± s.d.)</td>
<td>1.6 ± 1.4</td>
<td>1.7 ± 1.4</td>
</tr>
<tr>
<td>Alignment*b (mean degrees ± s.d.)</td>
<td>2.6 ± 4.7</td>
<td>1.0 ± 1.9</td>
</tr>
<tr>
<td>% with Kellgren and Lawrence grade ≥2</td>
<td>63.4</td>
<td>67.5</td>
</tr>
</tbody>
</table>

*aWOMAC 3.0 Likert version used; subjects were asked to evaluate pain in both knees. Scores could range from 0 to 20.

*bAmong 77 knees without follow-up, only nine had alignment measured at baseline. Alignment is in degrees and values represent varus alignment (valgus limbs were treated as negative values).

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### Table 2. Osteophyte size and risk of progression by baseline Kellgren and Lawrence grade

<table>
<thead>
<tr>
<th>Baseline Kellgren and Lawrence grade</th>
<th>Osteophyte z score* in progressors</th>
<th>Osteophyte z score in non-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (123 knees)</td>
<td>0.13 (±1.08)</td>
<td>−0.05 (±0.99)</td>
</tr>
<tr>
<td>3 (161 knees)</td>
<td>0.12 (±1.01)</td>
<td>−0.06 (±0.99)</td>
</tr>
</tbody>
</table>

*z score calculated for each joint space narrowing grade, where 0 = mean osteophyte score for that grade, +1 = 1 S.D. above the mean.
In the first longitudinal evaluation of the effect of osteophyte size on the structural progression of knee OA, we found that overall osteophyte score modestly increased the risk of progression, an effect mediated, partly, by the association of osteophytes with malalignment. The relation of osteophytes to progression was complex. First, osteophytes tended to be associated with ipsilateral malalignment—medial with varus and lateral (less so) with valgus. While a higher osteophyte score increased the risk of ipsilateral progression, this association was weakened when we adjusted for limb alignment. Conversely, osteophytes decreased the risk of progression on the other side of the joint, but that association too was attenuated by adjustment for alignment. This suggests that the effect of osteophytes on progression was mediated by malalignment, a potent risk factor for progression.

How can our findings be explained? We suggest that osteophytes may not have any primary effect themselves but rather they serve as markers for two factors that strongly affect the risk of progression. First, they are highly correlated with limb malalignment. We found this especially for medial osteophytes and believe that our failure to find a similar strong linear association with lateral osteophytes is due to the predominant medial osteoarthritis in this sample of subjects (there were small medial osteophytes in many knees with lateral compartment osteoarthritis). We regard the more salient association of lateral osteophytes with valgus

![Figure 2](image-url)

**FIG. 2.** Relation of compartment-specific osteophyte score with alignment. (a) Medial osteophytes. (b) Lateral osteophytes.

**Table 3.** Compartment-specific osteophyte score and risk of progression in the same side (ipsilateral) and other side (contralateral) of the joint

<table>
<thead>
<tr>
<th></th>
<th>Risk of ipsilateral progression [OR (95% CI)]</th>
<th>Risk of ipsilateral progression adjusted for limb alignment [OR (95% CI)]</th>
<th>Risk of contralateral progression [OR (95% CI)]</th>
<th>Risk of contralateral progression adjusted for alignment [OR (95% CI)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>All knees</td>
<td>1.9 (1.5, 2.5)</td>
<td>1.5 (1.1, 2.0)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.7 (0.5, 1.1)</td>
</tr>
<tr>
<td>Only knees with tibiofemoral disease(^a)</td>
<td>1.8 (1.4, 2.3)</td>
<td>1.4 (1.1, 1.9)</td>
<td>0.6 (0.4, 0.8)</td>
<td>0.7 (0.5, 1.0)</td>
</tr>
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</table>

\(^a\)Odds ratio is per s.d. increase in osteophyte score. For the compartment-specific osteophyte score, 1 s.d. increase = 1.4 (scale 0–6). All odds ratios are adjusted for age, sex and BMI.

\(^b\)Defined as Kellgren and Lawrence grade of 0 (K/L grade scored on only the PA view).

**Discussion**

In the first longitudinal evaluation of the effect of osteophyte size on the structural progression of knee OA, we found that overall osteophyte score modestly increased the risk of progression, an effect mediated, partly, by the association of osteophytes with malalignment. The relation of osteophytes to progression was complex. First, osteophytes tended to be associated with ipsilateral malalignment—medial with varus and lateral (less so) with valgus. While a higher osteophyte score increased the risk of ipsilateral progression, this association was weakened when we adjusted for limb alignment. Conversely, osteophytes decreased the risk of progression on the other side of the joint, but that association too was attenuated by adjustment for alignment. This suggests that the effect of osteophytes on progression was mediated by malalignment, a potent risk factor for progression.

How can our findings be explained? We suggest that osteophytes may not have any primary effect themselves but rather they serve as markers for two factors that strongly affect the risk of progression. First, they are highly correlated with limb malalignment. We found this especially for medial osteophytes and believe that our failure to find a similar strong linear association with lateral osteophytes is due to the predominant medial osteoarthritis in this sample of subjects (there were small medial osteophytes in many knees with lateral compartment osteoarthritis). We regard the more salient association of lateral osteophytes with valgus
malalignment as being represented by the most valgus versus neutral quartiles of alignment, not the varus alignment seen in Fig. 2b.

A second factor probably affecting progression is the existence of disease in the compartment. In animal models, osteophytes develop at sites of adjacent cartilage loss [17]. Thus, the association of osteophyte size with an increased risk of ipsilateral progression may not reflect an effect of osteophytes, per se, but rather that large osteophytes serves as a marker for nearby cartilage loss. This may explain the findings of one previous longitudinal radiographic study of OA [8], which reported an association of osteophytes with progression only in knees in which the joint space was minimally narrowed or normal. In these knees, osteophytes may have served as the evidence for nearby cartilage loss not yet detectable as joint space narrowing on the radiograph.

Given the strong association of osteophytes with two risk factors for disease progression, malalignment and pre-existing cartilage loss, we speculate that any effect of osteophytes on progression independent of these factors would be hard to detect. Even so, our data suggest that osteophytes do not have any direct role in disease progression but may serve as markers of the location and severity of the pathologic process.

Our findings are relevant to osteophytes in the knee and not necessarily to osteophytes in other joints nor osteophytes in specific locations where shape and size may result in genuine joint stabilization. Nagaosa et al. [18] have noted that osteophyte shapes may differ and the curvature of an osteophyte or its placement near the joint capsule may stabilize the joint.

Since osteophytes may stabilize joints, our failure to find an effect of osteophytes on progression might suggest that joint instability and laxity may be less important as factors affecting progression than have been suspected.

There are a number of important limitations to our study. First, most of the study participants were men. Obviously, most patients with OA are women. Although it may be suspected that osteophyte size was greater in men, if anything, women tended to have slightly larger osteophytes. The relation of osteophytes to progression did not differ by gender. Our assessment of limb alignment occurred in the middle of the follow-up, not at baseline, and if osteophytes could affect limb alignment it is conceivable that osteophytes at baseline could have affected subsequent alignment. Additional analyses using the middle examination as baseline showed similar findings to the ones presented here.

Also, we employed a crude osteophyte scale. Two-dimensional radiographs may miss the three-dimensional extent and size of osteophytes, and their particular location may be important in terms of effects on joint stabilization.

In summary, osteophytes are strongly associated with malalignment to the side of the osteophyte, and malalignment is a potent risk factor for progression of OA. In analyses unadjusted for alignment, osteophytes on the side of the narrowing appeared to increase the risk of subsequent narrowing, but this effect did not persist when malalignment is adjusted for. Thus, we found no clear-cut independent relation of osteophyte size to the risk of progression of knee OA.

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The authors have declared no conflicts of interest.

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