Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study

F M Cicuttini, G Jones, A Forbes, A E Wluka

Objective: To determine whether cartilage volume loss is an independent predictor of knee replacement.

Design: 123 subjects with mild to moderate symptomatic radiographic knee osteoarthritis were recruited by either advertising, the Victorian branch of the Arthritis Foundation of Australia, treating general practitioners, orthopaedic surgeons, or rheumatologists; 113 completed the study. Magnetic resonance imaging was carried out at baseline and at 2 years on the symptomatic knee. Rate of change in tibial cartilage volume was calculated. Subjects were then followed up at year 4 to determine whether they had undergone a knee replacement.

Results: The rate of tibial cartilage loss over two years was an independent predictor of knee replacement at four years. For every 1% increase in the rate of tibial cartilage loss there was a 20% increase risk of undergoing a knee replacement at four years (95% confidence interval, 10% to 30%). Those in the highest tertile of tibial cartilage loss had 7.1 (1.4 to 36.5) higher odds of undergoing a knee replacement than those in the lowest tertile. WOMAC score at baseline, female sex, and tibial bone size (but not age and radiographic score) were also predictors of knee replacement.

Conclusions: The data suggest that treatment targeted at reducing the rate of knee cartilage loss in subjects with symptomatic osteoarthritis may delay knee replacement. This has important implications in terms of prevention and therapeutic interventions in osteoarthritis.
shrapnel in strategic locations, metal in the eye, and claustrophobia, were unable to walk 50 feet without the use of assistive devices, had hemiparesis of either lower limb, and if total knee replacement was already planned. At year 4, all subjects were contacted and asked whether they had undergone a replacement of the same knee in which they had baseline and year 2 MRI. This was confirmed by contacting the treating physician in all cases.

Weight was measured to the nearest 0.1 kg (shoes and bulky clothing removed), using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes removed) using a stadiometer. Body mass index (BMI) (weight (kg)/height 2 (m)) was calculated. Function and pain scales. Height was measured to the nearest 0.1 cm (shoes

### Table 1 Characteristics of the study population

<table>
<thead>
<tr>
<th>Joint replacement (n = 18)</th>
<th>No joint replacement (n = 95)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.1 (9.9)</td>
<td>63.1 (10.3)</td>
</tr>
<tr>
<td>Sex (per cent female)</td>
<td>67%</td>
<td>56%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.9 (5.8)</td>
<td>28.6 (4.9)</td>
</tr>
<tr>
<td>Tibial bone area (mm²)</td>
<td>3624 (517)</td>
<td>3413 (591)</td>
</tr>
<tr>
<td>WOMAC (pain, stiffness, function)</td>
<td>517.4 (172.9)</td>
<td>397.2 (222.5)</td>
</tr>
<tr>
<td>Pain</td>
<td>102.8 (35.3)</td>
<td>77.1 (41.2)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>51.5 (16.7)</td>
<td>37.4 (22.3)</td>
</tr>
<tr>
<td>Function</td>
<td>374.4 (138)</td>
<td>290.0 (170.1)</td>
</tr>
<tr>
<td>Kellgren-Lawrence radiographic grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>II</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Baseline tibial cartilage volume (mm³)</td>
<td>3526 (685)</td>
<td>3705 (932)</td>
</tr>
<tr>
<td>Annual loss of tibial cartilage (mm³)</td>
<td>274 (208)</td>
<td>194 (191)</td>
</tr>
<tr>
<td>Per cent tibial cartilage loss</td>
<td>7.6 (5.8)</td>
<td>5.0 (5.0)</td>
</tr>
</tbody>
</table>

Values are mean (SD). p Values are for the comparison between subjects who underwent knee replacement and those who did not. Comparisons were made using Student’s t test or the χ² test, as appropriate.

BMI, body mass index; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

### Table 2 Factors affecting risk of knee replacement

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis*</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age†</td>
<td>0.005</td>
<td>0.9</td>
<td>0.7 to 1.3</td>
</tr>
<tr>
<td>Sex (F v M)</td>
<td>2.3</td>
<td>9.9</td>
<td>1.5 to 65.4</td>
</tr>
<tr>
<td>BMI</td>
<td>0.05</td>
<td>0.9</td>
<td>0.8 to 1.1</td>
</tr>
<tr>
<td>Tibial bone area‡</td>
<td>0.001</td>
<td>1.2</td>
<td>1.0 to 1.4</td>
</tr>
<tr>
<td>Annual loss of tibial cartilage loss§</td>
<td>0.10</td>
<td>1.2</td>
<td>1.1 to 1.3</td>
</tr>
<tr>
<td>WOMAC*</td>
<td>0.002</td>
<td>1.5</td>
<td>1.1 to 2.0</td>
</tr>
<tr>
<td>Radiological grade of OA**</td>
<td>0.77</td>
<td>1.8</td>
<td>0.6 to 6.1</td>
</tr>
</tbody>
</table>

*Multivariate analysis with age, sex, BMI, % tibial cartilage loss, WOMAC score, and bone size in regression equation.
†Change per five year increase in age.
‡Change per 100 mm² increase in tibial bone area.
§Change per 1% increase in tibial cartilage loss.
*Change per 100 unit increase in WOMAC score.
**Based on Kellgren-Lawrence grade: change per unit increase in grade.

BMI, body mass index; CI, confidence interval; F, female; M, male; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.
of the results was used. If they were outside this range, the measurements were repeated until the independent measures were within ±20%, and the averages used. Repeat measurements were made blind to the results of the comparison of the previous results. The coefficient of variation (CV) for the tibial cartilage volume measures was 2.5%. The tibial plateau area was determined by creating an isotropic volume from the three input images closest to the knee joint, which were reformatted in the axial plane. The area was directly measured from these images. The CV for the total score, bone size, and baseline radiological severity of the osteoarthritis (p = 0.02 for trend). The correlation was linear, with evidence of a dose–response relation. WOMAC score at baseline, female sex, and tibial bone size were also predictors of a knee replacement.

We are not aware of any previous study that has examined the relation between loss of knee cartilage and progression to a knee replacement. The current gold standard for assessing structural change in osteoarthritis is joint space narrowing. Although it is well recognised that joint replacement is usually undertaken when there is little articular cartilage remaining, we are not aware of any studies that have examined change in joint space width and progression to joint replacement, nor are there data on baseline grade of osteoarthritis and subsequent progression to joint replacement after this time. In our study, severity of osteoarthritis at baseline was not an independent risk factor for progression to arthroplasty at year 4.

There has been much debate as to whether there are “fast” and “slow” losers of articular cartilage among subjects with osteoarthritis. Raynauld et al suggested this in a small MRI study of 32 subjects published in abstract form. To our knowledge no other study has confirmed this. In our previous study where we examined cartilage loss over two years we were not able to identify these subgroups clearly, and the rate of cartilage loss was normally distributed. In the current study, we report a positive dose–response relation between rate of tibial cartilage loss and progression to joint replacement, which does not support the concept of fast and slow losers.

Other factors that predicted progression to knee replacement in our cohort were being female, WOMAC score (pain, function and stiffness), and bone size. Previous studies have suggested that knee osteoarthritis tends to be more severe in women than in men. However, it has recently been found that despite more severe disease, women may be less likely to proceed to a joint replacement. This was not the case in our cohort. The finding that baseline pain and function level are predictors of a knee replacement are consistent with the current indication for joint replacement, which is both x-ray and symptom driven. In this study we found that the model examining factors affecting joint replacement was strengthened by the addition of bone size in the regression equation. The available data suggest that bone size is an important

### Table 3

<table>
<thead>
<tr>
<th>Rate of tibial cartilage loss</th>
<th>%</th>
<th>OR</th>
<th>Adjusted OR (95% CI)*†</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3% per annum (n = 37)</td>
<td>3 (8.1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3–8% per annum (n = 40)</td>
<td>7 (17.5)</td>
<td>2.4</td>
<td>1</td>
</tr>
<tr>
<td>&gt;8% per annum (n = 36)</td>
<td>8 (22.2)</td>
<td>3.2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Multivariable logistic regression adjusting for age, gender, BMI, % tibial cartilage loss, WOMAC score and bone size.

†p < 0.05 for trend.

CI, confidence interval; OR, odds ratio.

### DISCUSSION

In this cohort of 113 symptomatic subjects with mild to moderate osteoarthritis who were followed for four years, the rate of tibial cartilage loss between years 0 and 2 was an independent predictor of knee replacement at year 4. The correlation was linear, with evidence of a dose–response relation. WOMAC score at baseline, female sex, and tibial bone size were also predictors of a knee replacement.

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determinant of normal cartilage volume, independently of BMI, and thus it may simply be a confounder. However, there is emerging evidence that bone size plays a role in the initiation of this disease, while cartilage volume is the final pathway—an alternative explanation for these findings. This is the largest published longitudinal study of MRI measured knee cartilage volume of which we are aware. We recruited subjects with symptomatic osteoarthritis from a broad base and did not select for any particular subgroup of patients with osteoarthritis. Thus it is unlikely that we selected for a group which was more likely to lose cartilage. Nevertheless, this will need to be confirmed using larger numbers of subjects followed over longer periods, particularly to determine the role of other potential risk factors such as change in body weight and physical activity. A major strength of our study was that our main outcome (joint replacement) is clinically important and objective.

Conclusions

We have shown for the first time that the rate of structural change at the knee—articular cartilage loss—is an independent risk factor for subsequent replacement of that knee. This was independent of age, sex, baseline level of pain, and the radiological severity of osteoarthritis. This suggests that treatments targeted at reducing the rate of knee cartilage loss, even in more advanced disease, may delay knee replacement. This has important implications for prevention and therapeutic interventions in knee osteoarthritis.

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References


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