Association of patellar bone marrow lesions with knee pain, patellar cartilage defect and patellar cartilage volume loss in older adults: a cohort study

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Aim: To examine the cross-sectional and longitudinal associations of patellar bone marrow lesion (BMLs) with knee pain, cartilage defects and cartilage volume in older adults.

Methods: A total of 904 randomly selected subjects (mean 62.4 years, 49.9% female) were studied. Fat suppressed T1-weighted spoiled gradient recall and T2-weighted fast spin echo magnetic resonance imaging (MRI) sequences were used to assess cartilage volume, cartilage defects and/or BMLs at baseline (n = 904) and 2.6 (range: 1.4-4.8) years’ follow-up (n = 414). Knee pain was assessed by self-administered Western Ontario McMaster Osteoarthritis Index (WOMAC) questionnaire at baseline (n = 904) and follow-up (n = 790).

Results: The prevalence of any patellar BMLs was 19% and was higher in those with tibiofemoral BMLs. In multivariable analyses, patellar BMLs were positively associated with any knee pain at baseline and an increase in knee pain when going up/down stairs (odds ratio (OR): 1.67, 95% confidence interval (CI): 1.08, 2.59) but not with other knee pain subscales. Patellar BMLs were also associated with patellar cartilage defects both at baseline and change over time (OR: 1.76, 95% CI: 1.00, 3.70) but not tibiofemoral defects. Patellar BMLs were negatively associated with baseline and change in patella cartilage volume (β: −2.10%, 95% CI: −3.39%, −0.80%). These associations remained significant after further adjustment for tibiofemoral BMLs.

Conclusions: Patellar BMLs were consistently associated with increased knee pain especially going up/down stairs, increased patellar cartilage defects, and decreased patellar cartilage volume cross-sectionally and longitudinally, suggesting a predominantly compartment specific role for patellar BMLs.

Introduction

Osteoarthritis (OA) of the knee is characterised by structural abnormalities of whole joint including subchondral bone and cartilage. Magnetic resonance imaging (MRI) has revolutionised the assessment of joint structural changes in OA. Recently, bone marrow lesions (BMLs) have been recognized as an important feature of knee OA as they are associated with both clinical and structural outcomes. Both human and animal studies have shown that subchondral bone changes such as BMLs may precede cartilage damage. Epidemiological studies have consistently reported that baseline BMLs are associated with cartilage defects and cartilage volume loss. There is increasing but not totally consistent evidence that BMLs are associated with knee pain. Most of these studies have focused on BMLs at tibial and femoral sites, and...
their site-specific associations with cartilage lesions at tibia and femur.\textsuperscript{5,16–18}

Patella plays an important role in knee joint mechanics and any abnormality in patella may lead to change in function of the knee joint. Patellofemoral OA is very common and is an important contributor to anterior knee pain and disability.\textsuperscript{19} It can co-exist with tibiofemoral OA but most studies have focussed on tibiofemoral OA rather than patellofemoral OA.\textsuperscript{20} Similarly, most studies on BMLs have focused on tibiofemoral joint and it remains unclear whether patellar BMLs have a similar role as tibiofemoral BMLs in predicting knee pain and local cartilage changes.

A recent study reported that patellofemoral BMLs were associated with incident knee symptoms and patellofemoral cartilage damage;\textsuperscript{21} and another study reported that the risk factors for short-term progressive cartilage loss differed between tibiofemoral and patellofemoral compartments, and BMLs strongly predicted cartilage loss only in tibiofemoral compartment, suggesting potentially different roles of BMLs in these two compartments regarding structural progression.\textsuperscript{22} We hypothesized that patellar BMLs were associated with knee pain and joint pathological changes compartment-specifically. Aim of this population-based cohort study was, therefore, to describe the cross-sectional and longitudinal association between baseline patellar BMLs and knee pain, cartilage defects and cartilage volume in older adults.

Materials and methods

Subjects

The subjects were participants of the Tasmanian Older Adult Cohort (TASOAC) study, an ongoing prospective, population-based study that was initiated in 2002 and aimed to identify environmental, genetic, and biochemical factors associated with the development and progression of OA. Subjects (n = 1100) between ages of 50 and 80 years were randomly selected from the electoral roll in Southern Tasmania (population 229,000), with an equal number of men and women. The response rate to the invitations at baseline was 57%. Institutionalized persons and subjects with contraindications to MRI were excluded (n = 196). All research conducted within this manuscript is in compliance with the Helsinki Declaration and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All subjects gave informed written consent. Self-report of rheumatoid arthritis was recorded by questionnaire.

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, Bradford, MA, USA). Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated (kg/m\(^2\)).

Knee pain assessment

Knee pain was assessed using self-administered Western Ontario McMaster Osteoarthritis Index (WOMAC) scale with a 10-point scale from 0 (no pain) to 9 (most severe)\textsuperscript{23} at baseline and follow-up. Each component of knee pain (walking on flat surface, going up/down stairs, at night, sitting/lying, and standing upright) was summed to create total pain (0 to 45), and the presence of knee pain was defined as a total score or a subscale score of 1. Change in knee pain was calculated by subtracting baseline total or a subscale score from follow-up total or a subscale score. An increase in knee pain was defined as a change in the score of 1.

MRI

MRI scans of the right knees were performed at baseline and follow-up. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker, Cleveland, OH) with use of a commercial transmit-receive extremity coil. Image sequence included the following: (1) a T1-weighted fat saturation three-dimensional (3-D) gradient recall acquisition in the steady state, flip angle 30°, repetition time 31 ms, echo time 6.71 ms, field of view 16 cm, 60 partitions, 512 × 512-pixel matrix, acquisition time 5 min 58 s, one acquisition; sagittal images were obtained at a partition thickness of 1.5 mm without between-slice gap; (2) a T2-weighted fat saturation 2-D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 × 256-pixel matrix; sagittal images were obtained at a partition thickness of 4 mm with a between-slices gap of 0.5–1.0 mm.

Subchondral BML evaluation

Subchondral BMLs were assessed by a trained observer on T2-weighted MR images and was defined as areas of increased signal adjacent to the subcortical bone (Fig. 1). Patellar and femoral trochlear BMLs were scored using a modified version of Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee\textsuperscript{24}. Largest lesion among the multiple MR image was selected and scored. A scale from 0 to 3 was used, where 0 = absence, 1 = <25%, 2 = 25% to 50%, and 3 = >50% of the patellar or trochlear area. The intraobserver reliability of patellar BMLs in this study, expressed as intraobserver correlation coefficient (ICC), was 0.94. Presence of patellar or trochlear BMLs was defined as a score of BMLs of ≥1. Other knee subchondral BMLs were assessed by a trained observer using the same grading system at baseline and follow-up on a T2-weighted MRI at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, and the intraobserver reliability was 0.89–1.00, as previously described\textsuperscript{25}.

Cartilage morphology evaluation

Knee cartilage volume was determined on T1-weighted MR images with image processing on an independent workstation using Osiris software (University of Geneva, Geneva, Switzerland), as previously described\textsuperscript{26,27}. Total cartilage volume was divided into patellar, medial and lateral tibial cartilage volume by manually drawing disarticulation contours around the cartilage boundaries, section by section, which were then resampled for the final 3-dimensional rendering\textsuperscript{28}. The coefficients of variation (CVs) for this method in our hands were 2.1% to 2.6%\textsuperscript{29}.

Cartilage defects (0–4 scale) were determined at medial tibial, medial femoral, lateral tibial, lateral femoral, and patellar sites as previously described (Fig. 2)\textsuperscript{30,31}. We graded the cartilage according to the severity of the damage: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface; grade 2 = irregularities on the surface or bottom and loss of thickness <50%; grade 3 = deep ulceration with loss of thickness >50%; grade 4 = full-thickness chondral wear with exposure of subchondral bone. The presence of a cartilage defect was defined as a cartilage defect score of ≥2 at one site. Intraobserver reliability was 0.89–0.94 and interobserver reliability was 0.85–0.93\textsuperscript{32}. BMLs, cartilage volume measurements and cartilage defects were all done independent of each other.

Statistical analysis

T-tests or \( \chi^2 \) tests were used to compare differences in means or proportions as appropriate. Univariable and multivariable binary
logistic regression analyses were used to examine the associations between patellar BMLs and both baseline and increases in tibiofemoral BMLs, cartilage defects and WOMAC knee pains, before or after adjustment for age, sex, BMI and rheumatoid arthritis. Univariable and multivariable linear regression analyses were used to examine the associations between patellar BMLs and baseline or changes in knee cartilage volume, both before and after adjustment for the covariates. These associations were further adjusted for tibiofemoral BMLs. A P-value <0.05 (2-tailed) or a 95% confidence interval (CI) not including the null point (for linear regression) or 1 (for logistic regression) was considered statistical significance. All statistical analyses were performed on SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL).

Results

Characteristics of the subjects

A total of 904 subjects (49.8% female) aged between 50 and 80 (mean: 62.4 years) participated in this study and were included in the analysis. There were no significant differences in demographic factors (age, sex, and BMI) between these participants and those excluded due to contra indication to MRI (n = 196) (data not shown). The prevalence of any patellar BMLs was 19%, with 151 subjects (87 females, 64 males) having grade 1, 15 (7 females, 8 males) having grade 2 and 4 subjects (all females) having grade 3. Baseline characteristics of the participants are presented in Table I. The prevalence of any knee pain at baseline was 51.4%. 9% of the subjects increased their pain status from baseline and 76% remained unchanged. The prevalence of patellar cartilage defects at baseline was 40% and follow up was 47%. 11% of subjects had a progression of their patellar cartilage defects and 88% of subjects remained in the same grade. There were no significant differences between subjects with and without patellar BMLs in terms of age, BMI, tibial cartilage volume and tibial bone size. However, subjects with patellar BMLs had significantly lower patellar cartilage volume and higher percentage of female sex, tibiofemoral BMLs, tibiofemoral cartilage defects, patellar cartilage defects and total knee pain.

Over 2.6 years, 114 subjects were lost to the follow-up study due to: 28 deceased, 20 moved to other states or overseas, 15 had joint replacement, 28 physically unable, and others refused or no reason. The remaining 790 subjects completed the follow-up study and the first 414 had the follow-up MRI scans. The rest of the subjects did not complete the follow-up MRI scans due to the decommissioning of the MRI facility.
of the MRI machine in the hospital. There were no significant differences in baseline characteristics between subjects who had follow-up MRI and those who did not have follow-up MRI as previously reported. Patellar BMLs were significantly associated with an increase in any tibiofemoral BMLs and change in tibiofemoral BMLs total score (all \( P < 0.05 \)) in multivariable analyses.

**Patellar BMLs and knee pain**

There were significant associations between baseline patellar BMLs and baseline total WOMAC knee pain or pain when going up/down stairs, but not with other pain subscales, before and after adjustment for age, sex, BMI and rheumatoid arthritis in cross-sectional analyses. Longitudinally, baseline patellar BMLs were associated with an increase in knee pain when going up/down stairs over 2.6 years, but not with increases in total pain and other pain subscales (Table II). The associations with baseline pain and an increase in pain when going up/down stairs remained significant after further adjustment for tibiofemoral BMLs (Table II). We assessed patellar BMLs at follow-up, and found that change in patellar BMLs was not significantly associated with changes in total knee pain or change in knee pain when going up or down stairs (data not shown).

### Table I

Baseline characteristics of the participants

<table>
<thead>
<tr>
<th></th>
<th>Total sample</th>
<th>Without patellar BMLs</th>
<th>With patellar BMLs</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( n = 904 )</td>
<td>( n = 734 )</td>
<td>( n = 170 )</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>62.4 (7.4)</td>
<td>62.3 (7.4)</td>
<td>62.7 (7.4)</td>
<td>0.551</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>49.9</td>
<td>48</td>
<td>58</td>
<td>0.025</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7 (4.6)</td>
<td>27.7 (4.6)</td>
<td>27.7 (4.6)</td>
<td>0.964</td>
</tr>
<tr>
<td>Any knee pain (%)</td>
<td>51.4</td>
<td>49</td>
<td>69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medial tibial cartilage volume (ml)</td>
<td>2.3 (0.6)</td>
<td>2.3 (0.6)</td>
<td>2.3 (0.6)</td>
<td>0.416</td>
</tr>
<tr>
<td>Lateral tibial cartilage volume (ml)</td>
<td>2.8 (0.7)</td>
<td>2.8 (0.7)</td>
<td>2.7 (0.7)</td>
<td>0.733</td>
</tr>
<tr>
<td>Patella cartilage volume (ml)</td>
<td>3.2 (0.9)</td>
<td>3.3 (0.9)</td>
<td>2.9 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medial tibial bone area (cm²)</td>
<td>20.9 (3.1)</td>
<td>21.0 (3.1)</td>
<td>20.6 (3.0)</td>
<td>0.186</td>
</tr>
<tr>
<td>Lateral tibial bone area (cm²)</td>
<td>12.2 (2.2)</td>
<td>12.2 (2.2)</td>
<td>12.2 (2.0)</td>
<td>0.925</td>
</tr>
<tr>
<td>Presence of other knee BMLs (%)</td>
<td>34.6</td>
<td>31</td>
<td>51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MTF cartilage defects (%)</td>
<td>24.1</td>
<td>22</td>
<td>33</td>
<td>0.001</td>
</tr>
<tr>
<td>LTF cartilage defects (%)</td>
<td>22.3</td>
<td>20</td>
<td>32</td>
<td>0.001</td>
</tr>
<tr>
<td>Patellar cartilage defects (%)</td>
<td>40.4</td>
<td>30</td>
<td>83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Two-tailed \( t \) tests used for differences between means; \( \chi^2 \) test used for proportions (percentages).

Significant differences are shown in bold.

Mean (SD) except for percentages. BMI: body mass index; BMLs: bone marrow lesions; MTF: medial tibiofemoral; LTF: lateral tibiofemoral.

### Table II

Associations between patellar BMLs and WOMAC knee pain and an increase in WOMAC knee pain over 2.6 years

<table>
<thead>
<tr>
<th></th>
<th>Univariable OR (95% CI)</th>
<th>Multivariable* OR (95% CI)</th>
<th>Multivariable† OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee pain at baseline (Yes/No)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total WOMAC knee pain</td>
<td>1.68 (1.19, 2.36)</td>
<td>1.68 (1.18, 2.38)</td>
<td>1.52 (1.06, 2.16)</td>
</tr>
<tr>
<td>Pain on flat surface</td>
<td>1.17 (0.81, 1.69)</td>
<td>1.18 (0.81, 1.73)</td>
<td>1.05 (0.71, 1.55)</td>
</tr>
<tr>
<td>Pain on stairs</td>
<td>1.67 (1.19, 2.33)</td>
<td>1.67 (1.18, 2.35)</td>
<td>1.52 (1.07, 2.16)</td>
</tr>
<tr>
<td>Pain in bed</td>
<td>1.16 (0.81, 1.67)</td>
<td>1.14 (0.79, 1.65)</td>
<td>1.07 (1.04, 1.56)</td>
</tr>
<tr>
<td>Pain when sitting</td>
<td>0.92 (0.62, 1.35)</td>
<td>0.90 (0.61, 1.34)</td>
<td>0.85 (0.57, 1.27)</td>
</tr>
<tr>
<td>Pain when standing</td>
<td>0.86 (0.59, 1.27)</td>
<td>0.85 (0.57, 1.26)</td>
<td>0.74 (0.49, 1.12)</td>
</tr>
</tbody>
</table>

**Increase in knee pain**

| Total WOMAC knee pain | 1.26 (0.79, 2.00)       | 1.32 (0.82, 2.12)          | 1.22 (0.76, 1.99)          |
| Pain on flat surface  | 1.24 (0.72, 2.13)       | 1.33 (0.77, 2.32)          | 1.13 (0.64, 2.00)          |
| Pain on stairs       | 1.59 (1.04, 2.44)       | 1.67 (1.08, 2.59)          | 1.57 (1.01, 2.16)          |
| Pain in bed          | 1.08 (0.62, 1.87)       | 1.13 (0.65, 1.96)          | 1.12 (0.64, 1.96)          |
| Pain when sitting    | 1.31 (0.75, 2.29)       | 1.35 (0.77, 2.39)          | 1.29 (0.72, 2.29)          |
| Pain when standing   | 1.16 (0.67, 2.02)       | 1.19 (0.68, 2.09)          | 1.11 (0.63, 1.97)          |

Knee pain is defined as a pain score of \( \geq 20 \) (vs. no pain).

Increase in knee pain is defined as a change in the score of \( \geq 1 \) from baseline to follow-up (vs. no increase).

* Adjusted for age, sex, BMI and rheumatoid arthritis.
† Further adjusted for tibiofemoral BMLs.
‡ Further adjusted for interval between two visits. Significant differences are shown in bold.

### Table III

Associations between patellar BMLs and cartilage defects and increases in cartilage defects over 2.6 years

<table>
<thead>
<tr>
<th>Cartilage defects at baseline (Yes/No)</th>
<th>Univariable OR (95% CI)</th>
<th>Multivariable* OR (95% CI)</th>
<th>Multivariable† OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial tibial</td>
<td>1.11 (0.64, 1.91)</td>
<td>1.18 (0.67, 2.09)</td>
<td>0.87 (0.47, 1.60)</td>
</tr>
<tr>
<td>Medial femoral</td>
<td>1.69 (1.16, 2.47)</td>
<td>1.67 (1.13, 2.48)</td>
<td>1.39 (0.92, 2.10)</td>
</tr>
<tr>
<td>Lateral tibial</td>
<td>1.37 (0.90, 2.08)</td>
<td>1.38 (0.90, 2.13)</td>
<td>1.08 (0.68, 1.71)</td>
</tr>
<tr>
<td>Lateral femoral</td>
<td>1.83 (1.12, 2.97)</td>
<td>2.01 (1.22, 3.32)</td>
<td>1.64 (0.97, 2.76)</td>
</tr>
<tr>
<td>Patellar</td>
<td>11.07 (7.21, 17.01)</td>
<td>12.99 (8.28, 20.39)</td>
<td>11.94 (7.58, 18.79)</td>
</tr>
</tbody>
</table>

Cross-sectionally, baseline patellar BMLs were significantly and strongly associated with patellar cartilage defects, and, to a lesser extent, with femoral cartilage defects, but not with tibial cartilage defects in univariable and multivariable analyses (Table III). The association between patellar BMLs and patellar cartilage defects remained unchanged, but those between patellar BMLs and femoral cartilage defects became non-significant after further adjustment for tibiofemoral BMLs (Table III). Longitudinally, baseline patellar BMLs were significantly associated with an increase in patellar cartilage defects, but not with tibial and femoral BMLs, both before and after adjustment (Table III). The association between patellar BMLs and an increase in patellar cartilage defects remained largely unchanged after further adjustment for tibiofemoral BMLs.
Patellar BMLs and cartilage volume

Cross-sectionally, baseline patellar BMLs were significantly and negatively associated with baseline patellar cartilage volume but not with medial and lateral tibial cartilage volume in univariable and multivariable analyses (Table IV). Longitudinally, patellar BMLs were significantly and negatively associated with change in patellar cartilage volume before and after adjustment (Table IV). The significant associations remained after further adjustment for tibiofemoral BMLs (Table IV). In addition, baseline patellar BMLs were negatively associated with change in medial and lateral tibial cartilage volume but the associations became non-significant after further adjustment for tibial BMLs (Table IV). Change in patellar BMLs over 2.6 year was not significantly associated with change in cartilage volume over 2.6 years (data not shown).

The results remained largely unchanged when participants with rheumatoid arthritis were excluded from analyses, or after adjustment for a combined score of cartilage defects and BMLs at tibiofemoral compartments, or baseline patellar cartilage defects (data not shown). Trochlear BMLs were significantly associated with total WOMAC pain, knee pain when going up or down stairs, patellar cartilage defects and patellar cartilage volume cross-sectionally, but were not associated with increases in pain or cartilage pathology longitudinally (data not shown).

Discussion

To the best of our knowledge, this study is the first to describe the independent associations between patellar BMLs and knee clinical and cartilage abnormalities in older people. We found that patellar BMLs were associated with knee pain when going up/down stairs, patellar cartilage defects and patellar cartilage volume loss both cross-sectionally and longitudinally. Patellar BMLs were also significantly associated with tibial cartilage loss but these associations were not independent of tibial BMLs. Femoral trochlear BMLs were associated with the outcome measures cross-sectionally, but not longitudinally, suggesting that trochlear BMLs may not as important as patellar BMLs in inducing joint pain and structural changes.

Presence of BMLs in tibiofemoral compartments is one of the typically morphological abnormalities of subchondral bone related to OA in MRI studies. However, the exact type of pathology involved with these lesions is not known. Previous research found that tibiofemoral BMLs pattern zone mainly consisted of normal tissue (53% of the area was fatty marrow, 16% was intact trabeculae, and 2% was blood vessels) and a smaller proportion of several abnormalities (bone marrow necrosis [11% of area], necrotic or remodelled trabeculae [8%], bone marrow fibrosis [4%], bone marrow oedema [4%], and bone marrow bleeding [2%]) (data not shown). Possible cross-talk between subchondral bone and cartilage could induce catabolism of the cartilage (29,31) and can lead to pathological changes in cartilage. Histology of patellar BMLs has not been reported but should be similar with tibiofemoral BMLs, as we found that patellar BMLs were associated with increased tibiofemoral BMLs. The underlying reasons for the association between baseline patellar BMLs and increases in tibiofemoral BMLs are unclear but it may reflect the shared risk factors or similar mechanisms.

Knee pain is the most common symptom of knee OA and nearly half of the adult population over age of 50 has pain (8). Sources of knee pain in OA are becoming clearer. We previously reported that patellar BMLs are associated with knee pain (9,10). Consistent with this, patellar BMLs were associated with pain when going up/down stairs independent of tibiofemoral BMLs. Sharma et al. have reported similar results where isolated patellofemoral BMLs were associated with prevalent, incident and persistent knee symptoms (21). Patella faces more pressure when going up/down stairs than other movements and the pressure triggered by BMLs could stimulate the nociceptive fibers around the patella and cause pain. Anterior knee pain resulting from the patellofemoral OA has been known to be refractory to treatment (22), and patellar BMLs could be a main reason for anterior knee pain in patellofemoral OA. Currently there are no effective treatments for BMLs except for zoledronic acid that was shown to reduce BMLs and knee pain (23). Therefore, targeting BMLs such as using zoledronic acid may be an effective treatment for anterior knee pain in patellofemoral OA.

Studies have suggested that subchondral bone may play a role in cartilage degradation (24), and adjoining trabecular changes may be necessary for the progression of OA (25). We previously reported that the tibiofemoral BMLs are associated with compartment specific cartilage defects and cartilage loss (5). However, it remains unclear whether patellar BMLs have similar effects. We found that the presence of patellar BMLs in older adults was associated with patellar cartilage changes over 2.6 years, independent of tibiofemoral BMLs. These changes included patellar cartilage volume loss and patellar cartilage defect development/progression. Although patellar BMLs were associated with tibial cartilage volume loss, the associations decreased in magnitude and became non-significant after adjustment for tibial BMLs. These suggest that there is only local effect of patellar BMLs on cartilage. Roemer et al. reported that patellofemoral BMLs were associated with patellofemoral cartilage loss over 6 months, but was dependent on prevalent cartilage defects (22). We found that these associations remained significant after further adjustment with baseline patellar cartilage defects or tibiofemoral cartilage defects and BMLs indicating the independent
effect of patellar BMLs in cartilage loss. Our study further adds to the evidence for site-specific association between BMLs and cartilage changes with novel results at the patellar site.

Our results provide further support for the concept that subchondral bone changes may be primary and can lead to cartilage change12. The health and integrity of knee cartilage may be dependent on the mechanical properties of the underlying subchondral bone. Disrupted bone may be incapable of dissipating the forces on the joint during motion which can lead to cartilage breakdown, and it may also inhibit nutritional flow from bone marrow space to cartilage14. Subchondral bone has rich blood supply and is therefore responsive to the treatment. There are clinical trials utilising tibiofemoral BMLs as the outcome measure for the treatment of knee OA15,16. Patellar BMLs are potentially a new target for slowing cartilage loss in the therapy of patellofemoral OA.

There are a number of potential limitations to our study. We used a modified version of WORMS to score patellar BMLs and the numbers of subjects with grade 2 (15 subjects) and grade 3 (4 subjects) were low. This scoring was based on the largest dimension of BML in one slide, which may not represent the volume of BML. We were unable to separate BMLs into different types, e.g., traumatic bone contusions and fractures, osteonecrosis and bone infarcts, inflammation, tumour, transient idiopathic bone marrow oedema, red marrow and post-surgical alterations16, because we didn’t have specific imaging, patient characteristics, symptoms, and history to distinguish them. Patellar and tibiofemoral BMLs were assessed by different readers which may underestimate their correlations; however, tibiofemoral BMLs were only used for adjustment in the models to examine the independent associations of patellar BMLs. Another limitation of the study was that cartilage assessment was performed using a fat-suppressed T1-weighted gradient-echo sequence acquired in a single plane on a 1.5T imaging system which is no longer considered state-of the-art for evaluating articular cartilage. Thus, the ability to detect small superficial cartilage lesions such as fibrillation and fissuring and to identify subtle changes in the size and depth of cartilage lesions over time was limited. Cartilage defect scoring system was mostly dependent on the depth of the defect and not the cross sectional area, which may not capture the full progression of cartilage defects. However, it has been validated as accurate and reproducible37. The response rate for this study at baseline was 57%, possibly due to extensive protocol required for subjects in this old age group. This might have introduced a selection bias to our study. However, there were no significant differences in age, gender and BMI between those who responded and those who did not respond to our study invitation. We also had high rates of retention (82%) to offset this. We did not have a lateral or skyline radiographs to assess patellofemoral radiographic OA, so cannot comment on the association of patellar BMLs with patellofemoral radiographic OA. Lastly, measurement error may influence results. However, all measures were highly reproducible suggesting this is unlikely.

Conclusions

Patellar BMLs were consistently associated with increased knee pain especially going up/down stairs, increased patellar cartilage defects, and decreased patellar cartilage volume both cross-sectionally and longitudinally, suggesting a predominantly compartment specific role for patellar BMLs.

Author contribution

Ding 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: Ding, Jones and Cicuttini; Acquisition of data: Wang, Antony, Zhu, Han, Pan, Liu, Wang, Jin and Ding; Analysis and interpretation of data: Wang, Antony, Zhu, Han, Pan, Wang and Ding; Manuscript preparation: Wang, Antony, Zhu, Han, Pan, Wang, Jin, Liu, Cicuttini, Jones and Ding; Statistical analysis: Wang, Antony, Pan and Ding.

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Competing interest statement
All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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