Bone structural changes in osteoarthritis as a result of mechanoregulated bone adaptation: a modeling approach

L.G.E. Cox, B. van Rietbergen*, C.C. van Donkelaar, K. Ito
Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, The Netherlands

Objective: There are strong indications that subchondral bone may play an important role in osteoarthritis (OA), making it an interesting target for medical therapies. The subchondral bone structure changes markedly during OA, and it has long been assumed that this occurs secondary to cartilage degeneration. However, for various conditions that are associated with OA, it is known that they may also induce bone structural changes in the absence of cartilage degeneration. We therefore aimed to investigate if OA bone structural changes can result from mechanoregulated bone adaptation, independent of cartilage degeneration.

Method: With a bone adaptation model, we simulated various conditions associated with OA without altering the articular cartilage and we evaluated if mechanoregulated bone remodeling by itself could lead to OA-like bone structural changes.

Results: For each of the conditions, the predicted changes in bone structural parameters (bone fraction, trabecular thickness, trabecular number, and trabecular separation) were similar to those observed in OA.

Conclusion: This indicates that bone adaptation in OA can be mechanoregulated with structural changes occurring independent of cartilage degeneration.

Introduction

Osteoarthritis (OA) is a common cause of long-term disability. It is characterized by degeneration of cartilage and modification of the structural and material properties of subchondral bone. Patients suffer from chronic joint pain, restriction of motion, crepitus with motion, and joint effusions. For many years, pharmaceutical therapies have been focussed on cartilage. The bone changes were thought to occur secondary to cartilage degeneration, and not to play a major role in the disease process. However, it has been shown in animal studies that subchondral bone changes occur at early stages of OA, and that alterations to subchondral bone can lead to cartilage degeneration. Furthermore, there is an increased incidence of OA in patients with certain bone disorders, and it has been shown that bone cells derived from OA patients can directly influence cartilage metabolism.

For these reasons, the bone is considered as a therapeutic target as well, and in various OA patient and animal studies, the subchondral bone structure has been investigated. OA is associated with marked increases in subchondral bone fraction and trabecular thickness, accompanied by decreases in trabecular number and separation. The cause of these bone structural changes remains unresolved and a better understanding might help in developing bone-targeting therapies.

A wide variety of conditions is associated with OA. Obesity, strenuous exercise, and physically demanding professions are all known risk factors for OA, which is largely attributed to the high joint loads associated with these conditions. Other conditions that alter joint loads and are strongly associated with OA are (partial) meniscectomy, anterior cruciate ligament (ACL) injury, and joint malalignment. In addition, OA is associated with the bone disease osteopetrosis, which is characterized by a decrease in osteoclast number and activity. Finally, bone matrix mineralization and stiffness have been found to decrease in OA bone, and although it is unclear whether this should be regarded as a cause or an effect of OA, it has been suggested that bone sclerosis in OA occurs to counteract the decrease in matrix stiffness.

The conditions associated with OA do not only alter joint mechanics and bone cellular activities in distinct ways; in addition they differ in the time course in which these changes occur. For example, osteopetrosis is already present at birth, while obesity...
may lead to a gradual increase in load, and ACL injury may alter joint mechanics abruptly. Considering the wide variety of conditions associated with OA, it is clear that OA can develop via multiple pathways. It is also known for most of these conditions that they themselves can induce bone structural changes even in the absence of OA, via mechanoregulated bone adaptation. This may explain why bone structural changes can occur early in the OA disease process, independent of cartilage degeneration. However, it is unclear if these structural changes caused by mechanoregulated bone adaptation are similar to the changes observed in OA, or that bone structural changes can occur early in the OA disease function:

\[ f(x, x_k) = e^{-\frac{d(x, x_k)}{D}} \]  

(2)

depending on the distance between osteocyte \( k \) and location \( x \) on the bone surface \( d(x, x_k) \), and decay parameter \( D \). If the total osteocyte stimulus \( P(x, t) \) exceeds formation threshold \( k_{thr} \), bone is formed according to:

\[ \frac{dV_f(x, t)}{dt} = \tau (P(x, t) - k_{thr}) \quad \text{if} \quad P(x, t) > k_{thr} \]  

(3)

Here, \( \frac{dV_f(x, t)}{dt} \) is the change in bone volume at location \( x \) due to bone formation, and \( \tau \) is a time constant related to the rate of bone formation. Resorption is assumed to be triggered by randomly occurring microcracks. This means that the chance of resorption is equal at all locations \( x \) on the bone surface. Furthermore, it is assumed that at each location \( x \) where resorption occurs, the same amount of bone \( V_d \) is resored within one increment, making the change of volume due to resorption at this location:

\[ \frac{dV_r(x, t)}{dt} = \begin{cases} -V_d & \text{if} \quad r(x, t) \leq \int_{t}^{t + \Delta t} \int_{z}^{z + \Delta z} F_{res} \, dx \, dt \\ 0 & \text{if} \quad r(x, t) > \int_{t}^{t + \Delta t} \int_{z}^{z + \Delta z} F_{res} \, dx \, dt \end{cases} \]  

(4)

Here, \( r(x, t) \) is a random number between 0 and 1, and \( F_{res} \) is the resorption frequency, indicating the frequency with which new resorption pits are formed on the bone surface. The total change of bone volume becomes:

\[ \frac{dV(x, t)}{dt} = \frac{dV_f(x, t)}{dt} + \frac{dV_r(x, t)}{dt} \]  

(5)

**Methods**

**Computational model**

The computational model is based on the theory of Huiskes et al.\(^ {37} \), that describes the metabolic processes in bone as a result of bone tissue loading sensed by osteocytes. It was previously shown that this theory can be used to simulate basal bone remodeling, and the adaptation of trabecular bone to alternative loading conditions and changes in bone cellular activities.\(^ {38,39} \)

In the model, osteocytes are randomly distributed throughout the bone tissue, and each osteocyte produces a stimulus \( P \) in response to the local strain energy density (SED) rate. At each location \( x \) on the bone surface, the total osteocyte stimulus \( P(x, t) \) is calculated by summation of the stimuli by the surrounding osteocytes:

\[ P(x, t) = \sum_{k=1}^{n} f(x, x_k) \mu U(x_k, t) \]  

(1)

Here, \( U(x_k, t) \) is the SED rate at the location of osteocyte \( k \), \( n \) is the total number of osteocytes within the influence distance of \( x \), \( \mu \) is the osteocyte mechanosensitivity, and \( f(x, x_k) \) is a signal decay function:

**Finite element analysis**

To calculate the local SED values, finite element analysis was used. We evaluated our hypothesis in a 2D domain that represents part of the articular cartilage and bone below the articular cartilage. We used a square mesh of 200 \( \times \) 200 elements, with an element size of 50 \( \times \) 50 \( \mu m \). The model consisted of 194 rows of bone tissue and six rows of articular cartilage. In the bone tissue, osteocytes were randomly distributed. The mesh was loaded statically with 2 MPa compression in the vertical direction (perpendicular to the cartilage), and 1.2 MPa in the horizontal direction, which for a linear elastic material represents the maximum SED rate of a dynamic load of 1 MPa and 0.6 MPa at 1 Hz respectively.\(^ {40} \) The initial mesh and boundary conditions are shown in Fig. 1, as well as the different loads applied for the different simulations.

![Diagram](image_url)

**Fig. 1.** The different loading conditions: (a) normal, (b) obesity, strenuous exercise, (c) malalignment, ACL injury, partial meniscectomy.
The volume change is calculated per integration point. If an integration point volume is completely filled with bone, the relative density is one. If an integration point does not contain any bone tissue, the relative density is zero. At the trabecular surface, integration point volumes can be partially filled with bone, leading to a relative density of bone volume per integration point volume between zero and one. At these locations, the elastic modulus was calculated using Currey’s power law41:

\[ E(n, k) = E_b \rho(n, k)^\gamma \]  

(6)

Here, \( E_b \) is the elastic modulus of the bone matrix, \( \rho(n, k) \) is the bone volume density at integration point location \( n \) at time increment \( k \), and \( \gamma \) is a material constant. The model parameter values are in Table I. Since we used 2D analyses, parameters are related to area instead of volume. The derivation of the model parameter values was described in a previous paper39.

**Simulations of conditions associated with OA**

**High joint load**

Obesity, strenuous exercise, and physically demanding professions uniformly increase joint loads, while partial meniscectomy, ACL injury, and malalignment increase joint loads in a spatially non-uniform matter. ACL injury and varus alignment increase medial loading53,54, and valgus alignment increases lateral loading53,54, while for partial meniscectomy the redistribution of load depends on the location of the meniscectomy.

We simulated bone remodeling in response to both a spatially uniform and a spatially non-uniform increase in load (Fig. 1, Table II). For the uniform high load we chose a 40% increase compared to normal56. For the non-uniform increase in load we applied a ramp load on top of the cartilage, ranging from the normal load to a 40% increase53,55,56.

**Decreased bone matrix stiffness**

To simulate bone remodeling in response to a decrease in mechanical bone matrix properties, we decreased bone matrix stiffness by 40%, based on nanoindentation measurements from an OA patient study33.

**Bone disease**

Osteopetrosis is mainly characterized by a decrease in osteoclast number and activity31, and we simulated osteopetrosis by decreasing the corresponding model parameters (Table II). Because the amount of decrease in osteoclast number and activity varies for different forms and severities of the disease, no exact parameter changes could be derived from the literature. Therefore, we made an arbitrary choice to decrease the resorption frequency by 60% and the resorption cavity size by 30%.

**Simulation protocols**

First, we performed a simulation with the normal parameter set, until equilibrium was obtained. Subsequently, we used this ‘normal’ structure as starting point for the simulation of condition 1, condition 2, and condition 3 (Table II), assuming that these conditions develop at a certain time during adulthood. For condition 4, we did not use the normal structure as starting point, since osteopetrosis is already present at birth. Instead we started from the uniform structure that was also the starting point for the ‘normal’ simulation.

**Bone structure parameters**

To evaluate the effect of the different simulated conditions, we determined structure parameters from the simulated bone architectures. Bone density was determined by dividing the area of bone by the total area, and trabecular number by counting the trabecular intersections along each horizontal pixel row. Trabecular thickness was defined for each trabecular surface pixel as the smallest distance to another trabecular surface pixel, bordering a different marrow cavity. Trabecular separation was defined for each marrow cavity as the largest distance between two bone surface pixels bordering the marrow cavity.

**Results**

From the simulated structures (Fig. 2), bone structural parameters were determined. These parameters are in Table III, together with literature values determined from human cancelous bone at different sites. Trabecular dimensions for the normal simulation are similar to experimentally determined values (Table III), although the simulated bone fraction is slightly high, while trabecular number is slightly low compared to literature values. The explanation for these deviations is that in our simulations all trabeculae are interconnected in the 2D plane in contrast with normal bone structures, thereby leading to a higher bone fraction for the same trabecular number and thickness.

Experimentally determined changes in bone structure parameters as a result of OA vary considerably, depending on for example the severity of the disease, making quantitative comparison to our simulations inadvisable. However, to obtain an idea of the in vivo range of change in structural parameters, we included OA data from clinical and animal studies from the literature in Table IV.

**Table I**

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Variable</th>
<th>Value</th>
<th>Unit</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>Osteocyte density</td>
<td>1600</td>
<td>mm(^{-2} )</td>
<td>[42]</td>
</tr>
<tr>
<td>( D )</td>
<td>Osteocyte signal decay parameter</td>
<td>0.1</td>
<td>mm</td>
<td>[43]</td>
</tr>
<tr>
<td>( V_{sc} )</td>
<td>Resorption space</td>
<td>( 1.5 \times 10^{-3} )</td>
<td>mm(^3 ) h(^{-1} )</td>
<td>[44,45]</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>Material constant</td>
<td>3.0</td>
<td>–</td>
<td>[41]</td>
</tr>
<tr>
<td>( \mu )</td>
<td>Osteocyte mechanosensitivity</td>
<td>0.5</td>
<td>nmol mm(^{-1} ) h(^{-1} )</td>
<td>[41]</td>
</tr>
<tr>
<td>( \kappa_{th} )</td>
<td>Formation threshold</td>
<td>( 2.0 \times 10^{-4} )</td>
<td>nmol mm(^{-1} ) h(^{-1} )</td>
<td>[41]</td>
</tr>
<tr>
<td>( \tau )</td>
<td>Time constant</td>
<td>( 9.1 \times 10^{-4} )</td>
<td>mm(^3 ) mmol(^{-1} )</td>
<td>[41]</td>
</tr>
<tr>
<td>( F_{rs} )</td>
<td>Resorption frequency</td>
<td>12.8</td>
<td>mm(^{-1} ) h(^{-1} )</td>
<td>[41]</td>
</tr>
<tr>
<td>( E_b )</td>
<td>Elastic modulus bone</td>
<td>( 5 \times 10^1 )</td>
<td>MPa</td>
<td>[46–48]</td>
</tr>
<tr>
<td>( \rho )</td>
<td>Poisson ratio bone</td>
<td>0.3</td>
<td>–</td>
<td>[49,50]</td>
</tr>
<tr>
<td>( E_c )</td>
<td>Elastic modulus articular cartilage</td>
<td>6</td>
<td>MPa</td>
<td>[51,52]</td>
</tr>
<tr>
<td>( r_c )</td>
<td>Poisson ratio articular cartilage</td>
<td>0.49</td>
<td>–</td>
<td>[52]</td>
</tr>
</tbody>
</table>

**Table II**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Model parameter change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Obesity, strenuous exercise</td>
<td>Uniform 40% increase in load</td>
</tr>
<tr>
<td>2. Malalignment, ACL injury, partial meniscectomy</td>
<td>0–40% increase in load perpendicular to the joint surface (ramp load)</td>
</tr>
<tr>
<td>3. Decreased mineralization</td>
<td>40% decrease in bone matrix stiffness ( E_b )</td>
</tr>
<tr>
<td>4. Osteopetrosis</td>
<td>60% decrease in resorption frequency ( F_{rs} ) and 30% decrease in resorption cavity size ( V_{sc} )</td>
</tr>
</tbody>
</table>
From Fig. 2 and Table IV it can be seen that each simulated condition led to an increase in bone fraction and trabecular thickness, and a decrease in trabecular number and separation, in concurrence with experimental data from OA patients and animal studies.

The simulation representing joint malalignment and ACL injury resulted in the smallest changes in bone structural parameters. The explanation for this is that bone changes in this simulation were local, while the determined structure parameter values are an average for the whole mesh. The changes mostly occurred on the right side of the structure, underneath the area of the most highly loaded cartilage. Such localized sclerosis is in agreement with experimental data from OA patients with bone malalignment\(^{62}\).

The increase in bone fraction is the most marked in the simulation of osteopetrosis, which agrees with the association of osteopetrosis with severe sclerosis.

We calculated the average SED value in the bone tissue during the period of bone remodeling for each condition and compared these to the average SED value for the normal equilibrium simulation (Fig. 3). Obesity, strenuous exercise, malalignment, ACL injury, partial meniscectomy and decreased mineralization all led to an increase in SED. This was either due to an increase in both stress and strain resulting from an increase in load, or due to an increase in strain caused by a decrease in matrix stiffness. During remodeling, bone fraction increased such that the SED returned to the normal level or even decreased to slightly below the normal level. The SED values for osteopetrosis are not shown in Fig. 3, since we did not use the normal structure as input for this simulation. The average SED value in the bone was much lower in the simulation of osteopetrosis, due to the higher bone fraction.

We also determined the apparent bone stiffness at the onset of the conditions and after remodeling (Fig. 4). The stiffness before and at the onset of the conditions is not shown for osteopetrosis, since there was no clear onset point in this case, but at the end of this simulation the apparent bone stiffness was 172% higher than normal. As expected, the apparent bone stiffness at the onset of the condition decreased by approximately 40% in case of the decreased matrix stiffness, while there was no change in apparent bone stiffness at the onset of the conditions for the simulations in which the load was increased. Remodeling resulted in an increase in apparent bone stiffness for all conditions. In case of the increased loads, the increase in bone fraction that occurred during remodeling led to an apparent bone stiffness which was higher than normal (74% increase for obesity/exercise, and 17% increase for ACL injury/meniscectomy/malalignment), while the increase in bone fraction in case of decreased mineralization normalized the apparent bone stiffness (from 40% lower than normal at the onset of the condition to 8% lower than normal after remodeling).

**Discussion**

The bone structural changes that we predicted using a mechnoregulated bone adaptation model, are in agreement with bone structural changes observed in OA. This indicates that subchondral bone structural changes observed in OA can occur independent of

<table>
<thead>
<tr>
<th>Condition</th>
<th>BF</th>
<th>Tb.Th</th>
<th>Tb.N</th>
<th>Tb.Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Obesity, strenuous exercise</td>
<td>+32%</td>
<td>+29%</td>
<td>−25%</td>
<td>−20%</td>
</tr>
<tr>
<td>2. ACL injury, partial meniscectomy/malalignment</td>
<td>+11%</td>
<td>+11%</td>
<td>−2%</td>
<td>−7%</td>
</tr>
<tr>
<td>3. Reduced mineralization</td>
<td>+23%</td>
<td>+22%</td>
<td>−14%</td>
<td>−17%</td>
</tr>
<tr>
<td>4. Osteopetrosis</td>
<td>+63%</td>
<td>+7%</td>
<td>−22%</td>
<td>−68%</td>
</tr>
<tr>
<td>Literature data on OA(^{13–15,17,61})</td>
<td>+(18–80)%</td>
<td>+(13–87)%</td>
<td>−(9–15)%</td>
<td>−(18–26)%</td>
</tr>
</tbody>
</table>

---

**Table III**

<table>
<thead>
<tr>
<th>Bone structure parameters baseline simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulation</td>
</tr>
<tr>
<td>Bone fraction (BF)</td>
</tr>
<tr>
<td>Trabecular thickness (Tb.Th)</td>
</tr>
<tr>
<td>Trabecular number (Tb.N)</td>
</tr>
<tr>
<td>Trabecular separation (Tb.Sp)</td>
</tr>
</tbody>
</table>

**Fig. 2.** Simulated bone structures for different conditions: (a) normal, (b) obesity, strenuous exercise, (c) ACL injury, partial meniscectomy, malalignment, (d) reduced mineralization, (e) osteopetrosis.
cartilage degeneration, and that they do not need to result from disturbed mechanoregulation or inflammatory processes that occur as a direct result of the disease. However, this does not mean that cartilage degeneration cannot (indirectly) induce or promote bone structural changes in OA. Although in the current study we focused on the adaptation of the subchondral bone, altered joint mechanics also affect the articular cartilage. Pathology begins if the repair capacity of the osteochondral tissue has been exceeded, which usually is a process of many years. Once the degeneration has begun, the degenerative processes and mechanical adaptation likely interact. Degeneration of cartilage is thought to increase the stress in the subchondral bone, and additionally, it may lead to joint malalignment, which would both induce a remodeling response according to our simulations. Furthermore, the decrease in bone matrix stiffness observed in OA may be related to cartilage degeneration. In OA femoral heads, bone matrix stiffness was found to be most markedly decreased directly underneath the cartilage and in a study on OA knees, the bone structural changes were also most marked directly underneath the cartilage, and additionally seemed correlated to the degree of degeneration of the overlying cartilage.

Our simulations do not exclude the possibility that a different, pathological process influences bone formation and resorption in OA. However, they do show that it is likely that mechanoregulation is still present, ensuring that bone is formed at locations of high mechanical load, and resorbed at locations of low mechanical load.

If mechanoregulated bone remodeling is indeed the mechanism behind the bone structural changes in OA, what does this mean for the development of bone-targeting therapies? Currently, pharmaceutical therapies are being developed that target osteoblasts and osteoclasts, and decrease the bone remodeling rate. Although the bone turnover rate is indeed increased in OA, our study indicates that bone formation and bone resorption are not necessarily disturbed. Furthermore, inhibiting bone remodeling may negatively affect bone, since it may lead to higher local bone tissue loading as shown in Fig. 3.

In addition to the effect that bone-targeting therapies have on bone, they may have an effect on cartilage. It has been suggested that cartilage degeneration in OA is related to the subchondral bone stiffness. Both an increase and a decrease in apparent bone stiffness have been suggested to lead to cartilage degeneration. If both hypotheses hold, the effect of inhibiting bone remodeling on cartilage may depend on the underlying cause of the disease. Inhibiting bone remodeling in case high joint loads or osteopetrosis are the underlying cause of the disease may be beneficial, since this may prevent an increase in bone stiffness (Fig. 4). However, in case decreased mineralization is the underlying cause of the disease, inhibiting remodeling may have a negative effect on cartilage, since it may prevent ‘normalization’ of the apparent bone stiffness (Fig. 4). Of course, if inhibiting remodeling would prevent the replacement of normal bone tissue by less mineralized bone matrix, this may counteract the initial decrease in apparent bone stiffness observed in our simulations. Furthermore, it should be noted that other factors may play a role as well, as it has been shown that bone cells isolated from OA bone may directly alter cartilage metabolism in vitro.

In our model it is assumed that osteocytes can sense an SED equivalent loading measure and that they can stimulate osteoblast cells in their vicinity. Although these are assumptions, we have demonstrated in earlier studies that this model can explain a large number of trabecular bone features, and that its results are not strongly dependent on the choice of the exact load parameter sensed by the osteocytes or even the assumed regulation mechanism. In the present study we used a 2D model, which limits the structures that can be represented. However, a thorough parameter study showed that for this 2D model, alterations in bone structure parameters in response to a change in various model parameters are in agreement with experimental data from literature.

In conclusion, mechanoregulated bone remodeling may explain how various conditions associated with OA can directly induce OA-like bone structural changes, independent of changes occurring in the cartilage. Also, it may explain why bone structural changes can occur secondary to cartilage degeneration. Given the hypothesis underlying our theoretical work, we propose that decreasing the rate of bone remodeling in OA may increase bone tissue loading. Furthermore, we postulate that whether decreasing the rate of bone remodeling has a beneficial effect on cartilage degeneration may depend considerably upon the underlying cause of the disease.

Author contributions

All authors contributed to the conception and design of the study, analysis and interpretation of the data, and revision of the article. L.G.E. Cox performed the simulations and drafted the article. All authors granted final approval.

Conflict of interest

None.
Acknowledgments

This project is funded by the Royal Netherlands Academy of Arts and Sciences.

References