The Importance of Subchondral Bone in the Progression of Osteoarthritis

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In considering the contribution of subchondral bone to the pathogenesis of osteoarthritis (OA), I would like to expand the discussion to encompass subchondral mineralized tissues in general.

Some 30 years ago, Radin and others[1] suggested that changes in bone might be a cause of OA. It is still not clear how bone is involved in this disease, although there is no question that it is involved. The reason for this lack of knowledge is that we have relied largely on the presence of subchondral sclerosis in joint radiographs to judge whether or not the bone is abnormal. If bony sclerosis is apparent and the radiograph also shows joint space narrowing (JSN), we conclude that the patient has OA and an increased bone density. However, that bone is not the only mineralized tissue below the articular cartilage: we have trabecular bone, the subchondral cortical bone, and also the calcified cartilage that lies immediately below the hyaline articular cartilage. All of these tissues are mineralized, and each is different from the others physiologically, morphologically, and mechanically.

I would like to make 4 points:

1. If we are to understand the role of bone in OA we must distinguish between structural density and material density. These are not the same. In OA, the differences between them are even greater than in normal joints.
2. We need to consider calcified cartilage. We don't know much about its properties or how it behaves in OA, and much work remains to be done in this area.
3. When speaking about the role of "bone" in OA we must distinguish between the subchondral plate, which is cortical bone, and the subchondral trabecular bone. The 2 are involved differently in OA.
4. Finally, although microfractures of trabecular bone were initially considered to provide a mechanism for its stiffening[2], they do not play a role in degeneration of the joint in OA. On the other hand, another form of subchondral microdamage, i.e., microcracks, may play a physiologic, if not a mechanical, role.

Bone density and stiffness. The apparent density of bone is defined as the bone mass per total volume of the tissue. In OA, as the volume of the tissue increases, the apparent density increases. This can be seen histomorphometrically and accounts for the fact that bone volume/total volume of the tissue increases in OA.

In OA, the total volume of the subchondral trabecular bone increases, on average, by 10–15%[3], primarily as a result of thickening of the trabeculae and, perhaps, also some increase in the number of trabeculae. This change is apparent radiographically as subchondral sclerosis. If, however, we measure the amount of mineral present in the bone, we see something rather different: On the basis of density fractionation profiles, Grynpas, *et al*[4] and others[3] have demonstrated that subchondral cortical bone and trabecular bone from subjects with OA contain less highly mineralized bone than that from age-matched or younger control subjects. Thus, from a material standpoint — contrary to popular opinion — bone density does not increase in OA; it decreases.

What is the explanation for the reduction in material density of bone in OA? Figure 1 depicts subchondral bone from the knee joint of a rabbit that had been subjected to repetitive impulsive loading. The bone is undermineralized and exhibits a rather high degree of porosity and new remodeling sites. In a degenerating OA joint, the subchondral bone is remodeling, i.e., turning over very rapidly. Because turnover is so rapid, much of the bone has not had an opportunity to fully mineralize, reducing its stiffness.

Even though we tend to speak about the stiffness and density of bone interchangeably, where bone stiffness is related to apparent density, it is clear that they are not identical — although one may be an indication of the other. Because of the lower material density of bone in OA, the bone volume (i.e., the apparent density) must increase markedly to provide the degree of tissue stiffness that exists in a healthy person — or even in a person with osteoporosis. For example, given a stiffness of 400 MPa, the apparent density in a healthy individual might be 0.6 g/cm^3; to provide equivalent stiffness in a subject with OA would require 1.2–1.5 g/cm^3, i.e., a density $\geq$ 2 times greater than that needed by the healthy individual. Thus, the bone in OA joints may not be stiffer than that in normal joints.

Calcified cartilage. The calcified cartilage also plays a role in OA. Even though changes in bone may not increase the stiffness of the joint, changes in the calcified cartilage may do so. This is an area about which we know relatively little. The conventional wisdom is that the stiffness of the calcified cartilage is intermediate between that of the very stiff, dense bone below and the not very stiff and more compliant carti-

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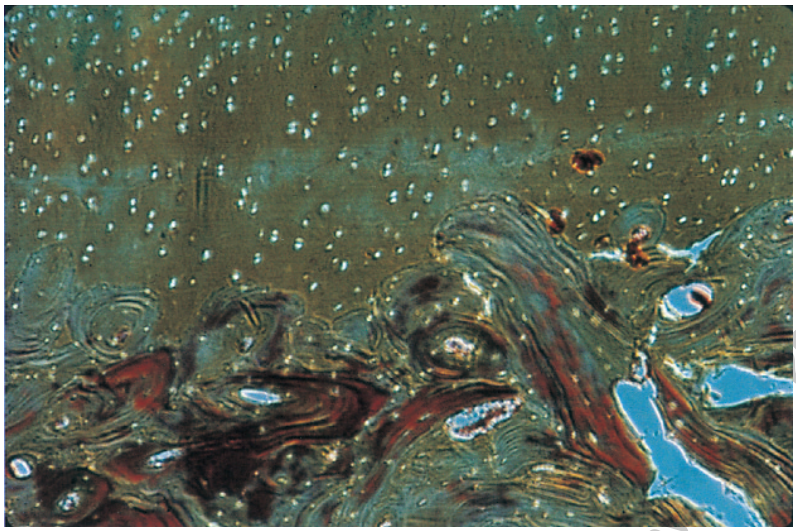

Figure 1. Pentachrome-stained section of bone from knee joint of a rabbit that developed OA after having been subjected to repetitive impulsive loading *in vivo*. The red areas are undermineralized areas of bone. Note the high degree of porosity and new remodeling sites. Because bone in the OA joint is turning over rapidly, the new bone does not have time to mineralize fully. Thus, its material stiffness is lower than normal.

lage above. Some evidence exists, however, that this is not the case, but that the calcified cartilage is more highly mineralized than the bone. When we measured the mineral content of bone and cartilage from the femoral head by microradiography, we found significantly more mineral in the calcified cartilage than in the underlying bone.

Calcified cartilage is involved in OA also in another way. In a rabbit model, in which OA was created in one knee by delivering repetitive impulsive loads of relatively modest magnitude (i.e., 1–1.5 times body weight), loading of the limb for 40 min daily for 6–9 weeks led to full-thickness loss of the articular cartilage over the next 6 months[5]. We found clear, albeit not statistically significant, increases in the thickness of the calcified cartilage in this model at 6–9 weeks[5] due to the fact that the tidemark, i.e., the demarcation between the articular cartilage and subchondral bone, began to advance and move toward the joint space. Notably, this occurred even with the brief period of loading employed. The increase in the thickness of the calcified cartilage occurred at the expense of a decrease in the thickness of the overlying hyaline cartilage. In OA, advance of the tidemark reduces the thickness of the hyaline articular cartilage and increases the thickness of the very stiff calcified cartilage.

Trabecular microfractures. What is the role of trabecular microfractures in OA? It has been suggested that the reason that subchondral bone becomes stiffer in OA is that trabeculae fracture and that the microfractures heal with callus formation (Figure 2). The callus would increase the bone volume, likely increasing stiffness of the joint and, when the callus healed, it would tend to mineralize more heavily than

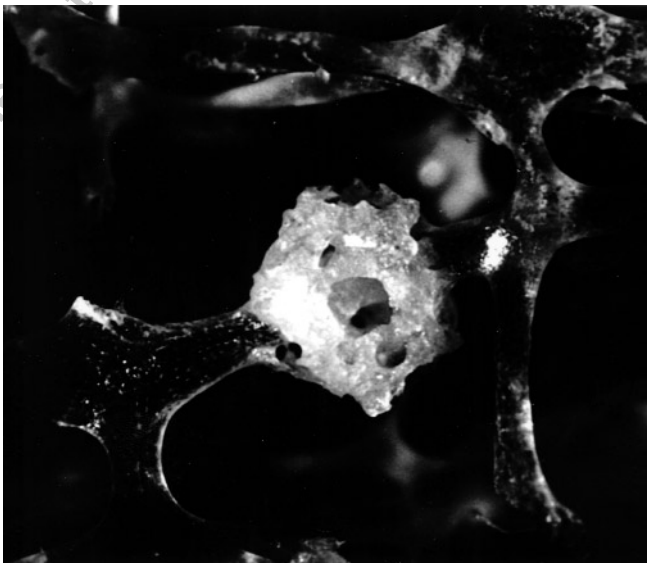

Figure 2. Electron photomicrograph of subchondral bone, showing a bulky microcallus at the site of a previous microfracture.

normal bone. Thus, it was proposed that the combination of these factors would increase the density and stiffness of the subchondral bone[2].

We tested the above premise in an experiment in which, under fluoroscopy, we placed a cylindrical metal implant in the tibial subchondral bone of sheep, within 1–3 mm of the osteochondral junction[6]. After implantation of the plug, the sheep were walked an hour a day for several years. The implant increased the stresses in the bone and led to an extensive remodeling reaction, which resulted in corticaliza-

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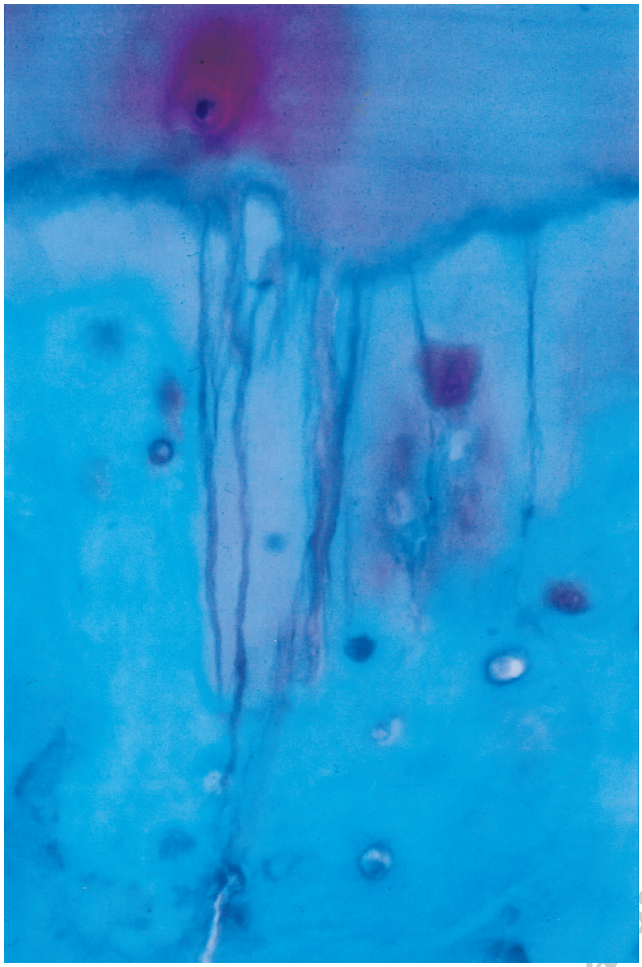

Figure 3. Histologic section of articular cartilage revealing multiple small cracks in the layer of calcified cartilage. With permission, from Sokoloff L. Arch Pathol Lab Med 1993;117:191-5.

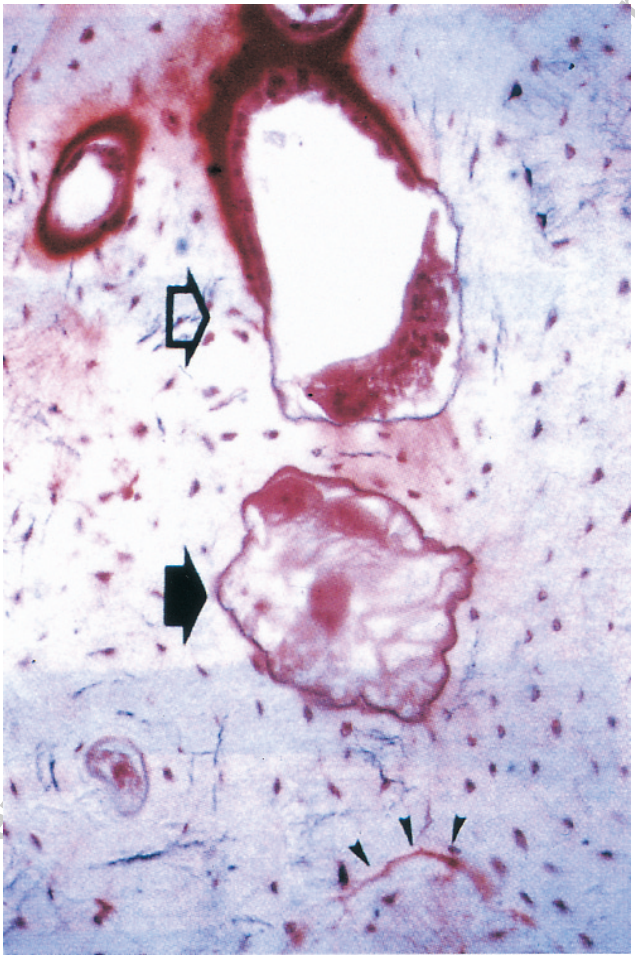

Figure 4. Biopsy of a stress fracture showing a microcrack (arrowheads). Two resorption spaces are digging toward the crack. Damage in subchondral tissues stimulates a remodeling response that leads to repair. The solid arrow indicates an active resorption site without new bone formation. The open arrow indicates a remodeling unit in which both resorption and formation are occurring. With permission, from Mori, *et al*. Musculoskeletal fatigue and stress fractures. CRC Press; 2001:151-9.

tion of the bone surrounding the plug, reaching to the osteochondral junction.

To help elucidate the stresses in the bone and cartilage, Brown, *et al*[7] created a finite element model. Their analysis showed that the plug and the corticalized surrounding bone would increase the stresses in the deep layers of the articular cartilage by no more than 50%. We do not know whether that increase is sufficient to cause OA, but this does not seem like much of an increase. It is not likely that increasing the density of the subchondral bone will greatly increase the stresses on cartilage in an OA joint. Further, if the metal plug were placed more than 1–1.5 mm from the osteochondral junction, modeling showed that it would have no effect on the overlying cartilage. Thus, trabecular microfractures probably do not have any real effect on the overlying cartilage in people with OA. It should be noted, further, that regardless of whether we have OA, everyone incurs trabecular microfractures. Indeed, in some cases, people without OA have been shown to have a larger number of microfractures than those who have OA[8].

For the above reasons I would like to lay to rest the idea that trabecular microfractures have anything to do with the etiology of OA. Elsewhere in these proceedings, Radin suggests that microfractures may play a role in OA by encroaching on capillaries in the marrow space and reducing marrow blood flow[9]. That possibility is open to question.

On the other hand, I would not suggest that damage to the subchondral mineralized tissues does not play a role in OA. Damage of a type other than trabecular microfracture may occur in subchondral cortical bone and calcified cartilage in OA, with important consequences, as discussed below.

Microcracks. Figure 3 depicts multiple small cracks within the layer of calcified cartilage. With proper staining, these cracks can be identified histologically[10] and can be measured[11]. On average, they are about 60 µm in length, with a range of 20–100 µm. By bulk staining the specimen

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with basic fuchsin we can distinguish cracks that are artifactually caused by cutting the tissue from cracks that were present during life.

Microcracks may have a physiologic, if not a mechanical, function. Osteoclasts are often seen in the cutting front at the terminus of a microcrack and a relationship has been demonstrated between cracks and remodeling[11]. Resorption spaces develop that remove the cracks and eventually repair the damage and create new tissue[12] (Figure 4). The presence of a crack will damage the canalicular processes, i.e., the communications between the cells in bone, leading to apoptosis of osteocytes. When these cells become apoptotic, for reasons that are not fully understood, bone remodeling is initiated. Figure 4 depicts a microcrack in a biopsy of a stress fracture with 2 resorption spaces, digging toward the crack. When damage occurs in the subchondral tissues it is likely that it will stimulate a remodeling response.

Conclusion. Earlier, I made the point that the increased rate of bone turnover in OA results in a decrease in the material density of the tissue. Why is the rate of bone turnover increased in a joint that is deteriorating because of mechanical overload? The answer is simple: mechanical overload causes microdamage, resulting in microcracks in subchondral bone that lead to remodeling of the bone to repair the microcracks. This hypothetical explanation can be tested. In any case, we believe it may be the reason that the rate of bone turnover is increased and the material density decreased in OA joints.

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