Knee cartilage defects in a sample of older adults: natural history, clinical significance and factors influencing change over 2.9 years

J. Carnes 1, O. Stannus 1, F. Cicuttini 1, C. Ding 1, G. Jones 1

1 Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia
2 Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

Objective: To describe the natural history of knee cartilage defects, and their relationship to cartilage volume loss and risk of knee replacement in a longitudinal study of older adults.

Design: 395 randomly selected older adults (mean age 62.7 years) had magnetic resonance imaging of their right knee at baseline and approximately 2.9 years later to determine cartilage defect grade (0–4), cartilage volume, medial and lateral tibial bone size, and presence of bone marrow lesions (BMLs). Height, weight, body mass index (BMI) and radiographic osteoarthritis were measured by standard protocols.

Results: At baseline higher grade cartilage defects (grade ≥ 2) were significantly associated with age, BMI, lateral tibial bone size, BMLs, and radiographic osteoarthritis. Over 2.9 years, the average defect score increased statistically significantly in all compartments; however, the majority of defects remained stable and regression of defects was rare. Baseline factors associated with increase in defect score over 2.9 years were radiographic osteoarthritis, tibial bone size, BMI and being female. In multivariate analysis, baseline cartilage defect grade predicted cartilage volume loss at the medial tibia, lateral tibia and patella over 2.9 years (β = 1.78% to 1.27% per annum per 1 grade increase, P < 0.05 for all comparisons), and risk of knee replacement over 5 years (odds ratio (OR) = 1.73 per 1 grade increase, P = 0.001).

Conclusion: Knee cartilage defects in older adults are common but less likely to regress than in younger life. They independently predict cartilage volume loss and risk of knee replacement, suggesting they are potential targets for intervention.

Introduction

Knee cartilage defects are commonly found in healthy individuals by magnetic resonance imaging (MRI)1, and in symptomatic individuals requiring arthroscopy2. The aetiology of cartilage defects remains unclear, although they are often thought to be related to trauma3. The prevalence and severity of cartilage defects are associated with age and body mass index (BMI) in healthy younger subjects4,5. They are associated with tibial bone size1, bone marrow lesions (BMLs)6, knee cartilage volume and type II collagen breakdown1. Cartilage defects are also associated with radiographic features of osteoarthritis including such as Kellgren–Lawrence score7 and osteophyte score8,9, and have been associated with knee pain in multiple settings10–12.

There is conflicting data regarding the natural history of cartilage defects. In 325 subjects largely without radiographic osteoarthritis (mean age 45 years), approximately 20% of subjects had an increase in knee cartilage defect grade over 2 years, with similar numbers decreasing13. In 84 healthy participants with a mean age of 57 years, approximately two-thirds had an increase in knee cartilage defect grade and approximately 5% decreased in grade over 2 years14. A study of 117 subjects with radiographic osteoarthritis (mean age 63.7 years) reported a similar percentage increase in knee cartilage defect grade and 15% decreasing in grade over 2 years15. There are less data using population-based samples in the elderly.

In rabbits articular condylar defects progress to osteoarthritis16. Cartilage defects are more prevalent than radiographic osteoarthritis in all age groups in humans17. In 86 healthy adults with mean age 54 years, prevalent knee cartilage defects predicted knee cartilage volume loss over 2 years18. In 325 healthy younger adults
(mean age 45 years), baseline defect grade and increase in defect grade over 2 years both predicted rate of cartilage volume loss per annum at the medial tibia, lateral tibia and patella\textsuperscript{30}. Cartilage defects predict site-specific progression of BMLs in the knee in an elderly population\textsuperscript{30}. In subjects with established knee osteoarthritis, higher baseline defect scores were associated with an increased risk of knee replacement over 4 years compared with lower defect scores\textsuperscript{25}. These data suggest cartilage defects have a causal role, or are on the causal pathway, in osteoarthritis but require further confirmation in different populations. The aim of this study, therefore, was to describe the natural history of knee cartilage defects and relationship to cartilage volume loss and risk of knee replacement in a longitudinal study of randomly selected older adults.

**Method**

**Subjects**

This study was conducted as part of the Tasmanian Older Adult Cohort Study, a prospective, population-based study aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of osteoarthritis. Baseline measures were first conducted in 2002 and follow-up measures taken approximately 2.9 years and 5 years later. Subjects between the ages of 50 and 80 years were randomly selected using computer generated random numbers from the electoral roll in Southern Tasmania (population 229,000), with an equal number of men and women. Subjects with contraindications to MRI (including metal sutures, presence of shrapnel, iron filings in the eye and claustrophobia) and institutionalised persons were excluded. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee, and all subjects were provided informed written consent.

**Anthropometrics**

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. BMI (kg/m\textsuperscript{2}) was calculated for each study subject.

**Knee cartilage defect assessment**

MRI scans of the right knee were performed at baseline and follow-up. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance imaging (MRI) scanner. Three-dimensional spoiled gradient recalled images were acquired in the coronal and axial plane. The following imaging parameters were used: a T1-weighted fat saturation 3D gradient recalled echo (T1W-FFE) sequence was used: a T1-weighted fat saturation 3D gradient recall echo sequence was used: the following image processing in an independent workstation using the software Osiris (University of Geneva, Geneva, Switzerland) by a single observer as previously described\textsuperscript{22,23}. Each BML was scored 0 if absent, 1 if present on one slice, and scored 2 if present on two consecutive slices, grade 3 if present on three or more consecutive slices). The BML with the highest score was calculated as: percentage change per annum = \[100 \times (\text{follow-up cartilage volume} - \text{baseline cartilage volume})/\text{baseline cartilage volume}\times \text{time between two scans in years}].

**Knee cartilage volume measurement**

Knee cartilage volume was determined by means of image processing on an independent workstation using Osiris (University of Geneva) by a single observer as previously described\textsuperscript{22,23}. The volumes of individual cartilage plates (medial tibial, lateral tibial and patella) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 μm and 1.5 mm thickness, continuous sections) for the final 3-dimensional rendering. Measurements made using this method have high intra- and interobserver reproducibility. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial, and 2.2% for lateral tibial cartilage\textsuperscript{23}. Rates of change in cartilage volume were calculated as: percentage change per annum = \[100 \times (\text{follow-up cartilage volume} - \text{baseline cartilage volume})/\text{baseline cartilage volume}\times \text{time between two scans in years}].

**BMLs**

BMLs were assessed using T2-weighted MR images by a trained observer as previously described\textsuperscript{20}. Each BML was scored 0–3 on the basis of lesion size (grade 1 if it was only present on one slice, grade 2 if present on two consecutive slices, grade 3 if present on three or more consecutive slices). The BML with the highest score was used if more than one lesion was present at the same site.

**Knee bone size measurement**

Knee tibial plateau bone areas were determined by means of image processing in an independent workstation using the software program Osiris as previously described\textsuperscript{25}. The bone area of the medial and lateral tibial plateau is uniform in nature and was directly measured from the reformatted axial images. The CVs for these measures in our experience are 2.2–2.6%\textsuperscript{25}.

**Radiographic osteoarthritis**

A standing anteroposterior semixed flexed view of the right and left knee with 150° of fixed knee flexion was performed in all subjects at baseline. Subjects were scored for compartment specific osteophytes and joint space narrowing on a scale of 0–3 (0 = normal and 3 = severe) according to the Altman atlas as previously described\textsuperscript{22}. The total radiographic osteoarthritis scores in medial and lateral tibiofemoral compartments were computed by summing the osteophyte and joint space narrowing scores. The presence of radiographic osteoarthritis was defined as any score of \[\geq 1\]\textsuperscript{22}. Skyline views were not available.
Knee replacement surgery

At the 5-year follow-up participants were asked whether they had undergone a total knee replacement since their first visit. Although MRI scans were taken of the right knee only at baseline, replacement surgery data were collected for both knees.

Data analysis

Student’s t-tests and Pearson’s χ² tests were used to examine the differences in our study sample between those who had a cartilage defect grade ≥2 in any compartment at baseline and those who did not. Paired t-tests were used to examine the difference between baseline and follow-up defect scores in the medial tibiofemoral, lateral tibiofemoral, patellar and all compartments combined. Crude and adjusted logistic regression were respectively used to examine the associations, before and after adjustment for potential confounders, between various predictors and any increase (change ≥1) in the summary cartilage defect scores for the medial or lateral tibiofemoral compartments. Crude and adjusted linear regression was used to examine the associations between percentage change in cartilage volume as an outcome, and baseline and change in cartilage defect scores as predictors, both before and after adjustment for potential confounders. Model building for both models used only variables which were significant in crude analysis and those considered confounders (e.g., age, sex and BMI) or those on the causal pathway (e.g., BMLs) as described in the footnotes to the tables. P values less than 0.05 (2-tailed) or 95% confidence intervals (CIs) not including the null point were regarded as statistically significant. All statistical analyses were performed using SPSS Statistics (version 19; Chicago IL).

Results

1100 subjects participated in the Tasmanian Older Adult Cohort (TASOAC) study. 978 subjects had baseline knee MRI scans. 829 subjects responded for follow-up (85% response). Reasons for loss to follow-up (n = 149) were 28 died, 20 moved out of state, 15 had a joint replacement, 28 were physically unable, and others gave no reason for their discontinuation. Of these only 395 subjects had follow-up MRI scans before the MRI machine was updated and became unavailable for research purposes. There were no statistically significant differences in baseline characteristics between those who had a follow-up MRI scan and the rest of the cohort as previously reported, thus 395 subjects (196 male, 199 female) with a mean age of 62.7 years (range 50–80) took part in this study.

The prevalence of knee cartilage defects with a score ≥2 at baseline was 9.9% at the medial tibia, 15.7% at the lateral tibia, 18.2% at the medial femur, 8.9% at the lateral femur, and 38% at the patella. Comparison of subjects with high-grade defects (defined as score ≥2 in any compartment, 49.1% of subjects) and low-grade defects (score <2 in all compartments) at baseline (Table I) revealed subjects with high-grade defects were statistically significantly older, had a higher BMI, higher prevalence of radiographic osteoarthritis in both medial and lateral tibiofemoral compartments, larger bone size of the lateral tibia and a higher prevalence of BMLs. Subjects with high-grade defects also lost statistically significantly more cartilage volume per annum over 2.9 years in the patellar compartment compared to the low-grade defect group, with a similar relationship of borderline significance in the medial tibiofemoral compartment. The majority of cartilage defects remained stable, however, regression of defects were rare in all compartments over 2.9 years [Fig. 1(A)], thus the average cartilage defect scores increased statistically significantly in all compartments over 2.9 years [Fig. 1(B)].

Baseline factors associated with an increase in cartilage defect score over 2.9 years (Table II) were presence of radiographic osteoarthritis in both medial and lateral compartments and tibial bone area in the lateral compartment. Statistically significant associations with increases in medial tibiofemoral cartilage defect score were also found when analysing radiographic osteoarthritis separately as joint space narrowing (odds ratio (OR) = 2.09 per grade, P = 0.001) and osteophytes (OR = 1.92 per grade, P = 0.046). Several variables that were non-significant in univariable analysis became statistically significant in multivariable analysis. In the medial compartment, these were BMI, tibial bone area and cartilage defect grade; and in the lateral compartment BMI, female gender and cartilage defect grade. After removing grade 0 and/or 4 defects from multivariable analysis, baseline cartilage grade no longer predicted an increase in defect score suggesting this result may be due to floor and ceiling effects (medial OR = 1.06, β = +29%, P = 0.771; lateral OR = 0.85, β = +27%, P = 0.508). There were no predictors of patella defect change.

Baseline cartilage defect grade predicted rate of cartilage volume loss per annum at the medial tibia, lateral tibia and patella after adjusting for age, sex, BMI, baseline cartilage volume, tibial bone size and radiographic osteoarthritis (Table III). After further adjustment for BMLs, only the association at the medial tibia lost significance. In addition, change in defect grade over 2.9 years predicted rate of cartilage volume loss per annum at the medial tibia and lateral tibia after adjusting for all confounders and retained significance after further adjustment for BMLs. In the medial and lateral tibiofemoral compartments, BMLs accounted for 6.2–24.4% of the variance. In the patellar compartment, the mediating effect BMLs had on cartilage volume loss was minimal (Table III).

Baseline cartilage defect grade also predicted risk of total knee replacement in the right knee (N = 8, OR = 1.78 per grade, P = 0.007), left knee (N = 7, OR = 2.83 per grade, P = 0.009), or either knee (N = 12, OR = 1.73 per grade, P = 0.001) over 5 years after adjusting for age, sex, BMI, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score, joint space narrowing, osteophytes and BMLs. This analysis was performed using the full TASOAC cohort (n = 768).

Discussion

In this sample of older adults, we found higher grade cartilage defects were very common and associated with age, BMI, lateral
was negatively associated with increase in defect score. Baseline cartilage defect grade predicted cartilage volume loss per annum at the medial tibia, lateral tibia and patella over 2.9 years, and risk of requiring a total knee replacement at 5 years in dose–response associations.

Knee cartilage defects were common, with roughly half the subjects having a grade 2 or higher defect in any site in the knee. This prevalence was greater than in healthy younger adults. Cartilage defects have the potential to progress or regress in grade; the trend, on average, in our sample over 2.9 years was to worsen. However, the majority of defects in our sample remained stable at follow-up, as previously described in healthy younger adults. Studies with smaller sample sizes have reported higher rates of increase, this may be due to differences in study design. One of these studies recruited subjects through advertising in newspapers, sporting clubs, and the hospital staff association. In another, all subjects had radiographic evidence of osteoarthritis at baseline. We found that presence of radiographic osteoarthritis at baseline significantly increases cartilage defect scores over 2.9 years, suggesting a possible explanation for this discrepancy in findings.

Regression of cartilage defects at follow-up was rare, differing from data in healthy younger adults. This could reflect declining mitotic and synthetic activity in chondrocytes that occurs with age in cartilage, with fewer cartilage defects regressing over time due to less self-repair in our older cohort. Our findings that age was significantly associated with higher defect scores at baseline, and approached significance for increasing medial tibiofemoral defect scores at follow-up ($P = 0.060$) have been previously reported in younger populations.

BMI was associated with higher grade cartilage defects at baseline, and was significant in multivariable analysis for increasing defect scores at follow-up. These results are consistent with studies in younger adults. BMI loss in younger adults over 2.3 years was associated with a decrease in medial tibiofemoral defects, suggesting weight loss could be an important strategy to delay knee cartilage defect progression. Unfortunately, in our sample the percentage of cartilage defects that decreased at follow-up was too small to allow for accurate identification of decreasing BMI as a protective factor for defect progression. Being female was significant in multivariable analyses for increasing lateral tibiofemoral cartilage defect scores and approached significance for increasing medial tibiofemoral cartilage defect scores ($P = 0.070$) at follow-up, consistent with findings in a younger cohort. Much of this was mediated by sex differences in tibial bone area.

Underlying structural mechanisms associated with formation and progression of cartilage defects appear to be tibial bone size, BMLs, and radiographic osteoarthritis at baseline. Over 2.9 years the average defect score increased in all compartments, however the majority of defects remained stable as regression of defects was rare. Factors associated with an increase in defect score at follow-up were radiographic osteoarthritis, tibial bone size, BMI and female gender. Baseline cartilage defect grade

### Table II
Compartment specific distribution of defect scores

<table>
<thead>
<tr>
<th>Score</th>
<th>Medial</th>
<th>Lateral</th>
<th>Patella</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>59</td>
<td>100</td>
<td>237</td>
</tr>
<tr>
<td>2</td>
<td>249</td>
<td>218</td>
<td>70</td>
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<tr>
<td>3</td>
<td>59</td>
<td>57</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>5–8</td>
<td>11</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

* Scores could vary from 0 to 4 in patella compartment and 0 to 8 in other compartments.
Factors associated with increase in tibiofemoral cartilage defects over 2.9 years

<table>
<thead>
<tr>
<th>Increase in medial cartilage defects</th>
<th>Crude OR (95% CI)</th>
<th>P value</th>
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<tr>
<td>Age</td>
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<td>Female</td>
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Increase in lateral cartilage defects

| Age                                  | 1.01 (0.98–1.04) | 0.443   | 1.02 (0.99–1.05)       | 0.229   |
| Female                               | 1.03 (0.67–1.58) | 0.882   | 2.71 (1.25–5.89)       | 0.012   |
| BMI                                  | 1.04 (0.99–1.09) | 0.086   | 1.06 (1.00–1.11)       | 0.044   |
| Lateral cartilage defects, per grade | 0.96 (0.77–1.20) | 0.735   | 0.58 (0.42–0.79)       | 0.001   |
| Lateral tibial bone area, per cm²    | 1.11 (1.00–1.23) | 0.049   | 1.35 (1.12–1.63)       | 0.002   |
| Lateral radiographic osteoarthritis  | 1.77 (1.05–2.97) | 0.031   | 1.87 (1.05–3.33)       | 0.034   |

Increase in patellar cartilage defects

| Age                                  | 1.00 (0.97–1.04) | 0.799   | 1.00 (0.97–1.04)       | 0.929   |
| Female                               | 1.43 (0.92–2.23) | 0.112   | 1.14 (0.51–2.56)       | 0.755   |
| BMI                                  | 0.98 (0.93–1.03) | 0.339   | 0.97 (0.92–1.02)       | 0.274   |
| Patellar cartilage defects, per grade| 1.07 (0.84–1.37) | 0.577   | 1.10 (0.84–1.45)       | 0.479   |
| Total tibial bone area, per cm²      | 0.96 (0.91–1.01) | 0.089   | 0.97 (0.89–1.06)       | 0.457   |
| Any radiographic osteoarthritis      | 1.00 (0.63–1.59) | 1.000   | 0.96 (0.59–1.20)       | 0.865   |

**Bold denotes statistically significant result.**

* Adjusted for all other predictors in table and BMLs.

and was associated with increase in cartilage defect scores over 2.9 years. Baseline grade of joint space narrowing and osteophytes both independently predicted increases in cartilage defect scores in the medial tibiofemoral compartment at follow-up, consistent with a study of older adults with symptomatic knee osteoarthritis.

Baseline cartilage defect grade and increase in defect score at follow-up predicted rate of cartilage volume loss per annum at the medial tibia, lateral tibia and patella except for increase in patellar defect score. This was largely independent of BMLs and other covariates. To our knowledge, this is the first study in older adults to demonstrate a dose–response relationship between baseline cartilage defect grade and rate of cartilage volume loss per annum at the medial tibia, lateral tibia and patella. The association has been previously shown in a convenience sample of young adults.

Baseline cartilage defect grade also predicted a 1.7 times increased risk per grade of requiring a total knee replacement over 5 years. This is the first study to demonstrate a dose–response relationship between baseline cartilage defect grade and the risk of requiring a total knee replacement. It is consistent with previous data where baseline defects were stratified between high grade and low grade in a population with established osteoarthritis. The association was significant despite the small number of knee replacements in this sample and appeared equally predictive in either the imaged knee or the non-imaged knee, but this requires confirmation in larger studies.

Baseline cartilage defect grade was negatively associated with increase in defect score over 2.9 years. Other studies reported this finding and suggested it may be due to floor and ceiling effects in defect change. We found that after removal of grade 0 and 4 baseline defects from multivariable analysis this association became non-significant. Our method of assessing defects had generated some controversy. However, current evidence demonstrates our method of measuring cartilage defects through T1-weighted fat saturated MRI gradient-recalled echo (GRE) sequences is highly comparable to T2-weighted fast spin echo (FSE) sequences. In addition, a study performed in participants with knee osteoarthritis found that images from both FSE and GRE type sequences showed similar agreement with arthroscopy.

Lastly, it is possible our model building created biased models which were over-adjusted for factors on the causal pathway such as BMLs. However, in practice, this made little difference. The changes in coefficients in Table III were mainly due to sex and body size differences in the unadjusted analysis and they changed little in Table IV or the knee replacement analysis.

In conclusion, knee cartilage defects in older adults are common but less likely to change than in younger life. They independently...

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### Table III

Factors associated with increase in tibiofemoral cartilage defects over 2.9 years

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1 Adjusted for BMLs in that compartment.
predict cartilage volume loss and risk of knee replacement suggesting they are potential targets for intervention.

**Author contributions**

Stannus had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design: Jones, Cicuttini, Ding.

Acquisition of data: Jones, Ding.

Analysis and interpretation of data: Carnes, Stannus, Jones, Cicuttini, Ding

Manuscript preparation: Carnes, Stannus, Jones, Cicuttini, Ding.

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**Conflict of interest**

No conflict of interest to declare.

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