Alterations in periarticular bone and cross talk between subchondral bone and articular cartilage in osteoarthritis

Steven R. Goldring

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Abstract: The articular cartilage and the subchondral bone form a biocomposite that is uniquely adapted to the transfer of loads across the diarthrodial joint. During the evolution of the osteoarthritic process biomechanical and biological processes result in alterations in the composition, structure and functional properties of these tissues. Given the intimate contact between the cartilage and bone, alterations of either tissue will modulate the properties and function of the other joint component. The changes in periarticular bone tend to occur very early in the development of OA. Although chondrocytes also have the capacity to modulate their functional state in response to loading, the capacity of these cells to repair and modify their surrounding extracellular matrix is relatively limited in comparison to the adjacent subchondral bone. This differential adaptive capacity likely underlies the more rapid appearance of detectable skeletal changes in OA in comparison to the articular cartilage. The OA changes in periarticular bone include increases in subchondral cortical bone thickness, gradual decreases in subchondral trabecular bone mass, formation of marginal joint osteophytes, development of bone cysts and advancement of the zone of calcified cartilage between the articular cartilage and subchondral bone. The expansion of the zone of calcified cartilage contributes to overall thinning of the articular cartilage. The mechanisms involved in this process include the release of soluble mediators from chondrocytes in the deep zones of the articular cartilage and/or the influences of microcracks that have initiated focal remodeling in the calcified cartilage and subchondral bone in an attempt to repair the microdamage. There is the need for further studies to define the pathophysiological mechanisms involved in the interaction between subchondral bone and articular cartilage and for applying this information to the development of therapeutic interventions to improve the outcomes in patients with OA.

Keywords: osteoarthritis, bone remodeling, articular cartilage, biomechanics

Introduction

The periarticular bone changes associated with osteoarthritis (OA) can be organized into distinct patterns based on the anatomic site and the structural and composition alterations in the bone. These changes include increased subchondral cortical thickness, alterations in the architecture and volume of subchondral trabecular bone, formation of new bone at the joint margins (osteophytes), development of subchondral bone cysts, bone marrow lesions (detectable by MRI) and advancement of the tidemark associated with vascular invasion of the calcified cartilage

[Goldring and Goldring, 2007; Goldring, 2009] (Figure 1). In addition, there also may be changes in the contour and shape of the subchondral cortical bone [Buckland-Wright, 2004; Bullough, 2004; Burr and Schaffler, 1997; Burstein and Gray, 2006; Messent *et al.* 2006; Radin and Rose, 1986].

The alterations in the periarticular bone that characterize the osteoarthritic process represent adaptations to local biomechanical and biological signals. These changes are mediated by bone cells that modify the architecture and properties

Correspondence to:
Steven R. Goldring, MD
The Hospital for Special
Surgery, 535 East 70th
Street, New York, USA
goldrings@hss.edu

Figure 1. Histologic features associated with advanced osteoarthritis. There is fragmentation and fissuring of the articular cartilage. Also, there is duplication of the tidemark with advancement of the calcified cartilage into the lower zones of the articular cartilage further contributing to thinning of the cartilage lining. [Courtesy of Edward DiCarlo, MD, Hospital for Special Surgery, New York, NY.]

of the bone through active cellular processes of modeling and remodeling [Goldring, 2009]. The cell-mediated process of adapting the bone to local mechanical influences is embodied in Wolff's hypothesis that states that the distribution and material properties of bone are determined by the magnitude and direction of applied load [Frost, 2003]. In accordance with this principle, increases in bone volume are reflective of increased load and decreases in bone mass reflect a relative decrease in the local loading history. The mechanical effects of loading on bone remodeling not only affect bone mass but also produce alterations in the contour and shape of the subchondral bone. The term 'bone attrition' has been used to describe the decrease or loss of bone height and contour that accompanies the osteoarthritic changes in bone [Neogi *et al.* 2009; Reichenbach *et al.* 2011]. As discussed below, these changes affect joint congruity and may create a biomechanical environment that adversely affects the articular cartilage and contributes to joint symptoms.

In addition to the role of mechanical factors, bone remodeling also may be initiated at sites of local bone damage resulting from excessive loading. This process is characterized by the appearance of microcracks in the bone and is distinct from traumatic bone injuries associated with fractures that disrupt the gross bone architecture [Bullough, 2004; Burr, 2004; Burr and Schaffler, 1997; Frost, 2003; Martin, 2007]. The targeted bone remodeling provides a mechanism for repair of bone damage, but under certain conditions may contribute to the formation of bone cysts that represent one of the radiographic and anatomic

hallmarks of OA [Bennell *et al.* 2011; Eriksen and Ringe, 2011; Goldring, 2009; McErlain *et al.* 2011]. Examination of the bone histology associated with local microdamage reveals regions of local fat necrosis and marrow fibrosis at various stages of healing [Taljanovic *et al.* 2008]. These regions correspond to the bone marrow lesions observed with MRI in patients with OA as described below.

The generation of new bone at the joint margins and periarticular enthesal sites results in the formation of osteophytes that represent an additional radiologic and morphologic feature of OA. The new bone is added by a process of endochondral ossification that recapitulates the cellular mechanisms of bone growth that occur during skeletal growth and development in which new bone is formed by replacement of a cartilaginous matrix [Bullough, 2004; Scharstuhl *et al.* 2002, 2003; van der Kraan and van den Berg, 2007].

The periarticular bone is not a homogeneous structure and is organized into the subchondral bone plate that consists of cortical compact bone. The subchondral plate transitions into a network of cancellous trabecular bone. The subchondral bone is separated from the overlying articular cartilage by a zone of calcified cartilage. The interface between the subchondral bone and calcified cartilage is marked by the so-called tide-mark, which is a region of enhanced metachromatic staining. As discussed below, during the course of OA progression the zone of calcified cartilage undergoes marked alterations in its cellular composition and structural organization with

expansion and advancement into the overlying articular cartilage associated with the penetration of the calcified cartilage by vascular elements that extend from the subchondral bone and adjacent marrow space [Buckland-Wright, 2004; Bullough, 2004; Burr, 2004; Lane *et al.* 1977; Walsh *et al.* 2007; Walsh *et al.* 2010]. This process recapitulates the vascular invasion of the growth plate that occurs during the development and growth of long bones and results in duplication of the tide-mark and advancement of the calcified cartilage into the deep zones of the articular cartilage leading to local cartilage thinning.

The properties of subchondral bone that determine its capacity to absorb, distribute and transfer load also are influenced by the organization and composition of the organic bone matrix and the mineral content [Bau *et al.* 2002; Burket *et al.* 2011; Day *et al.* 2001; Donnelly *et al.* 2010; Faibish *et al.* 2006; Meunier and Boivin, 1997]. In the absence of underlying genetic or acquired abnormalities of the mineralization process, the state of bone mineralization is highly dependent on the rate of bone remodeling. In the physiologic remodeling cycle, bone formation by osteoblasts is initiated by the deposition of the organic bone matrix (osteoid), which undergoes rapid mineralization. After this initial phase, the mineralization process continues, and this late phase of mineral accretion markedly affects the material properties of the bone matrix. When the rate of bone remodeling and turnover are high, the 'late' phase of mineral accretion is attenuated leading to a state of relative hypomineralization. This is associated with a reduction in the elastic modulus of the bone that is more easily deformed under load. In contrast, in conditions of low bone turnover, the continued deposition of mineral leads to an increase in the elastic modulus and the bone becomes resistant to deformation and more 'brittle'. During the progression of OA, marked changes occur in the rate and extent of remodeling in the subchondral cortical plate and the underlying trabecular bone. These alterations in bone turnover affect the state of mineralization and modify the capacity of the bone to deform under load [Buckland-Wright, 2004; Day *et al.* 2001, 2004].

There remains controversy regarding the initial structural and composition changes in OA and whether these alterations occur first in the bone or the articular cartilage. In addressing this issue, it is important to recognize that the

subchondral mineralized tissues and overlying articular cartilage form a functional biocomposite in which the individual components of this structural entity interact cooperatively and synergistically with each other to transfer and distribute load during weight bearing and locomotion. Therefore, because of their intimate structural and functional relationship any biological or biomechanical process that affects one of the components of this load bearing structure will affect the adjacent tissues.

The focus on the skeletal changes as the initial effector of the osteoarthritic process was influenced by the early studies of Radin and Rose who proposed that the pathogenesis of OA could be attributed to a primary alteration in periarticular bone [Radin and Rose, 1986]. They speculated that the osteoarthritic process was initiated by an increase in the thickness, volume and stiffness in the subchondral bone and that these changes resulted in increased load transfer to the overlying articular cartilage that adversely affected chondrocyte function and contributed to cartilage matrix loss. Their hypothesis is supported by the numerous studies that have demonstrated that the changes in periarticular bone occur very early in the development of OA. However, the cartilage and bone both have the capacity to respond to adverse biological or biomechanical signals and, therefore, it is more likely that both tissues undergo structural and functional alterations during the initiation and evolution of OA.

The detection of bone changes in OA prior to the appearance of detectable changes in the articular cartilage can be attributed to at least two factors. The first is the inability of standard radiographs to detect changes in the composition and properties of articular cartilage. To some extent this limitation can be addressed by the application of more recent magnetic resonance imaging techniques that can detect compositional and structural changes in the articular cartilage extracellular matrix. A second and more important factor that underlies the more rapid appearance of skeletal tissue changes in OA is related to the marked differential capacity of cartilage and bone to adapt to altered mechanical loads and damage. As discussed in the preceding section, both cortical and trabecular bone have the capacity to rapidly alter their architecture and structural properties via the cell-mediated processes of modeling and remodeling. In contrast, although recent studies have shown that chondrocytes can

also modulate their functional state in response to loading, the capacity of these cells to repair and modify their surrounding extracellular matrix is relatively limited in comparison to skeletal tissues [Goldring and Goldring, 2004, 2007; Hunziker, 2002; Little Goodwin *et al.* 2008; Maroudas *et al.* 1998; Plaas *et al.* 2007; Sandell and Aigner, 2001]. This differential adaptive capacity likely underlies the more rapid appearance of detectable skeletal changes in OA, especially after injuries that acutely alter joint mechanics.

Multiple different technologies have been used to detect the skeletal tissue changes in OA. Early studies utilizing isotope-labeled bone-seeking agents and radiographs [Buckland-Wright *et al.* 1991; Hutton *et al.* 1986; Macfarlane *et al.* 1991] demonstrated increased retention of the radiolabel at sites of enhanced bone remodeling associated with OA and provided evidence that the changes in bone turnover preceded detectable radiographic changes. Importantly these scintigraphic changes were predictive of the subsequent development of osteophytes and subchondral bone sclerosis [Dieppe *et al.* 1993; McCrae *et al.* 1992]. These studies also showed that the development of osteophytes and subchondral sclerosis preceded detectable changes in articular cartilage thickness assessed by joint space narrowing using radiographic techniques [Buckland-Wright, 2004].

A major challenge in assessing the temporal sequence of skeletal changes in OA relates to the difficulty in identifying the specific timing of disease initiation. For this reason, the study of individuals with OA associated with traumatic joint injury in which the onset of the pathologic process can be linked to the date of a specific injury have been particularly informative. For example, Buckland-Wright and coworkers [Buckland-Wright *et al.* 2000] employed quantitative macroradiography in a cross-sectional study of patients with anterior cruciate ligament rupture to define the sequence of periarticular bone changes. The major alterations postinjury involved thickening of the subchondral horizontal trabeculae that reached significance by 3–4 years. Osteophytes were detected in approximately 50% of the injured knees by the third year, but no changes were detected in joint space width or cortical plate thickness within these time intervals. In contrast, they observed that individuals with OA of the knee not associated with a discrete injury exhibited a different pattern of bone changes

in which there was an increase in cortical plate thickness that antedated the trabecular alterations. Based on these findings they concluded that the biomechanical and adaptive influences in these two populations differed [Buckland-Wright *et al.* 1994, 1996].

Additional studies have provided insights into the sequential structural changes the subchondral cortical and trabecular bone in OA. Karvonen and colleagues analyzed the bone mineral density of the subchondral trabecular bone in the knee joints of patients with early OA (Kellgren's grade 0–2) and observed reduced levels deep to the thickened cortical bone [Karvonen *et al.* 1998]. More recently, Messent and coworkers [Messent *et al.* 2005a, 2005b, 2005c] utilized a computerized method of textural image analysis (Fractal Signature Analysis) to assess the architecture of subchondral trabecular bone in the knee joints of patients with medial compartment OA. They observed that the progression of OA was associated with an increase in vertical trabeculae, which tended to be thinner and fenestrated. These changes indicate that the trabecular bone in the subcortical compartment was relatively osteoporotic and these findings are consistent with the decrease in mineral density detected in this region reported by Karvonen and colleagues [Karvonen *et al.* 1998]. In the studies by Messent and colleagues, they noted that the horizontal trabeculae increased throughout the course of OA and that the size varied depending on whether the patients had early or late stage OA. They speculated that the thickened cortical plate and retention of the horizontal trabeculae was associated with increased load-bearing stresses in this region, and that the development of osteoporotic changes in the trabeculae beneath this region was related to reduced transmission of load and represented a form of so-called 'stress shielding'.

Recent studies by Chan and colleagues have provided potential mechanistic insights into the molecular signals by which mechanical factors modulate subchondral bone remodeling [Chan *et al.* 2011]. They examined the expression of *SOST* and additional components of the Wnt- β -catenin pathway in osteochondral samples from human OA tissue and from osteochondral sections from sheep and mice with surgically induced OA. The *SOST* gene encodes the protein sclerostin, which is a potent inhibitor of the Wnt pathway that contributes to the regulation of bone formation, and the expression of this gene has

been shown to be regulated in part by mechanical factors [Robling *et al.* 2008]. They noted that osteocyte *SOST* expression was locally decreased in regions of bone sclerosis and speculated that increased mechanical loading in these regions could be responsible for the downregulation of *SOST* with a resultant increase in localized bone formation. Surprisingly, they also detected *SOST* expression in articular chondrocytes and noted that the increased expression was localized to regions of focal cartilage damage. The role of *SOST* in regulating chondrocyte differentiation and activity is complex and the mechanisms and consequences of its increased expression by chondrocytes in regions of cartilage damage remains unclear.

It is important to appreciate that changes in bone volume represent only one of the factors that determine the mechanical properties of bone and that additional influences, including the architecture and material properties of the bone, also contribute to its capacity to transmit load. The studies of Day and coworkers have been particularly informative in illustrating this concept. They constructed finite-element models from microCT scans of subchondral trabecular bone obtained from the proximal tibiae from cadaver specimens from subjects with early cartilage damage [Day *et al.* 2001] and used mechanical testing and finite-element analysis to determine the effective tissue modulus of the bone. They found that the volume fraction of trabecular bone was increased, consistent with the changes reported by Messent and colleagues but observed that the tissue modulus of the bone was reduced in the condyles in which there was damage in the overlying articular cartilage. They attributed the reduction in tissue modulus to a decrease in mineral density, which they speculated was related to incomplete mineralization due to an increase in the rate of bone remodeling and turnover. These observations are paradoxical and indicate that the properties of the subchondral bone in certain stages of OA progression may be associated with a decrease rather than an increase in the bone tissue modulus, i.e. stiffness, despite an increase in overall bone volume. These conclusions, if correct, have significant implications with respect to treatment strategies for targeting subchondral and periarticular bone remodeling in OA. For example, therapeutic agents such as bisphosphonates that inhibit bone resorption and reduce bone turnover would increase bone mineral content by reducing bone turnover. This would lead to an

increase in subchondral bone stiffness, which in turn may alter the pattern of load transfer through the cartilage and potentially adversely affect cartilage homeostasis. The lack of efficacy of a recent trial with risedronate in reducing progression of the cartilage changes in OA highlight the complexity of the issues surrounding the influences of bone adaptation and its effects on the natural history of OA [Bingham *et al.* 2006; Buckland-Wright *et al.* 2007].

As discussed above, the presence of duplication of the tidemark and advancement of the zone of calcified cartilage into the overlying hyaline articular cartilage is an additional finding associated with OA [Bullough, 2004; Burr and Schaffler, 1997; Lane *et al.* 1977; Pulai *et al.* 2005]. Previous histologic studies of this zone demonstrated that this process was associated with the penetration of the calcified cartilage by vascular elements and formation of new calcified cartilage and bone, recapitulating morphological features of the growth plate [Bullough, 2004; Burr and Schaffler, 1997; Lane *et al.* 1977]. More recently, Walsh and coworkers [Ashraf *et al.* 2011; Suri *et al.* 2007; Walsh *et al.* 2007; Walsh *et al.* 2010] used immunostaining techniques to analyze the osteochondral junction in an animal model of OA and in tissue samples from patients undergoing arthroplasty for OA. They observed the presence of sensory nerve fibers expressing nerve growth factor (NGF) in the vascular channels associated with osteochondral angiogenesis and speculated that the sensory fibers in these regions could be a potential source of symptomatic pain. They also noted that the regions of vascular invasion were associated with localized bone marrow replacement by fibrovascular tissue expressing vascular endothelial factor (VEGF). VEGF expression was also detected in chondrocytes in proximity to the angiogenesis and they hypothesized that this growth factor could provide the signals for recruitment of the vascular elements. The advancement of calcified cartilage and resultant thinning of the articular cartilage would be predicted to increase the mechanical stresses in the deep zones of the cartilage matrix that could contribute to altered chondrocyte function and adversely affect cartilage matrix homeostasis.

The presence of so-called 'bone marrow edema' is an additional feature of OA. This term was introduced in 1988 by Wilson and colleagues who noted the presence in subchondral bone from patients with OA of localized regions of

increased signal intensity using fluid sensitive magnetic resonance sequences [Wilson *et al.* 1988]. Analysis of the histologic changes corresponding to the anatomic site of the bone marrow lesions has revealed the presence of fat necrosis and localized marrow fibrosis associated with microfractures of the trabecular bone at various stages of healing indicating that the MRI signal was not generated by actual 'edema' [Leydet-Quilici *et al.* 2010; Taljanovic *et al.* 2008]. Importantly, although longitudinal studies reveal that the bone marrow lesions may come and go, their presence correlates overall with the severity of joint pain and with progression of OA cartilage and bone changes [Felson *et al.* 2001, 2007; Hernandez-Molina *et al.* 2008; Hunter *et al.* 2006; Lo *et al.* 2005; Reichenbach *et al.* 2008; Roemer *et al.* 2010; Taljanovic *et al.* 2008; Tanamas *et al.* 2010]. The correspondence of the sites of bone marrow lesions with regions of bone and cartilage damage strongly supports a primary role for a mechanical and traumatic etiology for the subchondral bone marrow changes [Bennell *et al.* 2011; Eriksen and Ringe, 2011]. The presence of microfractures with localized bone remodeling is consistent with activation of bone repair processes that accompany targeted bone remodeling [Burr, 2004; Burr and Schaffler, 1997; Cardoso *et al.* 2009; Martin, 2007]. Of interest, the bone cysts associated with OA frequently develop in the focal areas of bone damage and necrosis, supporting the concept that their pathogenesis also is related to a mechanical process [Bancroft *et al.* 2004; Carrino *et al.* 2006]. In addition to the role of mechanical loading and microdamage in the pathogenesis of bone marrow lesions, there is evidence that impaired blood flow and local ischemia may also contribute to the disturbance in subchondral bone remodeling [Findlay, 2007]. These changes in subchondral bone blood flow could also interfere with the supply of nutrients and other products to the overlying cartilage and in this way adversely affect chondrocyte function and cartilage matrix homeostasis.

Osteophytes are an additional characteristic finding in OA and their presence has served as a useful radiographic marker of OA initiation and progression. They are localized to the margins of OA joints, and numerous lines of investigation implicate local biomechanical factors in their appearance and growth. Although there remains controversy regarding their functional role, several observations suggest that they may serve to stabilize the joint rather than contributing to joint

dysfunction and OA progression [Guyton and Brand, 2002; Messent *et al.* 2007; Perry *et al.* 1972; van der Kraan and van den Berg, 2007]. This conclusion is supported by the observations of Pottenger and colleagues, who noted that removal of medial and lateral osteophytes from the knee joint results in increased joint instability [Pottenger *et al.* 1990]. Felson and coworkers [Felson *et al.* 2005] provided further evidence that osteophytes may not have a direct role in OA progression but rather serve as a marker of nearby cartilage loss and joint pathology. They employed fluoroscopic techniques to examine osteophyte size and the risk for development of structural progression of knee OA. They found that the large osteophytes did not appear to affect the risk of structural progression and that the relationship between osteophytes and progression were at least in part explained by the association of the structural change with malalignment.

Studies in animal models of OA have been particularly informative in defining the sequence of events associated with osteophyte formation [van der Kraan and van den Berg, 2007]. These studies indicate that the osteophyte is initiated by proliferation of periosteal cells at the joint margin followed by differentiation of these cells into chondrocytes, which hypertrophy and through the process of endochondral ossification create an enlarging skeletal outgrowth at the joint margin. The local production of growth factors, including transforming growth factor- β and bone morphogenic protein-2, has been implicated in this process [Blaney Davidson *et al.* 2007; Zoricic *et al.* 2003]. Their role in osteophyte formation is supported by studies in which intra-articular injection of these growth factors into joints induces osteophyte formation, and inhibition of the activity or interference with their signal pathways results in inhibition of osteophyte formation [Scharstuhl *et al.* 2002, 2003; van Beuningen *et al.* 1998, 1994, 2000].

In addition to the role of mechanical factors in the pathogenesis of the structural and functional changes in cartilage and bone, there is evidence that biological processes also affect the remodeling and adaptations of these tissues. In part, these effects are mediated by products derived from other joint tissues, including for example the synovium, menisci and adipose tissues. However, there is also evidence that there is direct communication between the subchondral bone and cartilage via a process of diffusion that

permits exchange of soluble products that have the capacity to modulate the activities of resident cells in these tissues [Amin *et al.* 2009; Findlay, 2010; Pan *et al.* 2009]. The vascular invasion of the calcified cartilage in OA tissues, and the advancement of the tidemark represent biological processes that may result from these types of interactions [Ashraf *et al.* 2011; Suri *et al.* 2007; Walsh *et al.* 2007, 2010].

In summary, OA is characterized by marked alterations in the composition, structure and functional properties of periarticular bone. These changes are mediated by the cells that remodel and model bone under physiological conditions, and an understanding of the pathophysiological processes associated with the skeletal changes in OA provides a rationale framework for developing therapeutic interventions that have the potential to modify the natural history of OA. Although results in animal models of OA have shown beneficial effects, to date, therapies that specifically modify bone cell activity and remodeling have not been shown to be of benefit in studies of humans with OA. In part, this lack of success can be attributed to the marked heterogeneity of the patient populations with OA and the complex processes associated with skeletal remodeling. In addition, further information is needed regarding the biological and biomechanical interactions between the periarticular bone and articular cartilage. Nevertheless, improved diagnostic tools for assessing bone properties and turnover and for modulating the activity and function of bone cells are becoming available, providing potential opportunity for the targeting of skeletal tissue changes in OA for therapeutic intervention.

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The authors declare no conflicts of interest in preparing this article.

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