Alterations to the Subchondral Bone Structure during Osteoarthritis: Bone Adaptation versus Endochondral Bone Formation

INTRODUCTION
Subchondral bone structure is altered in osteoarthritis (OA). Both the cause of the alterations and their effect on cartilage are subject of debate. Previously, we demonstrated that the changes in bone structure can be explained by physiologic bone remodeling in response to changes in joint loading or bone tissue mineralization [1]. In that study, the decrease in cartilage thickness in OA was considered to result from cartilage degeneration, while changes in the bone were considered to result from remodeling of the existing bone. An alternative hypothesis is that during OA, mineralized cartilage is replaced by bone tissue via endochondral ossification [2]. These changes of the mineralized cartilage lead to reduced cartilage thickness and changes in bone structure. However, the mechanism of the latter theory is very different from the first theory and endochondral ossification may lead to a different subchondral bone structure compared to adaptation of the existing bone tissue. Since endochondral ossification starts from a homogeneous mineral distribution, a more refined structure may be expected.

Our aim was to investigate if we could distinguish between structural changes in OA that result from adaptation of an existing bone structure, and structural changes that result from endochondral ossification. For this purpose, we used a combined experimental and numerical approach.

METHODS
Bone adaptation simulations
We used a mechanoregulated bone adaptation model that has previously been validated for both bone remodeling and the replacement of mineralized cartilage with bone tissue [3,4]. In the model, bone and mineralized cartilage are resorbed by osteoclasts. Resorption of bone is assumed to be triggered by randomly occurring microcracks, while resorption of mineralized cartilage is assumed to result from osteoclast delivery by blood vessels that randomly penetrate the mineralized cartilage in OA. The formation of bone by osteoblasts is regulated by osteocytes in response to mechanical loading.

We performed four simulations, representing: 1) baseline, 2) bone adaptation under increased joint loading, 3) endochondral ossification under normal joint loading, and 4) bone adaptation under increased joint loading combined with endochondral ossification. For the final structures, we determined the bone volume fraction (BV/TV), and trabecular number (Tb.N), thickness (Tb.Th), and separation (Tb.Sp).

Experiments
We examined 32 human OA tibia plateaus, obtained after total knee replacement (University Hospital Maastricht, The Netherlands). We cored cylindrical specimens perpendicular to the articular surface, with a diameter of 8 mm. Preferably, one specimen was analyzed for each compartment of the plateau. However, for 11 plateaus, specimens from one compartment could not be used for further analysis, due to limited sample height or the presence of cysts, leading to a total of 53 specimens (25 medial, 28 lateral). For each specimen, we graded cartilage degeneration according to the ICRS OA scoring system. Subsequently, the specimens were scanned with a microCT scanner at a resolution of 21 μm, and BV/TV, Tb.N, Tb.Th, and Tb.Sp were determined at different distances from the cartilage, between 0 and 4 mm depth.

RESULTS

Table 1: Simulated change in bone structure parameters compared to baseline.

<table>
<thead>
<tr>
<th>Sim.</th>
<th>Bone Structure Parameters</th>
<th>Baseline</th>
<th>Sim. 2: High load</th>
<th>Sim. 3: Normal load + Ossification</th>
<th>Sim. 4: High load + Ossification</th>
</tr>
</thead>
<tbody>
<tr>
<td>BV/TV</td>
<td>↑</td>
<td>=</td>
<td>↑</td>
<td>↓</td>
<td>=</td>
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<tr>
<td>Tb.N</td>
<td>↑</td>
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<tr>
<td>Tb.Th</td>
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</tr>
<tr>
<td>Tb.Sp</td>
<td>=</td>
<td>↑</td>
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</tr>
</tbody>
</table>

The bone structure changed compared to baseline for simulations 2, 3, and 4, such that all simulated conditions were distinct (figure 1, table 1).

DISCUSSION
To evaluate whether bone structural changes in OA result from adaptation of an existing bone structure, or from endochondral ossification, we compared our simulation results to the experimental data. In the samples with ICRS 4, BV/TV was increased and Tb.Sp was decreased. According to our simulations, these observations could both be explained by bone adaptation and endochondral ossification under high loading conditions, but not by endochondral ossification under normal loading conditions. The increase in Tb.Th that was observed in the experiments was in correspondence with adaptation under high loading conditions, but not with the other simulations. Finally, the experimentally determined increase in Tb.N was predicted for endochondral ossification under both normal and high loading conditions, but not for adaptation of the existing bone architecture.

As each of the simulations could explain specific experimental observations, while neither could individually explain all experimental data, we conclude that the cause of the bone structural changes observed in the experiments was probably multifactorial, and that both high loading conditions and endochondral ossification may have played a role.

SIGNIFICANCE
Both subchondral bone changes and cartilage thinning are important during OA. This study indicates a close relationship between these factors. This fundamental insight may contribute to the development of treatments to delay OA.

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REFERENCES