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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 subchondral bone cyst development. However, the exact mechanism remains speculative. We used an established computational mechano-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 marrow 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.

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 talus, 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

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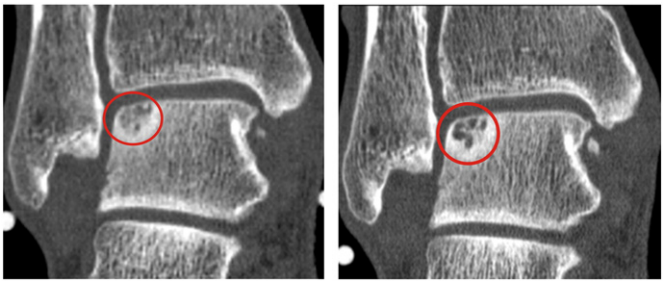

Fig. 1. Multiple cystic lesions in the talus, which developed a sclerotic rim. (a) CT image of the talus, coronal view. (b) CT image of the same patient, 11 months later.

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:

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

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, μ is the osteocyte mechanosensitivity, and $f(x,x_k)$ is a signal decay function:

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

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:

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

Here, $\frac{dV_f(x,t)}{dt}$ is the change in bone volume at location x due to bone formation, and τ 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:

$$F_{res}^{Acc} = \iint F_{res}\,dx\,dt.$$

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_{cl} is resorbed, making the change of volume due to resorption at this location:

$$\frac{dV_r(x,t)}{dt} = \begin{cases} -V_{cl} & if \quad r(x,t) \le F_{res}^{Acc} \\ 0 & if \quad r(x,t) > F_{res}^{Acc} \end{cases}.$$

The total change of bone volume becomes:

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

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:

$$E(x,t) = E_b\rho(x,t)^{\gamma}.$$

Here, E_b is the elastic modulus of the bone matrix and γ 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 μm × 50 μm. 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