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Review

Role of bone architecture and anatomy in osteoarthritis ☆

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ABSTRACT

When considering the pathogenesis of osteoarthritis (OA), it is important to review the contribution of bone in addition to the contribution of cartilage and synovium. Although bone clearly plays a role in determining the distribution of biomechanical forces across joints, which in turn plays a role in the initiation of OA, it has also more recently been appreciated that bone may contribute in a biological sense to the pathogenesis of OA. Far from being a static structure, bone is a dynamic tissue undergoing constant remodeling, and it is clear from a number of radiographic and biochemical studies that bone and cartilage degradation occurs hand in hand. Whether the initial instigating event in OA occurs in cartilage or bone is not known, but it is clear that bony changes occur very early in the pathogenesis of OA and often predate radiographic appearance of the disease. This review focuses on the structural variants of both hip and knee that have been associated with OA and the ultrastructural bone changes in these sites occurring in early OA pathogenesis.
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Contents

Introduction

In considering osteoarthritis (OA) as a "whole joint" disease, it is important to acknowledge the contribution of bone in addition to cartilage and synovium to the pathogenesis of the disease. Well-known radiographic features of OA, such as bony sclerosis and osteophyte formation, are helpful in diagnosis of OA but are thought to be results

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of the disease process rather than causative. Changes in bone certainly occur as a result of OA, but changes in bone architecture and biology may also contribute to the development of OA. Not only does bone in part determine the distribution of biomechanical forces across the joint, but changes in the bone itself may contribute to the evolution of OA in ways that are now beginning to be appreciated. This review will highlight the emerging evidence that bone plays a key role in the pathogenesis of OA, with special focus on the hip and knee joints. We will highlight the role of bone shape as a risk factor for OA in the hip and knee. This subject has also been the topic of prior reviews by our research group and others [1–6].

Does bone start the ball rolling in OA?

Bony changes appear very early in the course of OA and in some studies have been shown to precede cartilage changes. Petersson and colleagues studied subjects with chronic knee pain over a 3-year period and compared serum levels of bone and cartilage turnover markers between subjects that did and did not develop incident knee OA. Subjects with knee OA at baseline were excluded. They found that elevations in both bone sialoprotein (BSP) and cartilage oligomeric matrix protein (COMP) occurred early in the course of incident knee OA, suggesting that bone turnover and cartilage turnover are concurrent processes [7]. Hunter and colleagues corroborated these findings, reporting that women with knee OA characterized by osteophytes have an increase in the bone degradation marker urinary deoxypyridinoline (DPD) compared to age-matched twin controls [8]. Radiographic studies have also garnered support for the idea that bone may be involved in the early pathology of OA. Increased subchondral bone turnover detected by radionuclide bone scan, for example, was found to precede the radiographic appearance of knee OA (as defined by joint space narrowing on plain film) by as much as 5 years [9,10].

Perhaps the most persuasive evidence that bone contributes to the pathogenesis of OA comes from animal studies. In experimental models, surgical damage to subchondral bone leads to subsequent deterioration of the overlying articular cartilage, suggesting that bony changes may precede the cartilaginous changes of OA, at least in this model [11]. Muraoka and colleagues studied a strain of guinea pigs with spontaneously-occurring knee OA using a combination of histology, microfocal computed tomography (CT), and serum and urinary markers of bone turnover. They reported that animals with spontaneous knee OA demonstrate increased thickness of the subchondral bone plate, together with increased serum osteocalcin (a bone formation marker) and decreased urinary N-telopeptide (a bone degradation marker). Importantly, these changes were present before any histologic evidence of cartilage degradation [12]. In a mouse model of osteogenesis imperfecta, mice bearing a mutation of the bone-specific *Col1a1* gene demonstrate the premature, aggressive development of OA at 2 months of age, as compared to wild-type mice, who demonstrated OA at 22 months of age [13]. Importantly, $Col1a1^{-/-}$ mice have genetically normal cartilage, so the degradation of articular cartilage in this animal model of OA occurs as a result of alterations in bone itself, as opposed to being the primary pathologic lesion.

One observation creating interest in the contribution of bone to the pathogenesis of OA in humans is that the bone mineral density (BMD) of patients with OA appears to be increased even at sites unaffected by OA [14]. This observation has led to the idea that osteoporosis and OA represent opposite ends of a spectrum of bone homeostasis. Detailed studies of the sequence of changes unfolding in the development of OA, however, suggest that this idea may be overly simplistic. Animal models indicate that early in OA, there is resorption of subchondral bone, which is followed by an overexuberant repair process that leads to sclerosis of subchondral bone as well as new bone formation in the form of osteophytes [15]. In humans, subchondral cortical bone in early OA of the knee shows changes of osteoporosis, and it is only later in the disease that cortical sclerosis appears, usually after joint space narrowing has become apparent radiographically [16]. As OA progresses, the subchondral cortical bone becomes sclerotic, and osteophytes form at both the medial and lateral margins of the tibiofemoral joint [2].

The two main hypotheses of how bony changes may lead to cartilage deterioration are: (1) changes in bone may alter the distribution of biomechanical forces across the joint cartilage, which in turn leads to cartilage degeneration [17], and (2) altered bone metabolism results in the release of soluble biomediators causing the breakdown of overlying cartilage. In support of the first hypothesis, Buckland-Wright and colleagues used macroradiography, an imaging technique using traditional X-ray beam equipment to increase the spatial resolution of the image compared to traditional plain films, to study in detail the early architectural changes of knee OA in humans [18]. They found that in advanced stages of knee OA, the trabeculae of subcortical bone remodel from the normal, cross-hatched pattern to a largely parallel pattern, which weakens the microarchitecture of the bone [16]. Animal models also support this idea. Wohl and colleagues studied the biomechanical properties of the knee joint in dogs following surgically-induced OA and found decreased yield stress and elasticity after transection of the anterior cruciate ligament [19]. In support of the second hypothesis, it is now known that channels connecting the subchondral bone to the overlying articular cartilage in the form of microcracks exist [20], and in vitro studies demonstrate a soluble mediator produced by osteoblasts may promote cartilage breakdown via diffusion through these channels [21,22].

Changes in subcortical bone in early OA: a detailed look

A number of radiologic studies have supported the hypothesis that changes in subchondral bone may precede cartilage damage in OA. Using 3-Tesla, high-resolution magnetic resonance (MR) with parallel imaging, Bolbos and colleagues found a significant decrease in apparent bone volume to total volume (BV/TV) ratio in subjects with early knee OA as compared to healthy controls [23]. Both MR and multidetector row CT images demonstrate that early in the course of knee OA, trabecular bone thins, with individual trabeculae decreasing in diameter [24,25]. Apparently, this decrease in trabecular thickness is the product of greatly increased bone turnover, with bone turnover increasing by as much as 20-fold concurrent with a much more modest net decrease in bone mineral density [26]. Later in the disease process, an apparent increase in the overall number of bone trabeculae occurs, corresponding to the appearance of sclerosis on plain films, but this apparent increase in trabecular number may not confer increased bone strength, as evidenced by microarchitectural studies [16]. These complex dynamics of subchondral bone changes may help explain the observation that both very high and very low trabecular bone mineral densities of the tibia have been associated with the radiographic changes of knee OA [27].

A technique to study bone morphometry using fractal analysis has been developed and applied to imaging of subchondral bone anatomy in OA [28,29]. This technique can be applied using traditional radiographs or three-dimensional imaging of bone. Fractal analysis produces a description of trabecular bone microarchitecture based on the number, size, and cross-linkage of trabeculae, corresponding to a measure of bone microtexture and directional physical properties [30,31]. Messent and colleagues applied fractal analysis to macroradiographs of the knee and found bone loss in the medial compartment of subjects with early OA, corresponding to a decrease in trabecular number [32]. Kraus and colleagues demonstrated that the fractal signature of the medial tibial plateau derived from plain radiographs of the knee predicted progression of OA with greater accuracy than clinical variables such as age, sex, BMI, and the presence or absence of knee pain [30].