Clinical significance of bone changes in osteoarthritis

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Abstract: Osteoarthritis (OA), the most common form of arthritis, is now understood to involve all joint tissues, with active anabolic and catabolic processes. Knee OA in particular is considered to be a largely mechanically-driven disease. As bone adapts to loads by remodeling to meet its mechanical demands, bone alterations likely play an important role in OA development. Subchondral bone changes in bone turnover, mineralization, and volume result in altered apparent and material density of bone that may adversely affect the joint's biomechanical environment. Subchondral bone alterations such as bone marrow lesions (BMLs) and subchondral bone attrition (SBA) both tend to occur more frequently in the more loaded knee compartments, and are associated with cartilage loss in the same region. Recently, MRI-based 3D bone shape has been shown to track concurrently with and predict OA onset.

The contributions of structural abnormalities to the clinical manifestations of knee OA are becoming better understood as well. While a structure-symptom discordance in knee OA is thought to exist, such observations do not take into account all potential factors that can contribute to between-person differences in the pain experience. Using novel methodology, pain fluctuation has been associated with changes in BMLs, synovitis and effusion. SBA has also been associated with knee pain, but the relationship of osteophytes to pain has been conflicting.

Understanding the pathophysiologic sequences and consequences of OA pathology will guide rational therapeutic targeting. Importantly, rational treatment targets require understanding what structures contribute to pain as pain is the reason patients seek medical care.

Keywords: bone, osteoarthritis

Introduction

Osteoarthritis (OA) is the most common form of arthritis, and knee OA in particular is a leading cause of disability among older adults [Guccione *et al*. 1994; Lawrence *et al*. 2008]. With the aging of the population, rising prevalence of obesity, and lack of definitive treatments to prevent the disease or halt its progression, the public health impact of OA continues to grow. A better understanding of the pathophysiology of OA and development of more sensitive biomarkers is needed to identify and test rational treatment targets to reduce the burden of this common condition.

While OA has traditionally been considered a disease of cartilage degeneration, it is being increasingly recognized as a disease of the whole joint involving all joint tissues [Dieppe, 2011]. Specific pathologic changes, such as osteophytes, the first definitive sign of radiographic OA, are a clear indication that bone changes occur in early OA. However, radiography is relatively insensitive in detecting the earliest changes. With the advent of magnetic resonance imaging (MRI) of the knee, it has become apparent that the majority of radiographically 'normal' knees have some abnormality detectable on MRI. For example, in the Framingham Osteoarthritis Study, knees without any evidence of radiographic OA (i.e. Kellgren and Lawrence grade 0), 88% have at least one abnormality on MRI (unpublished data). With the use of newer imaging modalities and advances in the understanding of molecular mechanisms and disease pathology, OA is now known to involve an active repair process and is therefore not solely degenerative or destructive [Brandt *et al*. 2006, 2008, 2009].

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Supporting the recognition that OA is a disease of the whole joint, there is mounting evidence that subchondral bone plays an important role in OA. Bone remodeling in the OA joint occurs preferentially in the subchondral plate. Surgical specimens from persons with OA have demonstrated that subchondral bone changes, including subchondral bone attrition which is a flattening or depression of the subchondral bony surface unrelated to gross fracture, are common [Bullough, 1998]. Further, in radiographically normal tibiofemoral knee joints, subchondral bone changes on MRIs, such as bone marrow lesions (BMLs), are common. Changes in bone turnover, mineralization, and bone volume result in altered apparent and material density of bone [Burr, 2003, 2004]. Specifically, subchondral bone in OA has increased thickness and volume, but is weaker and less mineralized than normal bone [Buckland-Wright, 2004; Grynpas *et al.* 1991; Li and Aspden, 1997a, 1997b; Radin and Rose, 1986]. With alterations in its properties, subchondral bone may be less able to absorb and dissipate energy, thereby increasing forces transmitted through the joint and predisposing the articular surface to deformation. It has been proposed that these changes in the subchondral bone could adversely affect the biomechanical environment of the overlying cartilage, predisposing the cartilage to subsequent loss of integrity [Radin and Rose, 1986].

Whether these bony changes are a cause or consequence of other changes in OA remains controversial. The potential for alterations in subchondral bone to contribute to the early pathology of OA is supported by a number of animal models that demonstrate cartilage lesions in relation to damage to subchondral bone through loading [Carlson *et al.* 1994; Radin *et al.* 1972, 1984; Radin and Rose, 1986; Wu *et al.* 1990]. Other experimental animal models demonstrate subchondral bone changes very early after induction of disease [Anderson-MacKenzie *et al.* 2005; Hayami *et al.* 2006]. In humans, increased subchondral bone turnover, as measured by bone scintigraphy, has been associated with progression of radiographic OA and with pain upon joint loading [Dieppe *et al.* 1993; McCrae *et al.* 1992]. Recent MRI studies have demonstrated increased tibial plateau size and alterations of the bony surface contour (subchondral bone attrition), even at the preradiographic OA stage [Ding *et al.* 2006; Dore *et al.* 2010; Reichenbach *et al.* 2008]. Further, such MRI studies have also demonstrated that these bone lesions themselves are associated with development and worsening of cartilage loss [Davies-Tuck *et al.* 2010; Felson *et al.* 2003; Hunter *et al.* 2006; Neogi *et al.* 2009a; Roemer *et al.* 2009; Wluka *et al.* 2008, 2009].

It has been hypothesized that cartilage loss is a mechanically mediated process that is more likely to occur in regions subjected to high stress; such areas of high stress are influenced by bone shape [Williams *et al.* 2010]. Understanding the implications of bony alterations on the biomechanical environment of the joint is critical as biomechanics are known to play an important role in knee OA. The association of static malalignment and higher dynamic knee adduction moments with knee OA progression supports the importance of mechanical influences in knee OA pathogenesis [Miyazaki *et al.* 2002; Sharma *et al.* 2001]. Yet little beyond that is known about the potential full range of mechanical effects in knee OA. Pertinent to the recognition of the importance of biomechanics in knee OA, bone is known to be a dynamic tissue that adapts to loads by remodeling to meet its mechanical demands (Wolff's Law) [Chen *et al.* 2010; Goldring, 2008]. The normal functioning of a diarthroidal joint is dependent upon stability provided by ligaments, tendons and musculature; appropriate load distribution across the joint surfaces which is dependent upon the geometry and material properties of the articulating joint tissues; and joint congruity. While chondrocytes can modulate their functional state in response to loading [Hunziker, 2002], their capacity to do so is limited compared with bone [Goldring, 2008]. This loss of synchronous adaptation to the biomechanical environment is likely important in contributing to the eventual pathologic changes that occur in the setting of inadequate repair responses. Since alterations in joint geometry can affect load distribution and joint congruity, this can lead to maldistribution of biomechanical loads to previously relatively underloaded regions of cartilage and may contribute to cartilage breakdown [Bullough, 1981].

Joint geometry has an obvious role in predisposing to OA in conditions such as developmental hip dysplasia. Femoroacetabular impingement has also been recognized as contributing to hip OA [Doherty *et al.* 2008]. Recently, more subtle morphologic differences have been studied for their relation to risk of OA. Two-dimensional modeling of the hip joint shape demonstrated particular shapes to be associated with radiographic OA changes, supporting the importance

of joint geometry to the normal functioning of the joint [Gregory *et al.* 2007; Lynch *et al.* 2009]. Given the spherical nature of the hip joint, studying the morphology of the hip joint is relatively easier than the more complex shape of the knee joint. Nonetheless, joint shape modeling has now also been extended to three-dimensional evaluation of the knee [Bredbenner *et al.* 2010; Neogi *et al.* 2011]. MRI-based three-dimensional bone shape of the knee has been shown to track concurrently with knee OA onset, and to predict the incidence of radiographic knee OA 12 months before its onset [Neogi *et al.* 2011]. The potential effects of altered bone shape and resultant altered biomechanical load can be inferred from investigations of the impact of articular contact stress on knee OA. Using discrete element analysis, higher baseline contact stress was associated with increased risk of incident symptomatic knee OA in a longitudinal cohort study of persons with knees at risk for OA [Segal *et al.* 2009]. Such investigations highlight the critical importance of abnormal biomechanics on joint pathology. It is likely that some aspects of the joint shape are reflective of biomechanical stresses, such as habitual activities that may influence bone shape during development and beyond, whereas other aspects are likely genetically determined. For example, differences in hip morphology have been demonstrated to exist between White and Asian (Chinese) women, which is a plausible explanation for the difference in hip OA prevalence [Dudda *et al.* 2011]. These differences may be related to genetic differences, differences in frequency of activities such as squatting, or both.

In addition to bone shape or morphology, the pathologic bone abnormalities found in OA are also thought to be important biomechanically. The bony lesion most studied to date in this regard is BMLs. These subchondral bony lesions have been shown to occur more commonly at sites of increased biomechanical loading [Felson *et al.* 2003; Hunter *et al.* 2006]. That is, medial BMLs are more likely to occur and to progress in varus aligned knees, while similar relationships are seen for lateral BMLs in valgus aligned knees. It has been hypothesized that microfractures and subchondral remodeling, as evidenced by alterations in the apparent and material properties of subchondral bone, are due to chronic overload and are reflected by the presence of BMLs on MRI [Roemer *et al.* 2010]. Radiologically, BMLs in OA are noncystic subchondral areas of ill-defined hyperintensity on T2-weighted or proton-density-weighted fast spin echo images on MRI [Bergman *et al.* 1994; Zanetti *et al.* 2000]. Histologically, BMLs appear to have features suggestive of a localized infarction reaction, with active and chronic remodeling processes [Bergman *et al.* 1994; Hunter *et al.* 2009a; Zanetti *et al.* 2000]. Histomorphometric evaluation has demonstrated BMLs to have many of the same features noted to occur in OA bone, but to a greater extent; these changes include increased bone volume fraction, decreased tissue mineral density, increased trabecular thickness and spacing but decreased number, and to be more plate-like than bone in other areas of the same (osteoarthritic) knee [Hunter *et al.* 2009a]. Such alterations may make these areas more mechanically susceptible.

In keeping with this hypothesis, subchondral bone attrition, a depression or flattening of the bony surface, tends to occur concomitantly and/or develop in the same subregions as where BMLs are present [Roemer *et al.* 2010]. Similar to BMLs, subchondral bone attrition is also associated with malalignment, occurring more frequently medially when there is varus alignment, and laterally when there is valgus alignment [Neogi *et al.* 2010a]. BMLs and subchondral bone attrition have also been demonstrated to have effects on the overlying cartilage. BML presence, incidence and progression have been associated with development and worsening of cartilage loss, including in locations adjacent to the BMLs [Davies-Tuck *et al.* 2010; Felson *et al.* 2003; Hunter *et al.* 2006; Roemer *et al.* 2009; Wluka *et al.* 2008, 2009]. Subchondral bone attrition itself also increases the risk for cartilage loss to occur in the same subregion [Neogi *et al.* 2009a]. In contrast to subchondral bone attrition, BMLs not only increase in size, but have been shown to also regress over time [Davies-Tuck *et al.* 2009; Hunter *et al.* 2006; Kornaat *et al.* 2007; Roemer *et al.* 2009].

The biomechanical implications of the fluctuation of BMLs are not clear presently. However, the fluctuating nature of BMLs provides an opportunity to determine whether such fluctuations correspond to the fluctuating nature of pain in knee OA. Based upon qualitative data, symptoms in knee OA are thought to progress through various stages, with pain initially occurring with activity, later becoming more constant in nature, and finally also being punctuated by unpredictable episodes of intense pain [Hawker *et al.* 2008]. The intermittent nature of pain has been noted in

large-scale knee OA cohort studies as well [Neogi *et al*. 2010b]. As pain is the most common symptom associated with knee OA, and is the primary reason that patients seek medical attention, whether there are pathologic features that underlie such fluctuating pain experiences are important to understand as they may be rational targets for treatment development. This is particularly of relevance since successful treatments must not only address the underlying pathologic processes, but also be clinically relevant.

One of the difficulties in understanding pathologic features contributing to pain in knee OA is the observed so-called structure–symptom discordance. That is, persons with radiographic knee OA may have minimal or no symptoms, while others without radiographic changes may have substantial knee symptoms [Hannan *et al*. 2000]. However, such observational studies have been unable to account for potential confounders that may limit the ability to discern a relationship between structure and symptoms. For example, the pain experience is influenced by many factors that differ from person to person, such as genetics, psychosocial factors and sociocultural environment, among others, many of which are unmeasurable. Without accounting for such differences, the true relationship between structure and symptoms cannot be validly evaluated. When such between-person variability and confounding factors are accounted for by using a within-person knee-matched study design (i.e. naturally paired knees in which one knee has pain, whereas the other does not; both knees are influenced by the same person-level factors), a strong association between radiographic severity and knee pain can be discerned, even at the earliest stages of knee OA [Neogi *et al*. 2009b]. Such findings suggest that certain structural lesions within the knee are a cause of knee pain. Experimental injection of a local anesthetic into the knee joint leading to pain reduction is further direct evidence that some structural pathology within the knee must be responsible, at least in part, for knee pain [Creamer *et al*. 1996].

Which tissues are likely sources of pain is becoming better understood. Cartilage is unlikely to be an important source of pain in early OA since it is aneural, although at later stages neurovascular invasion may contribute to pain. An awake arthroscopic evaluation of the knee demonstrated that probing of the cartilage itself was not painful, but other structures such as synovium and ligaments were painful; bone itself was not probed as it is known to be painful [Dye *et al*. 1998]. A number of studies have demonstrated an association of BMLs and subchondral bone attrition with pain [Felson, 2005; Felson *et al*. 2001, 2007; Hernandez-Molina *et al*. 2008; Torres *et al*. 2006]. In a systematic review, in addition to BMLs, synovitis was noted to be related to pain [Yusuf *et al*. 2011]. Both features (BMLs and synovitis) are known to fluctuate in nature. This fluctuation in pathologic features can be considered a natural experimental condition, providing a unique opportunity to determine whether the changes in these lesions are associated with changes in pain, thereby providing compelling evidence of their link to pain short of conducting intervention studies. Using novel analytic methodology, the fluctuation in these features was indeed shown to be associated with fluctuation in knee pain; an increase in the size or number of the lesion was associated with increased knee pain, while a decrease was associated with decreased knee pain [Zhang *et al*. 2011]. Such data provide support to pursuit of therapeutics that can target BMLs and synovitis as one potential strategy for treating and/or preventing pain in OA.

The possibility of targeting bone for OA treatment is attractive given the known pathologic changes and the capacity for bone to be modulated. Despite the potential importance of bone remodeling and consequent alterations in bone geometry and material properties to OA pathogenesis, bone remodeling as a therapeutic target remains controversial. In the high bone turnover state of OA, mineral deposition may be attenuated, leading to relative hypomineralization and weaker bone that is more easily deformed [Day *et al*. 2001; Li and Aspden, 1997b]. Thus, OA bone may have increased stiffness overall due to increased subchondral bone thickness and volume, despite its inferior material properties [Radin and Rose, 1986]. These properties of bone have implications for whether antiresorptive therapies (e.g. bisphosphonates), would be potentially beneficial in OA. In addition, the timing of such intervention is likely important as they should ideally be considered during phases of high bone turnover, rather than during phases with minimal bone turnover, in which case bisphosphonate therapy could theoretically increase stiffness and interfere with potentially necessary bone remodeling. Animal data has supported the potential for agents to be beneficial in OA [Saag,

2008]. While not directly relevant for knee OA, a secondary analysis of spinal OA in a trial of alendronate demonstrated less spinal osteophyte and disc space narrowing progression [Neogi *et al.* 2008]. Consistent with this finding, in an observational study of knee OA, alendronate use was associated with less BMLs, subchondral bone attrition, and knee pain than those not using alendronate; however, interpretation of such observational data is limited by potential residual confounding [Carbone *et al.* 2004]. A randomized controlled trial of risedronate suggested potential benefit on knee symptoms and structure [Spector *et al.* 2005], but a subsequent larger trial failed to demonstrate any such benefits [Bingham *et al.* 2006]. More recently, a trial of intravenous zolendronic acid resulted in a 6-month reduction in BMLs and pain, and maintained the BML reduction at 12 months, although the pain effect was no longer noted [Laslett *et al.* 2011]. A trial of another agent that has potential bone-modifying effects, calcitonin, was recently reported to improve pain, function, and cartilage volume, but not radiographic joint-space width [Karsdal *et al.* 2011].

These recent trials provide hope for the feasibility of developing and testing disease-modifying OA drugs (DMOADS). Randomized controlled trials in OA have been hampered by slow X-ray and MRI-based cartilage changes. In two large knee OA cohorts, the Multicenter Osteoarthritis (MOST) Study and Osteoarthritis Initiative, ~6% of knees develop incident OA over a 30–36 month period (unpublished data). In the initial risedronate trial, the joint-space width progression in the placebo arm was ~0.085 mm/year [Spector *et al.* 2005]. These data highlight the difficulty in using radiographic endpoints for trials, necessitating long followup and large sample sizes to detect differences between treatment arms. Cartilage assessments on MRI have not substantially improved these issues, with cartilage volume change estimated to be approximately 1% per year [Hunter *et al.* 2009b]. Given the capacity of bone to change more rapidly than radiographic features or cartilage, further investigation of bone imaging biomarkers appears warranted. Further, given the recognition of bone pathology as being of relevance for both the biomechanical abnormalities and pain in OA, specific targeting of bone for OA disease modification should continue to be pursued. A recent study demonstrated changes (increase and decrease) in BML size even as early as 6 and 12 weeks [Felson *et al.* 2011]. Such findings support the feasibility of pursuing therapeutic interventions for BMLs with shorter duration trials. Despite its promise, though, a greater understanding is needed regarding the implications of altering bone remodeling and adaptive responses to stresses as some responses are appropriate and necessary, while others may be maladaptive and contribute to abnormal biomechanics; these effects may also differ by stage of disease. In addition, targeting structural pathology without addressing concomitant biomechanical abnormalities contributing to the disease may not allow effects of successful treatments to be actualized.

In summary, the shift in thinking about OA as a degenerative disease of cartilage to one of a dynamic pathology process involving all of the tissues of the joint is an important step towards identifying treatment targets that can address the disease of the whole joint. The study of bone in OA not only provides a potentially more sensitive tissue to continue developing as an imaging biomarker and indicator of biomechanical stresses in the joint, but also a rational therapeutic target.

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Conflict of interest statement

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

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