Conclusion

As noted, arguments exist in favor of hip OA over knee OA as a human model for development of an OA drug, in particular the greater capacity of hip OA to demonstrate symptomatic and structural effects and the possibility of using requirement of joint replacement as an outcome measure. Indeed, the only argument favoring the knee over the hip is the lack of standardization in obtaining MRI views and the paucity of MRI analyses in subjects with hip OA. Because of the other advantages of the hip relative to the knee, it is our opinion that requirement for hip arthroplasty should be further evaluated as a primary outcome measure for OA clinical trials.

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INCREASED BIOLOGICAL ACTIVITY OF SUBCHONDRAL MINERALIZED TISSUES UNDERLIES THE PROGRESSIVE DETERIORATION OF ARTICULAR CARTILAGE IN OSTEOARTHROSIS

David B. Burr

The view that stiffer subchondral bone predisposes the joint to progressive osteoarthrosis (OA) by increasing stresses in the overlying cartilage is now giving way to the view that a dynamic process of progressive subchondral thickening, as the result both of increased bone turnover and reactivation of the secondary center of growth, is of pathogenetic importance in OA. This suggests a fundamental change in orientation in our understanding of the role of subchondral bone in OA: rather than being a mechanical consequence of a stiffer subchondral plate, the bone changes in OA represent the biological response of the subchondral bone and calcified cartilage to the altered joint mechanics that drive the process.

One reason for this change in viewpoint is that the stiffness of the tissue (i.e., the elastic modulus) has been shown to be reduced locally[1], under the influence of increased vascularization and a more rapid remodeling rate. The cause of the increased local bone turnover is not known, but it may be induced, in part, by the formation of microcracks that can initiate targeted repair[2]. These changes in the bone are intimately associated with reactivation of the secondary center of ossification, causing movement of the tidemark and thinning of the articular cartilage. A recent review[2] states: "The existing data are consistent with the view that reactivation of the secondary center of ossification and not the stiffening of the metaphyseal trabecular bone is a mechanism of cartilage loss in idiopathic OA. The stiffening of the subchondral calcified structures would appear to be etiologically incidental and... locally transient" (p. 681).

A thickened subchondral plate does not predispose to progressive joint deterioration[3,4], although the plate may thicken as the arthrotic process progresses[5,6] and may even predict joint space narrowing[7]. Indeed, subchondral thickening — which includes thickening of the calcified cartilage layer as a result of reactivation of the secondary center of ossification — may be required for the progression of OA.

Increased bone turnover may be a necessary precondition for subchondral bone to become thicker. In a study that compared 2 strains of guinea pig that develop spontaneous OA, Huebner, *et al*[6] showed that the strain with the higher rate of bone turnover at a young age had the greatest increase in subchondral bone thickness and developed more severe OA. The strain with the less severe form of OA exhibited a thicker subchondral plate initially, but a lower rate of bone turnover and no progressive thickening of the plate. In both these models, the progression of OA is associated with a high bone turnover rate and increasing thickness of subchondral bone, rather than initial thickening of the subchondral plate.

A current view of the interaction of mechanics and biology that integrates these various observations is that abnormalities in joint mechanics that prevent attenuation of impact initiate new bone remodeling and reactivate the secondary center of ossification. The accelerated bone turnover reduces the elastic modulus of the tissue, but results in thickening of the subchondral plate. Reactivation of the secondary center allows advancement of the tidemark into the hyaline articular cartilage, further increasing the thickness of the mineralized subchondral plate and reducing the thickness of the cartilage (Figure 9). Thus, the mechanical derangement of the tissues induces biological responses in both bone and calcified cartilage that fuel the progression of articular cartilage thinning, resulting in increased shear stress and progression to complete loss of cartilage.

There now seems to be general agreement that the cancellous bone distant from the subchondral cortical plate is

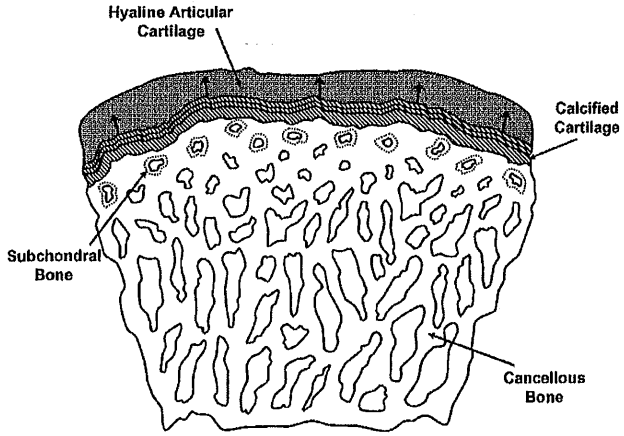

Figure 9. Multiple processes occurring in the subchondral bone and calcified cartilage accompany degeneration of the overlying articular cartilage in OA. Tidemark advancement (vertical arrows, duplicated lines) thickens the calcified cartilage and simultaneously thins the articular cartilage. This results in net thickening of the subchondral mineralized tissues and may be responsible for the observation that subchondral sclerosis accompanies progressive OA. Concurrently, increased turnover in the subchondral cortical bone will increase its porosity (dotted lines around pores). Cancellous bone beneath the subchondral cortical plate does not contribute to the degenerative process, but it is dynamic and may become osteopenic early in the degenerative process, leading to a full-thickness cartilage loss. The early reduction in bone is reversed later, and the volume increases by about 15% in the later phases of progressive OA, further contributing to the presence of "subchondral" sclerosis.

not primarily involved in this process[2,8]. Finite element models demonstrate that healing trabecular microfractures do not cause increased stress in the overlying cartilage; only processes that occur within 1–1.5 mm of the tidemark will have a significant effect on articular cartilage stresses, and only in the deeper layers of the radial zone. On the contrary, loss of cancellous bone and metaphyseal osteopenia may occur in the early phases of joint deterioration in OA[9] if the overlying subchondral plate thickens, becomes sclerotic, and absorbs more of the load-bearing force through the joint, thereby reducing the load on the underlying cancellous structure, i.e., providing a stress-shielding effect.

The observation that increased bone turnover is part of the pathogenesis of OA has focused attention on therapeutic modalities that may suppress the increase in bone remodeling and subchondral vascularization generated by mechanical events. Interest has concentrated on bisphosphonates, which are the pharmaceutical agents most commonly used to suppress high rates of bone turnover in postmenopausal osteoporotic women. The results of studies using the bisphosphonates in OA have generally been disappointing. They have shown clearly that these agents can significantly suppress bone turnover rates (which was already known), but have failed to show that this has a secondary effect on the articular cartilage. A preclinical study using the canine anterior cruciate ligament transection (ACLT) model appeared to show a direct, but detrimental, effect of a bisphosphonate on the articular cartilage of the knee: treated dogs exhibited a decrease in proteoglycan concentration of the cartilage matrix, even though the bisphosphonate effectively suppressed revascularization of the subchondral bone in comparison with placebo-treated controls[10]. In contrast, in rats who were subjected to ACLT, treatment with alendronate at fairly low doses (0.03 or 0.24 μg/kg/week) for 2 or 10 weeks appeared to have some beneficial effects on the articular cartilage, as assessed histologically and by markers of collagen degradation[11]. Whether this was a direct effect or was secondary to the suppressed vascular invasion of subchondral bone and calcified cartilage is not clear. However, one mechanism for chondroprotection under these conditions could be alendronate-induced suppression of matrix metalloproteinases 13 (MMP-13) in cartilage and MMP-9 in bone.

Recently, another antiresorptive agent, calcitonin, was shown to prevent increases in bone volume and bone density that occur after ACLT in dogs[12]. The investigators suggested that preservation of subchondral bone prevented increase in cartilage deformation that would occur by removing the underlying bony trabecular support, thereby reducing tensile and shear stresses in the articular cartilage. This explanation seems unlikely, however, insofar as osteoporosis, in which significant loss of trabecular bone occurs, tends not to co-associate with OA. Further, independent of any effect it may have on bone, calcitonin is known to stimulate proteoglycan and collagen synthesis by chondrocytes. Unfortunately, histomorphometry was not performed in this study, so that it is not clear whether the increase in bone volume involved thickening of the subchondral plate or whether calcitonin prevented tidemark advancement.

Mixed results have been obtained with administration of estrogen replacement therapy[8] in OA, even though it is well known that estrogen may have direct effects on osteoblasts and chondrocytes. In culture, hyaluronic acid has been shown to reduce the level of some markers of stimulated osteoblastic bone formation (e.g., osteocalcin), but not of markers more indicative of fully differentiated osteoblasts (e.g., alkaline phosphatase)[13].

Despite these mixed therapeutic results, the most recent evidence appears to suggest that increased biological activity in the subchondral mineralized tissues — including increased bone turnover, progressive thickening of the subchondral plate, and tidemark advancement — are important to the progressive deterioration of the overlying articular cartilage in OA.

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COMMENT

Eric L. Radin

The definitive treatment of disabling OA remains amputation of the joint and replacement with prostheses; the intermediate treatment remains palliative. That amputation is the definitive treatment and we can do nothing to slow the process[1] reflects our continued failure to find a biological cure. This failure is due to an inadequate understanding of the pathophysiology of OA. Relevant findings are less than abundant in the current literature. OA is common and there is no shortage of research in this field, but the effort continues to be focused, in the main, not on the failing organ, i.e., the joint, but on articular cartilage and its cells.

There are too many non-relevant data from a plethora of journals, which is destroying meaningful communication. Of the 3484 OA articles published in the past 2 years, 560 (one in 6) were review articles! Most research offers little that is new: mostly more sophisticated techniques and analyses than those used earlier. Most recent papers on genetics/molecular biology and biochemistry of OA focus on metalloproteases and other inflammatory mediators. This may explain why progress is being made in rheumatoid arthritis and not in OA. In addition, we continue to confuse early cartilage changes with progressive OA. Meaningful work demands a clear and clinically relevant understanding of OA and observations that run long enough to demonstrate true OA.

The major funding source for this research, the US National Institutes of Health (NIH), has failed to play a leadership role in finding a cure for OA. The result has been a waste of most of the monies spent on this effort. However, it is hard to blame the NIH for this. They take their direction from the scientific community. The NIH has instituted OA initiatives, but their direction has followed the crowd, guided by consensus meetings driven by the technical expertise of currently well-funded participants and, recently, by commercial interests, rather than by the need for a cure. It has become almost impossible to obtain funding for studies that are biomechanical, do not focus on cartilage, or do not look at cells. Finding a cure demands that the OA research community address the response of the joint, as an organ, to deleterious mechanical forces. To search for a pill for mechanically induced organ failure is in opposition to its pathophysiology.

The problem with NIH funding judgment relates to the nature of science and the nature of OA. It is always difficult to accept new truths. Technological progress is always less threatening than new concepts[2].

As long as the research community fails to clearly differentiate between primary inflammatory and primarily mechanical joint failure, talent and resources will continue to be wasted on expeditions to exploit intermediate metabolic and inflammatory interventional opportunities. Clinically, the only cures, when they can be fashioned, will need to be mechanically teamed with the biological. That is the nature of mechanically induced joint failure.

Let me suggest that to find a cure for OA we must start with clinically relevant basic work on joint wear. If you don't believe the little that has already been done, repeat it. A cure for OA needs to be sought by teams. Further, it is not enough to have connective tissue biology and biomechanics functionally incorporated in these teams. Knowledgeable clinicians need to be on them, too. And the teams need to be free of potential conflicts of interest, such as pressures to obtain research funding and tenure, rather than to work for a cure.

It is not easy to construct such teams. The nature of good scientists is that they are independent and egocentric. They like to do what they know and can do well. Relevant OA research will require using established techniques in new ways, learning new things and inventing new techniques. It is risky. Basic scientists have been forced to become independent entrepreneurs, totally dependent on peer-reviewed