The role of pressurized fluid in subchondral bone cyst growth

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ABSTRACT

Pressurized fluid has been proposed to play an important role in subchondr al bone cyst development. However, the exact mechanism remains speculative. We used an established computational mechanism-regulated bone adaptation model to investigate two hypotheses: 1) pressurized fluid causes cyst growth through altered bone tissue loading conditions, 2) pressurized fluid causes cyst growth through osteocyte death. In a 2D finite element model of bone microarchitecture, a narrow cavity was filled with fluid to resemble a cyst. Subsequently, the fluid was pressurized, or osteocyte death was simulated, or both. Rather than increasing the load, which was the prevailing hypothesis, pressurized fluid decreased the load on the surrounding bone, thereby leading to net bone resorption and growth of the cavity. In this scenario an irregularly shaped cavity developed which became rounded and obtained a rim of sclerotic bone after removal of the pressurized fluid. This indicates that cyst development may occur in a step-wise manner. In the simulations of osteocyte death, cavity growth also occurred, and the cavity immediately obtained a rounded shape and a sclerotic rim. Combining both mechanisms increased the growth rate of the cavity. In conclusion, both stress-shielding by pressurized fluid, and osteocyte death may cause cyst growth. In vivo observations of pressurized cyst fluid, dead osteocytes, and different appearances of cysts similar to our simulation results support the idea that both mechanisms can simultaneously play a role in the development and growth of subchondral bone cysts.

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Introduction

Bone cysts, also referred to as intraosseous ganglia or geodes, are generally located in the trabecular bone near the articular surface. They are frequently associated with osteoarthritis and osteochondral lesions resulting from a traumatic event, but they may also develop idiopathically [1]. On radiographs, bone cysts are visible as areas of radiolucency. They usually have a fibrous lining [2–10] and can be surrounded by a rim of sclerotic bone [2,4,5,11–13]. Fig. 1a,b shows multiple cystic lesions in a tarsus, which developed a sclerotic rim in the course of time.

Regarding the etiology of bone cysts, different theories have been proposed. One theory states that pressurized synovial fluid enters the bone through a fissure and fractures trabeculae, thereby causing an area of osteolysis [14]. According to this theory, a rim of sclerotic bone may result from the displacement of trabeculae by the fluid together with bone formation in response to the increased strain [14]. Although there is not much evidence indicating that pressurized fluid fractures trabeculae, loading conditions of the surrounding bone may indeed be altered in the presence of pressurized fluid. This may induce a mechanoregulated bone adaptation response. According to a second theory, pressurized fluid may decrease perfusion and oxygen supply, thereby leading to osteocyte death and ensuing osteolysis [15,16]. This alternative hypothesis is partly supported by a clinical study in which high intraosseous pressure was associated with low intraosseous pO2 and osteonecrosis [17], and by an animal study in which osteocyte lacunae close to an area of high fluid pressure were empty, indicating cell death [18].

The underlying assumption for both hypotheses is that pressurized fluid plays a crucial role in the development of bone cysts. Supporting evidence for this assumption can be found in the literature. First, bone cysts usually contain fluid [2,3,5,7–9,19]. This has been attributed to synovial fluid intrusion [14,15] because the cartilage overlying the cysts is often damaged [3,16,14] and a connection between the cyst and the joint space is frequently found [11,16,20–22]. In addition, free inflow of contrast medium from the joint space into a cyst has been demonstrated [16]. The contrast medium accumulated in the cyst, indicating that cysts are enclosed cavities in which pressure can build up. This is confirmed by an experimental study in which cyst pressure closely resembled intra-articular pressure in two patients [23]. High fluid pressure may also explain the pain associated with cysts [1]. Patients with bone cysts mostly experience pain in relation to load-bearing activity [4,9,20], which seems to be in agreement with...
Fig. 1. Multiple cystic lesions in the talus, which developed a sclerotic rim. (a) CT image of the talus, coronal view. (b) CT image of the same patient, 11 months later.

dynamic fluid pressure resulting from synovial fluid intrusion through an osteochondral lesion upon joint loading [1]. In addition, high intraosseous pressure is associated with pain in osteoarthritis [24].

Bone cysts can develop in the course of months. They are usually discovered and surgically treated in a late stage, after they have become symptomatic. A better understanding of the etiology of subchondral bone cysts may help in obtaining earlier diagnoses and developing less invasive treatment options. If cyst growth indeed is solely caused by altered mechanical conditions and/or localized osteocyte death, this means that the bone adaptation mechanism remains intact around cysts. During normal bone adaptation, osteocytes are thought to act as mechanosensors and regulate osteoblast and osteoclast activity [25–27]. This adaptive process has been described by mathematical models, which can successfully predict alterations in bone microarchitecture in response to changes in mechanical loading and bone cell metabolism [28,29].

In the current study, we used an established computational mechanoregulated bone adaptation model to evaluate whether altered loading conditions and/or osteocyte death, resulting from the presence of pressurized fluid, could result in cyst growth, as observed clinically. Since multiple studies suggest that the connection between the cyst and the joint space may become closed in the course of time [6,14,22], we also investigated the effect of restriction of fluid inflow in our simulations.

Methods

Computational model

The computational model is based on the theory of Huiskes et al. [30] that describes the modulation of metabolic processes in bone in response to bone tissue loading sensed by osteocytes. In the current study, we used the model to predict bone architectural changes in response to altered bone tissue loading near a cavity filled with pressurized fluid, and to predict bone architectural changes in response to osteocyte death near the boundary of a cavity. 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. At each location $x$ on the trabecular bone surface, the total osteocyte stimulus $P(x,t)$ is calculated by summation of the stimuli of the surrounding osteocytes:

$$P(x,t) = \sum_{k=1}^{n} f(x,x_k) \mu(x_k,t).$$

Here, $U(x_k,t)$ is the strain energy density 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:

$$f(x,x_k) = \frac{e^{-D|x-x_k|}}{\|x-x_k\|_2^2},$$

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:

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

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. Model parameter $F_{res}$ indicates the chance of a new resorption pit being formed per mm$^2$ of bone tissue and per hour. The accumulated chance of a new resorption pit to be formed within a volume of tissue and within a time interval then can be described as:

$$F_{res}^{acc} = \int F_{res} dx dt.$$

In the present description it is assumed that the volume and time step are small enough such that $F_{res}^{acc} = 1$. Since in our model both the element volume and time step are constants, $F_{res}^{acc}$ is a constant as well such that this condition could be checked easily. To determine whether resorption occurs at location $x$ on time point $t$, a random number $r(x,t)$ between 0 and 1 is generated and resorption only occurs when this number is smaller than $F_{res}^{acc}$.

Furthermore, it is assumed that at each location $x$ where resorption occurs, the same amount of bone $V_f$ is resorbed, making the change of volume due to resorption at this location:

$$\frac{dV_f(x,t)}{dt} = \frac{dV_f(x,t)}{dt} + \frac{dV_f(x,t)}{dt}.$$

With this volume change, the local relative bone density $\rho(x,t)$ (ranging between 0 and 1) can be calculated. As remodeling only occurs at the trabecular bone surface, the local relative density is 1 for all trabecular elements, 0 for the bone marrow elements, and between 0 and 1 for the bone surface elements. The local density influences the elastic modulus of the tissue $E(x,t)$ according to:

$$E(x,t) = E_0 (\rho(x,t))\gamma.$$  

Here, $E_0$ is the elastic modulus of the bone matrix and $\gamma$ is a material constant.

Finite element model

We evaluated the two different mechanisms of bone cyst growth in a 2D domain that represents part of the articular cartilage and bone below the articular cartilage. We used a rectangular mesh of 200×310 elements, with an element size of 50 $\mu$m × 50 $\mu$m. The model consisted of 300 rows of bone tissue and 10 rows of articular cartilage, which were modeled as isotropic linear elastic materials. In the bone tissue, osteocytes were randomly distributed. The mesh was loaded statically with 1.6 MPa compression in the vertical direction (perpendicular to the cartilage), and 1.2 MPa in the horizontal direction. In a previous study it was shown that for a linear elastic material, the strain energy density values for these loading conditions represent the maximum strain energy density rate of a dynamic load of 0.8 MPa and 0.6 MPa at 1 Hz [31]. The choice for the applied loads is not straightforward, since reported cancellous (long) bone stress values cover a wide range [32,33]. However, in this study the exact applied load values are not...
that important, since they are ‘scaled’ via the osteocyte mechanosensitivity, which is chosen such that a realistic bone turnover rate and bone structure parameters are obtained. The model parameter values are in Table 1 and the derivation of these values was described previously [29].

Cyst growth

To evaluate the hypothesis that altered loading conditions in the presence of pressurized fluid in a cyst may cause cyst growth, a single marrow cavity was filled with fluid in the model. The fluid pressure inside this cavity was set equal to the pressure applied to the articular cartilage, representing a connection between the cyst and the joint space. Under these conditions, the bone was allowed to remodel for 2500 h. Subsequently, the fluid was removed to simulate closure of the communication, and the bone was allowed to remodel for an additional 1500 h. To test the second hypothesis, that osteocyte death may cause cyst growth, a single fluid was removed to simulate closure of the connection to the joint space, halted cyst growth and further bone remodeling was ended to simulate closure of the communication, and the bone was allowed to remodel for an additional 2500 h. Subsequently, the strain energy density distribution was calculated.

For each simulation increment we calculated the average strain energy density of the cyst boundary elements, the average osteocyte stimulus in these boundary elements, and the surface area of the cavity. To evaluate the effect of the application of fluid pressure and osteocyte death on the strain energy density, osteocyte stimulus, and cyst area, we normalized these values to those calculated before applying fluid pressure and osteocyte death.

To verify that the development and growth of cyst-like cavities in our simulations does not depend on the specific simulation conditions, we varied multiple simulation parameters. For the fluid pressure series and the osteocyte death series, we performed simulations for initial cyst cavities at two different distances from the cartilage, with two different initial cyst cavity sizes, and for two different initial structures. In addition, we performed osteocyte death simulations and combined simulations for three different distances of osteocyte death (D\text{dead}) of 0.015 mm, 0.03 mm and 0.06 mm, and for a decreasing osteocyte signal with decreasing distance from the cyst cavity:

\[ P(x, t) = P(x, t) \times \left( \frac{d_{\text{cyst}}(x, t)}{D_{\text{dead}}} \right) \text{ for } d_{\text{cyst}}(x, t) < \sqrt{D_{\text{dead}}}. \]

with \(d_{\text{cyst}}(x,t)\) the distance to the cyst, and \(D_{\text{dead}}\) set at 0.03 mm.

Finally, we investigated whether the effect of fluid pressure in our 2D simulations is comparable to the effect of fluid pressure in 3D structures. For this purpose, we used a square (3 mm × 3 mm) and cube (3 mm × 3 mm × 3 mm) of bone tissue, containing a circular or spherical cavity in the center respectively with a radius of 1.5 mm. Static 1.6 MPa compression was applied perpendicular to all sides of the square and cube. To investigate the effect of fluid pressure, the cavity was subsequently pressurized with 0, 0.8, 1.6, and 2.4 MPa, after which the strain energy density distribution was calculated.

Results

Based on our simulations starting from different initial bone structures, with different sizes and locations of the initial cyst, and for different distances within which osteocyte death occurred, we conclude that the development and growth of a cyst-like cavity is not strongly dependent on the specific simulation conditions, although the rate of cyst growth may vary (Appendix A). Therefore, for each of the two proposed cyst growth mechanisms, and the combination of both, the results of only one simulation series are shown. For the shown osteocyte death simulation results, no osteocyte signal was produced by osteocytes within 0.03 m of the cyst cavity.

Bone remodeling in response to pressurized fluid inside the cavity led to growth of the cavity, which obtained an irregular shape (Figs. 2b and c). Subsequent removal of the pressurized fluid, to simulate closure of the connection to the joint space, halted cyst growth and resulted in a rounded cavity surrounded by a sclerotic rim (Fig. 2d). The reason for the growth of the fluid-filled cavity is that, in contrast with the trabecular overloading hypothesis, pressurized fluid inside the cyst decreased the strain energy density in the bone tissue surrounding the cyst (Fig. 3a). The osteocytes in close vicinity to the cavity responded to this decrease in mechanical loading by producing less osteoblast

<table>
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<th>Variable</th>
<th>Value</th>
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<td>(n)</td>
<td>Osteocyte density</td>
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<td>mm(^{-2})</td>
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<td>Osteocyte signal decay parameter</td>
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**Fig. 2.** Bone remodeling in response to cyst fluid pressure. (a) A marrow cavity is filled with pressurized fluid. (b) and (c) Growth of the cavity in response to the cyst fluid. (d) Development of a rounded cavity surrounded by a sclerotic rim after removal of the pressurized cyst fluid.
stimulatory signal (Fig. 3b), resulting in net bone resorption and thus growth of the cavity (Fig. 3c). After removal of the pressurized fluid the strain energy density at the boundary of the cavity was initially increased, and the bone remodeled such that the strain energy density returned to its normal level (Fig. 3a). This remodeling initially increased the size of the cavity, but after stabilization of the strain energy density cyst growth was halted (Fig. 3c).

The simulations mimicking osteocyte death directly resulted in the development and growth of a rounded cavity with a sclerotic rim (Figs. 4a–c). Prohibition of further osteocyte death halted cyst growth (Fig. 4d). In contrast with the fluid pressure simulation, the strain energy density values at the boundary of the cavity did not change in case cell death occurred (Fig. 5a). The osteocyte signal decreased at the boundary of the cavity (Fig. 5b), and similar to what happened in a pressurized cyst, this decrease in osteoblast stimulatory signal resulted in net bone resorption and thus growth of the cavity (Fig. 5c). When further osteocyte death was prohibited, the osteocyte signal gradually increased back to its normal level (Fig. 5b), because the bone containing the dead osteocytes was replaced with viable bone tissue, and cyst growth was halted (Fig. 5c).

In the simulation for which the bone microarchitecture is shown in Fig. 6, the combination of pressurized fluid and osteocyte death resulted in the rapid growth of an irregularly shaped cavity (Figs. 6a–c and 7c). Removal of the pressurized fluid and prohibition of further osteocyte death to simulate closure of the connection to the joint space, halted cyst growth and resulted in a rounded cavity surrounded by a sclerotic rim (Fig. 6d).

The decrease in the strain energy density in the bone tissue surrounding the cyst (Fig. 7a), was comparable with the strain energy density decrease in the fluid pressure simulation (Fig. 3a). Due to the combination with osteocyte death, the decrease in osteocyte stimulus was larger in the combined simulation (Fig. 7b), resulting in faster growth of the cavity. Removal of the pressurized fluid and prohibition of further osteocyte death led to an increase in osteocyte stimulus and formation of a sclerotic rim, thereby slightly decreasing the size of the cavity.

The effect of fluid pressure on the strain energy density in the surrounding bone tissue is comparable between a 2D and a 3D geometry (Fig. 8). Increasing the fluid pressure up to a pressure equal to the external load decreases the strain energy density. A further increase will increase the strain energy density values, but for a pressure of 1.5 times that of the external load, the strain energy density in the bone tissue is still lower compared to that in the simulation without fluid pressure.

**Discussion**

In this study, we aimed to evaluate whether altered loading conditions and/or osteocyte death, as a result of pressurized fluid, could lead to subchondral cyst growth, through mechanoregulated bone adaptation. Both conditions induced growth of a cystic cavity in our simulations, but an intriguing difference in the process of cyst growth was present between the two situations. The mechanisms involved are explained in the following two paragraphs.

Interestingly, the presence of pressurized fluid led to a decrease in the strain energy density in the trabeculae surrounding the cyst, in contrast with the overloading hypothesis of Landells [14]. The pressurized fluid in the cavity counteracted the compression loading on the bone. Nevertheless, remodeling in response to the presence of pressurized fluid did result in growth of the cavity, because the stress-shielding by the fluid induced net bone resorption. However, the appearance of the cyst was irregular. Although this is unlike the generally accepted rounded shape of the sclerotic rim, irregularly shaped cysts are observed as well (Figs. 1 and 9). To obtain the rounded

**Fig. 3.** (a) The average strain energy density (SED) in the elements at the boundary of the cavity. (b) The average osteocyte stimulus in these boundary elements. (c) The surface area of the cavity.

**Fig. 4.** Bone remodeling in response to osteocyte death. (a) Osteocytes in close vicinity to a marrow cavity are killed. (b) and (c) Growth of the cavity in response to dead osteocytes. (d) When further osteocyte death was prohibited, to mimic closing of the communication between the cyst and the joint space, a rounded cavity with a sclerotic rim remained.
cyst-like appearance, a period of pressure release was required in the model. Pressure release may be related to (temporary) closure of the connection to the joint space [6,14,22]. This could also explain why fluid is not always found inside cysts [6,12,14]. Alternatively, pressure release may occur if resorption of trabeculae increases the size of the bony cyst cavity in a step-wise manner. The enlarged cavity may not be immediately filled by the fibrous, fluid-containing cyst, thereby temporarily releasing pressure. This could for example explain the cystic appearance in Fig. 9d, with a fibrous lining that does not seem to fill the cavity completely.

Remodeling in response to osteocyte death in close vicinity to the cavity also led to the development and growth of a cyst-like cavity in our model. Although it is not surprising that the simulation of osteocyte death resulted in bone loss, it is remarkable that osteolysis was not random, but led to the development of cavities which resembled cysts that are found in vivo. Bone adaptation in response to osteocyte death resulted in cavities with a rounded shape and a thickened rim, which could not have been predicted without performing these simulations. The decrease in osteoblast stimulatory signal resulted in net bone resorption at the inner boundary of the cavity. This in turn increased the load on the trabeculae surrounding the cavity, thereby stimulating the development of a sclerotic rim.

Combining fluid pressure and osteocyte death resulted in the largest decrease of osteocyte signal, and therefore the fastest growth of the cavity. For the simulation results of osteocyte death shown in this paper, osteocytes within 30 μm of the edge of the cavity were assumed to be dead. Because the osteocyte influence distance was larger than 30 μm, this means that the osteoblast stimulatory signal

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**Fig. 5.** (a) The average strain energy density (SED) in the elements at the boundary of the cavity. (b) The average osteocyte stimulus in these boundary elements. (c) The surface area of the cavity (bottom).

**Fig. 6.** Bone remodeling in response to the combination of fluid pressure and osteocyte death. (a) A marrow cavity is filled with pressurized fluid and osteocytes in close vicinity to the cavity are killed. (b) and (c) Growth of the cavity in response to fluid pressure and dead osteocytes. (d) When the pressurized fluid was removed and further osteocyte death was prohibited, to mimic closing of the communication between the cyst and the joint space, a rounded cavity with a sclerotic rim remained.

**Fig. 7.** (a) The average strain energy density (SED) in the elements at the boundary of the cavity. (b) The average osteocyte stimulus in these boundary elements. (c) The surface area of the cavity.
was decreased but not absent at the inner boundary of the cavity (Fig. 5b).

It should be noted that we did not aim to investigate whether fluid pressure can cause osteocyte death, but whether osteocyte death can cause the development and growth of cyst-like cavities. Indications exist that osteocyte death occurs during cyst development. Necrotic bone tissue [16,21] and dead osteocytes [35] have been found around cysts. In addition, it has been shown that cysts are preceded by areas of bone marrow edema [36,37], which is associated with osteonecrosis [38]. However, it is unclear if osteocyte death always occurs and if it is the result of the presence of pressurized cyst fluid. For these reasons, we simulated osteocyte death by suppressing osteocyte signaling within a certain distance from the cyst boundary rather than making osteocyte death dependent on the fluid pressure. Similarly, we simulated closing of the connection to the joint space by instantaneously removing the pressurized fluid and/or prohibiting further osteocyte death. Although this may be non-physiologic, it is an adequate approach for our study since we aimed to investigate the effect of closing on cyst growth rather than the mechanism of closing itself.

Our simulation results show resemblance to the different appearances of cysts observed clinically. Fluid pressure led to an irregularly shaped cyst without a clearly defined sclerotic rim, similar to the cyst in Fig. 9b, and subsequent release of the fluid pressure led to a regularly shaped cyst surrounded by a rim of sclerotic bone, similar to the cyst in Fig. 9a. Osteocyte death directly resulted in a regularly shaped cavity, surrounded by sclerotic bone. Furthermore, we observed that in the simulation where we combined fluid pressure and osteocyte death, the cavity grew towards the articular surface, similar to the cyst in Fig. 9c.

In our simulations, growth of the cyst is accompanied by the resorption of trabeculae, which results in openings between the cyst and the intraosseous space. Openings between cysts and the intraosseous space are also present in vivo (Fig. 9d, [6–8,21,34]). The fluid seems to be contained inside the cyst by the fibrous lining [4,5,8], which is supported by the surrounding bone. Because we did not take into account the fibrous lining of the cyst, we defined an adjacent cavity as part of the cyst once a connection with the cyst was established. This stepwise increase in cyst size occurred a few times in both simulations, as can be seen in Figs. 3c and 5c. In vivo, probably first the fibrous tissue encapsulating the cyst fluid needs to expand to fill the enlarged cavity. Therefore, the stepwise changes in cyst size may be more gradual in vivo.

Defining an adjacent cavity as part of the cyst was only possible because we performed our analyses in 2D. In 3D, no separate cavities can be identified, since most of the marrow cavities are interconnected. The choice for 2D simulations limited the structures that can be represented.

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![Fig. 8. The strain energy density distribution in bone tissue surrounding a fluid-filled cavity, for different pressures applied to this cavity in 2D (top) and 3D (bottom).](image)

![Fig. 9. Different cyst appearances, adapted from Harrison et al., 1953, Woods, 1961, and Schrank et al., 2003. a) Regularly shaped cavity, surrounded by a rim of sclerotic bone [21]. b) Irregularly shaped cavity, without a clearly defined sclerotic rim [10]. c) Cavity with a large opening to the joint space, without a clearly defined sclerotic rim [34]. d) Cavity with a clear fibrous lining, surrounded by a discontinuous rim of bone [21].](image)
and it is unclear if a 2D cyst-like cavity is representative of the in vivo situation. However, with a 3D simulation of a fluid-filled cavity we verified that pressurized fluid causes similar stress shielding of the surrounding tissue in a 3D enclosed cavity (Fig. 8). And similar to our 2D simulations, a decrease in osteocyte signal would cause net bone resorption in 3D. Furthermore, we did show in a previous study 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 [29].

In the model used in the current study, it is assumed that osteocytes can sense a strain energy density equivalent loading measure and that they can stimulate osteoblast cells in their vicinity. Although it is not known if these assumptions are entirely correct, we have demonstrated in earlier studies that this model can explain a large number of trabecular bone features [31], and that its results are not strongly dependent on the choice of the exact load parameter sensed by the osteocytes [39] or even the assumed regulation mechanism [40].

In conclusion, according to our simulation results mechanoregulation bone adaptation in response to pressurized fluid may lead to cyst growth, via each of the two mechanisms proposed in the literature. Both altered loading and osteocyte death may result in a decrease in bone forming signal at the boundary of the cavity, which in turn may lead to net bone resorption and thereby cyst growth. We cannot conclude that one hypothesis is better than the other, but the time-dependent process of cyst growth was remarkably different. In case of osteocyte death, simultaneously a sclerotic rim developed, while in case of altered loading, pressure release was required to obtain a sclerotic rim. The presence of pressurized fluid and dead osteocytes and the different appearances of cysts in vivo, provide supporting evidence for the idea that both mechanisms can simultaneously play a role in the development and growth of subchondral bone cysts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.bone.2011.06.028.

References