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Adaptation of subchondral bone in osteoarthritis

J.S. Day, J.C. van der Linden, R.A. Bank, M. Ding, I. Hvid, D.R. Sumner and H. Weinans

Abstract. Osteoarthritis is a chronic joint disease with pathological changes in the articulating cartilage and all other tissues that occupy the joint. Radin and coworkers have suggested the involvement of subchondral bone in the disease process. However, evidence for an essential role in the etiology has never been proven. Recent studies showing reduced chemical and mechanical properties of subchondral bone in various stages of the disease have invigorated interest in the role of subchondral bone in the development and progression of the disease. The current study showed that the concept of bone adaptation might explain subchondral stiffening, a process where subchondral bone becomes typically sclerotic in osteoarthritis. In addition, we report reduced mechanical matrix tissue properties as well as an increase in denatured collagen content. In conclusion, although osteoarthritic bone tissue contains increased denatured collagen and has reduced matrix mechanical properties, the widely accepted concept of subchondral stiffening is compatible with the process of normal bone adaptation.

1. Introduction – The role of bone in osteoarthritis

Osteoarthritis has been described as an “organ failure” where pathological changes in the cartilage, bone, synovium and other soft tissues interact resulting in failure of the joint. Indications of disease progression include destruction of the cartilage in combination with abnormal growth of the subchondral bone resulting in thickened subchondral bone plate, osteophytes and deformation of the affected joint (Fig. 1). Although little is known about the relation between bone and cartilage in the etiology of osteoarthritis, clinical management has focused mainly on chondroprotective strategies.

The role of bone in disease pathogenesis requires examination, as the subchondral bone plate provides a mechanical base for the cartilage while supplying a large proportion of its nutrient requirements [8, 35]. Sclerosis of the subchondral plate can be observed on X-rays of osteoarthritic patients and increased stiffness and bone mineral density (BMD) of the subchondral plate is considered a hallmark of osteoarthritis. Subchondral bone is altered in the earliest stages of osteoarthritis [9,10,18,20,45] as the subchondral plate thickens and bone volume fraction is increased in the weight bearing areas of trabecular bone [23,25,31,39]. The structure of the trabecular bone is also altered to consist of thick, widely spaced trabeculae [24,36]. Although osteoarthritis has been repeatedly associated with increased BMD,
both in the affected joint and appendicular skeleton [7,17,18,27,29,38,45,56,60], the relation between BMD and disease progression is not clear [6,29,34].

Radin et al. [53,54] were the first to propose a link between subchondral bone mechanics and disease progression. Based on observations of increased stiffness [51] and decreased energy absorbing capacity [52] of osteoarthritic bone they proposed that stiffening of the subchondral plate was an initiating factor in osteoarthritis. According to their hypothesis, trabecular microfracture due to impulsive loading initiates bone remodeling in the subchondral plate. This leads to localized stiffening that in turn produces increased shear stress in the cartilage, culminating in cartilage breakdown.

2. Mechanical testing of arthritic bone: Scale effects

In spite of evidence of the involvement of mechanical factors in the development of osteoarthritis, there is little data available regarding the mechanical properties of osteoarthritic bone. Upon examination of the available literature (summarized in Table 1), the concept of subchondral stiffening seems to present a paradox since arthritic bone has been reported to be both stiffer and more compliant than normal bone. However many of these studies fail to recognize that bone’s mechanical properties can be altered at a minimum of two distinct levels of organization. Because bone is a cellular (i.e. foam-like) material, its mechanical properties are influenced both by the material properties of the calcified matrix and the porosity of the structure as a whole. Matrix properties are measured at the micron scale and are commonly referred to as ‘bone matrix quality’. Apparent or functional level measurements are made at the millimeter to centimeter scale and reflect the matrix level properties combined with the effects of bone mass and trabecular architecture (Fig. 2).

At this time, only two studies have measured both the apparent and matrix level properties of arthritic bone. Day et al. [16] used a combination of standard mechanical testing and micro finite element modeling to determine both the apparent and matrix Young’s modulus of cadaveric specimens. Tibiae with mild cartilage damage in the medial compartment and intact cartilage on the lateral side were compared to intact controls. In these specimens, the matrix modulus was reduced by approximately 50% in the arthritic group with a larger reduction on the medial side. The apparent modulus was not significantly different from controls, but the ultimate stress was reduced on the medial side in the arthritic specimens [23]. Li and Aspen [39–41] used a combination of standard compression and ultrasonic testing to measure the
Table 1

A review of previously published mechanical testing results for osteoarthritic specimens. Although there have been multiple tests of osteoarthritic bone, many have used test methods that do not discriminate between matrix and apparent properties.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of bone</th>
<th>Location</th>
<th>Disease progression</th>
<th>Test method</th>
<th>Finding</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radin et al.</td>
<td>subchondral plate</td>
<td>tibial plateau</td>
<td>early and late stage OA</td>
<td>drop test</td>
<td>65% reduction in impact energy in early OA</td>
<td>apparent properties</td>
</tr>
<tr>
<td>Lereim et al.</td>
<td>subchondral plate</td>
<td>tibial plateau</td>
<td>late stage OA</td>
<td>Brinell hardness (5 mm indentor)</td>
<td>50% reduction in hardness in OA</td>
<td>mixture of apparent and tissue properties</td>
</tr>
<tr>
<td>Pugh et al.</td>
<td>trabecular bone</td>
<td>femoral condyle</td>
<td>mild cartilage damage</td>
<td>dynamic apparent stiffness</td>
<td>40% increase in apparent modulus</td>
<td>apparent properties</td>
</tr>
<tr>
<td>Finlay et al.</td>
<td>trabecular bone</td>
<td>tibial plateau</td>
<td>late stage OA</td>
<td>4 mm indentor</td>
<td>result varied by location and disease progression</td>
<td>apparent properties</td>
</tr>
<tr>
<td>Hvid et al.</td>
<td>trabecular bone</td>
<td>tibial plateau</td>
<td>late stage OA</td>
<td>osteopenetrometer (2.5 mm indentor)</td>
<td>result varied by location and knee alignment</td>
<td>mixture of apparent and tissue properties</td>
</tr>
<tr>
<td>Li &amp; Aspden</td>
<td>subchondral plate and trabecular bone</td>
<td>femoral head</td>
<td>late stage OA</td>
<td>standard compression testing and ultrasound</td>
<td>15% increase in apparent modulus</td>
<td>apparent properties</td>
</tr>
<tr>
<td>Ding et al.</td>
<td>trabecular bone</td>
<td>tibial plateau</td>
<td>mild cartilage damage</td>
<td>standard compression testing and finite element modelling</td>
<td>30% decrease in apparent modulus</td>
<td>apparent properties</td>
</tr>
<tr>
<td>Brown et al.</td>
<td>trabecular bone</td>
<td>femoral head</td>
<td>late stage OA</td>
<td>standard compression testing</td>
<td>Arthritic apparent modulus was decreased compared to normal bone with equal bone mass</td>
<td>apparent properties (also with correction for BMD)</td>
</tr>
</tbody>
</table>

mechanical properties of bone taken from patients undergoing hip arthroplasty for osteoarthritis. They found a 15% increase in the apparent modulus of the trabecular bone and a 15% decrease in the matrix modulus of the subchondral bone plate compared to a control group. In common to both of these studies, one on early and the other on late-stage osteoarthritis, was a finding of increased bone volume fraction and decreased matrix properties in the arthritic groups.

3. Bone mechanosensors, remodelling and adaptation

It is important to note that bone remodeling and adaptation is driven by the cells and thus occurs at a scale that is closer to the tissue level than the apparent level. The cells that generate and resorb the bone matrix are the osteoblasts and osteoclasts, respectively. Osteoclasts make resorption cavities on the surfaces of the trabeculae in the range of 20 to 60 microns deep. During normal turnover osteoblasts fill this cavity with collagen that slowly mineralizes thereafter (Fig. 3). It has long been known that the osteoclastic resorption and osteoblastic apposition are a coupled mechanism, often referred to as a Bone
Fig. 2. Definitions of the apparent level and the matrix level. The matrix modulus was defined as the modulus effective at the scale of tens to hundreds of microns. The apparent modulus was effective at the scale of millimeters to centimeters and includes both the influence of the matrix modulus and the influence of trabecular architecture.

Multicellular Unit or a BMU. It has been recently discovered that an important coupling mechanism between osteoblasts and osteoclasts occurs due to cell binding molecules expressed on their cell membranes. Osteoblasts express a molecule called RANKL on the cell membrane and by physically making contact with the osteoclast they initiate osteoclast activity by binding to RANK at the osteoclast membrane [11, 48, 58, 66]. However many details on where osteoclasts start their activity, why they stop resorbing bone and what triggers the osteoblasts to express RANKL are unknown.

It is generally believed that mechanical loading or deformation of the bone matrix is an important aspect in bone remodeling regulation. During normal bone turnover there is often a small deficit in
refilling the resorption cavity by the osteoblasts. Therefore each BMU cycle results in a small amount of net bone loss. Disuse (unloading the bone) stimulates this net bone loss while mechanical loading counteracts it. Although several hypotheses have been proposed in the literature, it is unclear how the hormonal, paracrine and autocrine factors interact with mechanical loading [13,14,48,57,61].

An important consequence of turnover is the renewal of bone and repair of microdamage within the matrix. However, abnormally high turnover leads to bone with a relatively lower mean age. Since the mineralization of bone is a slow process, there is also a resultant reduction in mean mineralization and a concomitant reduction of bone stiffness [49,50].

4. Simulation of bone adaptation in osteoarthritis

Previously in this paper we have demonstrated that the calcified matrix stiffness is reduced and the bone volume fraction increased in osteoarthritis. We have also demonstrated that bone adaptation is most likely driven by either osteoblasts or the osteocyte network acting as mechanoreceptors at a local (matrix) level. It therefore seems plausible that the increase in bone volume fraction observed in osteoarthritis is an adaptive response to the increased bone strain that is experienced as the matrix becomes more compliant. In order to test whether this sequence of events is compatible with the concept of subchondral stiffening we have constructed a simulation of bone adaptation driven by matrix level strain. We have created models of the subchondral trabecular bone from high-resolution microCT scans and simulated bone apposition in response to degeneration of the matrix. By analyzing the resulting apparent Young’s modulus we could investigate the compatibility of the concept of subchondral stiffening with that of a reduced matrix modulus.

Cylindrical bone specimens of epiphyseal trabecular bone were obtained post mortem from the medial compartment of 4 donors (ages: 58, 61, 62, 80) [21]. The donors had no record of musculoskeletal disease and the donor tibiae did not exhibit any macroscopic pathology. The samples were taken 1 mm distal to the subchondral bone plate, were 7.5 mm in both diameter and length and were orientated such that the axes of the cylinders were parallel to the longitudinal axes of the tibiae. Specimens were scanned with a 3D voxel size of 20 µm using a microtomographic system (µCT20, Scanco Medical AG, Zurich, Switzerland).

Cubic data sets were extracted from the resulting image stacks. Each cube was taken from the centre of the sample and had an edge length of 4.3 mm. The image data were converted into finite element models with 20×20×20 µm 8 node brick elements and isotropic material properties. A linear elastic modulus of 5 GPa and Poisson’s ratio of 0.3 were assigned to all bone elements and confined compression tests were simulated [16,32,37,64]. The models were solved using in-house code that implemented the element-by-element method on a desktop computer [64]. The apparent stiffness (quotient of applied stress and the applied strain at the scale of the entire sample) of each sample was then calculated from the output of the finite element models.

Degeneration of the calcified matrix and the subsequent adaptation process was simulated using an inverse approach. Instead of reducing the elastic modulus of the elements and then incrementally adding bone voxels, the adaptive response was first simulated by adding bone voxels to all surfaces using a dilation algorithm (Morph3D, R.A. Peters, Vanderbilt University). These bone voxels were assigned the same material properties as the existing matrix resulting in homogenous matrix properties. Next, the finite element models were solved and the maximal principal strain was calculated for each element. Because of the linear nature of the finite element models, the matrix modulus could be scaled to a value
that would normalize the median strain for the model. By repeating this process for a number of steps a tissue response curve could be generated.

As expected, an increase in the bone volume fraction was necessary to compensate for the decreased matrix modulus. In spite of the decline in the local matrix modulus, the increase in volume fraction resulted in an overall increase in the apparent modulus of the models (Fig. 4). When the matrix modulus was reduced to approximately 25% of its original value the adaptive response led to a solid block of bone with an apparent Young’s modulus that was 4 times the original. A more moderate (and realistic) reduction of 20% for the matrix modulus resulted in a 25% increase in the apparent Young’s modulus.

5. More on bone matrix properties in osteoarthritis

The reason for a reduced bone matrix modulus in osteoarthritis is unclear. Possible explanations include: lower mineralization levels due to increased bone remodeling, abnormal mineralization, or defects in the collagen matrix.

While there is some debate on whether systemic breakdown of mature collagen is elevated in arthritic patients [1,30,42,59,62], there is considerable evidence that remodeling activity is increased in the subchondral bone of arthritic joints [2,20]. Increased remodeling activity results in a lower mean age of the bone matrix by reducing the time available for passive mineralization of the matrix [50]. Thus increased remodeling activity results in a lower mean level of mineralization, and thus a reduced modulus in osteoarthritic bone [12,31,43,45,55,56].

In addition to lower mineralization levels, there have also been observations of abnormalities in the collagenous matrix of osteoarthritic bone. Bailey et al. [3] have reported both increased collagen hydroxylation and the presence of an unusual type I homotrimer ([(\alpha_1)_1]) as opposed to the normal heterotrimer ([(\alpha_1)_2(\alpha_2)_1]) in osteoarthritic subchondral bone. Both increased hydroxylation and the formation of a type I homotrimer have been linked to a reduction in bone mechanical properties [5,46].
We have reported an increase in the proportion of denatured collagen in the epiphyseal trabecular bone of donors with mild cartilage damage (i.e. early osteoarthritis) [15]. In brief, trabecular bone samples were harvested from donors with early-stage osteoarthritis and normal controls. These samples were decalcified in EDTA before selectively digesting denatured collagen using α-chymotrypsin. By comparing the amount of hydroxyproline in the supernatant to that in the remaining insoluble matrix, the proportion of denatured collagen with respect to intact collagen could be measured in each specimen [4]. We found a 22% increase in denatured collagen in the medial condyle of the arthritic donors with respect to controls (Fig. 5). It has previously been demonstrated that mechanical toughness is inversely correlated to the denatured collagen content of bone [65]. The presence of elevated levels of denatured collagen may be the result of increased levels of MMPs in osteoarthritic bone [43,44].

6. Discussion

Recent advances have made it possible to examine the mechanical properties of bone matrix at multiple levels of organization. New methods such as high-resolution ultrasound and nanoindentation can be used to resolve the mechanical properties of bone osteons at the scale of single lamellae. Comparatively, the finite element derived matrix modulus is in fact the average effective matrix stiffness throughout the whole sample and includes effects such as trabecular architecture, matrix porosity, microdamage, etc. In this paper we have described a reduction in the matrix Young’s modulus in osteoarthritic bone as measured by multiple methods [16,39–41]. At this time, we are only beginning to understand the underlying chemical and/or physical explanation of this phenomenon. Reduced matrix properties may be, in part, due to hypomineralization of the bone matrix; a normal consequence of the increased remodeling activity in osteoarthritic joints. However, it is also likely that there is also a contribution due to degradation of the collagen network as evidenced by the presence of increased collagen hydroxylation, an unusual collagen homotrimer and an increase in denatured collagen content.

We have applied a simulation model to investigate the apparent paradox of subchondral stiffening in the presence of reduced bone quality (matrix stiffness). We employed an equilibrium model constructed assuming homogenous tissue properties and neglecting the temporal aspects of the bone remodeling cycle [33,63]. The model demonstrates that, in an equilibrium state, the concept of subchondral stiffening at the apparent level is not incompatible with reduced calcified matrix stiffness when adaptation is driven by strain at the cell level. The model does not attempt to model the full remodeling cycle (i.e.
resorption and formation phases) and does not examine the possibility of phase lags between tissue level degeneration and the adaptive response. The presence of a phase lag between degeneration of the matrix and the adaptive response may explain why an increased apparent modulus is reported in end-stage osteoarthritis [26,39–41] and a decreased apparent modulus is reported in less severe osteoarthritis [16, 26].

In vivo it is likely that the driving factors behind the formation of pathological bone are more complex than the adaptive model proposed here. It is unlikely that such a model can explain the formation of subchondral cysts or osteophytes. However, a great deal of insight into the disease progress can be gained by applying such models. For example, we can apply this model to the original hypothesis proposed by Radin who suggested that subchondral sclerosis in osteoarthritis created stiffness gradients in the subchondral bone resulting in shearing of the overlying cartilage. From the model results we can see that it is possible for the reduced matrix modulus to result in subchondral stiffening but from the experimental data it is likely that this is preceded by a period of increased compliance of the subchondral bone [16, 22,26]. It is of interest to note that the presence of a compliant region of subchondral bone would still, however, create stiffness gradients in the subchondral bone and thus shearing of the overlying cartilage.

Subchondral bone and overlying cartilage perform as a functional unit. Presently little is known about the interaction between the cartilage and bone in the etiology of osteoarthritis. Recent research indicates that bone is intimately involved in disease progression. While there is currently little evidence of a direct cause and effect relation between subchondral bone sclerosis and degeneration of the overlying cartilage, recent studies using bisphosphonates (bone antiresorptive compounds) have yielded interesting results with regard to both pain and cartilage degeneration [19,28,47]. Thus, true understanding of the etiology of osteoarthritis will require study of all of the tissues of the joint.

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