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Bone Marrow Lesions in Osteoarthritis: What Lies Beneath

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Abstract

Osteoarthritis (OA) is the most common joint disease in the United States, affecting more than 30 million people, and is characterized by cartilage degeneration in articulating joints. OA can be viewed as a group of overlapping disorders, which result in functional joint failure. However the precise cellular and molecular events within which lead to these clinically observable changes are neither well understood nor easily measurable. It is now clear that multiple factors, in multiple joint tissues, contribute to degeneration. Changes in subchondral bone are recognized as a hallmark of OA, but are normally associated with late-stage disease when degeneration is well established. However, early changes such as Bone Marrow Lesions (BMLs) in OA are a relatively recent discovery. BMLs are patterns from magnetic resonance images (MRI) that have been linked with pain and cartilage degeneration. Their potential utility in predicting progression, or as a target for therapy, is not yet fully understood. Here we will review the current state-of-the-art in this field under three broad headings: (1) BMLs in symptomatic OA: malalignment, joint pain and disease progression (2) biological considerations for bone-cartilage crosstalk in joint disease and (3) mechanical factors that may underlie BMLs and drive their communication with other joint tissues. Thus this review will provide insights on this topic from a clinical, biological and mechanical perspective.

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Keywords

Subchondral; Microdamage; Bone-Cartilage Crosstalk; Pain; TGF-β

Introduction

Osteoarthritis (OA) is the most common joint disease in the United States, affecting more than 30 million people [1], and is characterized by cartilage degeneration in articulating joints. This condition causes serious pain and/or restricted movement – and is extremely costly to national health systems. From a clinical perspective, OA can be viewed as a group of overlapping disorders, which result in similar morphologic and clinical outcomes - namely functional joint failure. However the cellular and molecular events which lead to these clinically observable changes are neither well understood nor easily measurable. Furthermore, it is now clear that other joint tissues, in addition to the articular cartilage, are crucially important in this process. While cartilage tissue is challenging to image clinically, due to its size and aqueous composition, bone tissue is more readily imaged. Changes in subchondral bone (sclerosis) at late stages of OA, identifiable by plain film x-ray, have long been recognized as a hallmark of OA. However, earlier bony changes, such as Bone Marrow Lesions (BMLs - detected by MRI), are a relatively recent discovery – and their potential utility in predicting OA progression, or as a target for therapy, is not yet fully understood. Here we will review the current state-of-the-art in this field from a clinical, biological and mechanical perspective.

BMLs in Symptomatic OA: Malalignment, Joint Pain and Disease Progression:

Understandably much of the early research into the pathophysiology of OA focused on articular cartilage, since it is the status of this tissue that primarily informs diagnosis. This has yielded vast amounts of crucial information on the pathological processes involved in cartilage breakdown, however it has not identified a targetable factor nor a treatment strategy that can be exploited. Thus, the current paradigm for understanding OA is as a ‘whole joint disease’. Other tissues that communicate with the joint - synovium, ligaments, menisci and periarticular muscles – play an important role in joint function, and are also likely to influence joint degeneration. Communication between bone and cartilage (termed here ‘bone-cartilage crosstalk’) is of particular interest due to the intimate linking and common lineage of their cells and tissues.

Bone tissue has a particularly strong association with articulating joints and has the capacity to adapt to damage or altered loading conditions [2]. Assessment of sclerosis and osteophyte formation in the subchondral and peripheral compartments is well established in clinical imaging for late-stage OA. More recently Bone Marrow Lesions (BMLs) have been identified as a useful clinical phenomenon that may inform disease management. BMLs, sometimes referred to as bone marrow edema or bone bruises, are defined as regions of hyperintense marrow signal in fluid-sensitive, fat-suppressed MR image sequences (Figure 1). BMLs have been associated with histological evidence of microscopic bone

microdamage [3] and are related to malalignment [4], pain [5, 6] and disease progression. Interestingly BML often appear before established joint degeneration occurs, and thus are possible candidates for the long-sought indicator OA that can be detected before irreversible cartilage degeneration. The identification of early indicators of degenerative disease has accelerated treatment of other conditions greatly. This is analogous to focusing on hypertension instead of the ultimate outcome of stroke and the use of bone density to predict bone fragility fractures. There is already evidence that BMLs are strongly related to OA; their presence increases the risk of cartilage loss [1], likelihood of OA progression [3], and of development of knee pain [8, 9].

The knee is a complex joint, with mechanical and biological functionalities that can be difficult to separate. However, knee malalignment is common and a potent risk factor for OA progression, and thus serves as a useful natural experiment to study mechanical alteration and subsequent biological changes. Importantly, one of the primary sequealae of knee malalignment is the formation of subchondral BMLs. Studies have shown a strong positive correlation between the extent of medial malalignment and the occurrence of local BMLs [4]. These data support the idea that altered mechanical forces lead to subchondral damage, represented by BMLs. In a study of more than 250 patients, medial BMLs were seen predominantly in patients with varus malalignment, while lateral lesions were mostly present in those with valgus changes. Thirty six percent of patients with medial BMLs showed medial progression, as compared with 8% of those without lesions (odds ratio for progression, 6.5 [95% CI, 3.0 to 14.0]). Sixty nine percent of medial progressors had associated lesions, and lateral lesions increased risk for progression in that compartment.

Another important parameter relating to OA, that can be clinically assessed, is pain. In measuring pain it is instructive to consider its potential sources within the joint. One tissue which is probably not involved is the articulating cartilage itself, which lacks any nerve supply. The periosteum has rich sensory nerve supply, as does the bone marrow space. Certain areas of mineralized bone, particularly those that are well vascularize, are also well innervated [7]. Synovial thickening, effusions, periarticular lesions and bursitis may also be sources of joint pain. A recent review reported an odds ratio (OR), linking pain with subchondral BMLs, ranging between 2.0 (no Confidence Interval (CI) reported) and 5.0 (CI: 2.4 to 10.5). The OR of pain with effusion or synovitis ranged between 3.2 (CI: 1.04 to 5.3) and 10.0 (CI: 1.1 to 149). The levels of evidence between other MRI features and pain were either limited and/or conflicting [6]. An important caveat to these cross-sectional studies is their inherently limitation due ot the co-existence of many pathological features. Thus isolating one amongst them, such as BMLs, and assigning causality can be problematic. Longitudinal studies where one pathological feature, can be monitored over time, along with changes in pain, are the ideal way to address this issue. Furthermore, targeted intervention studies would provide crucial information to this body of literature. Zhang et al (2011) showed an intriguing link between BMLs and joint pain which demonstrated that resolution of knee pain was associated with reduced BML size [8]. A randomized trial by one of the authors (DTF) showed that a knee brace designed to specifically target BMLs in OA of the patella-femoral (PF) joint, significantly reduced pain. Reduced knee pain was accompanied by shrinkage of BMLs in the PF but not the tibiofemoral joint and no change in synovitis was reported, suggesting that BML shrinkage was related to pain reduction.

Biochemical treatments targeting BMLs in OA have also started to show promising results. In a study by Laslett et al. (2012), the bisphosphonate Zoledronic Acid (ZA) was shown to reduce BML size and also joint pain [9]. In that study, patients with OA and associated BMLs were randomized to receive either ZA or placebo. Pain was measured using a visual analogue scale (VAS). Compared with placebo, VAS pain scores were reduced by ZA after 6 months (−14.5 mm, 95% CI −28.1 to −0.9). Reduction in total BML area was greater with ZA than placebo after 6 months (−175.7 mm^2, 95% CI −327.2 to −24.3) with a trend after 12 months (−146.5 mm^2, 95% CI −307.5 to +14.5). A greater proportion in the ZA group achieved a clinically significant reduction in BML size at 6 months (39% vs 18%, p=0.044). The results of a larger study are awaited.

In summary, clinical studies suggest that BMLs represent some form of mechanical damage in subchondral bone, and are related to joint degeneration. BMLs may also be a source of pain, and they appear to respond to mechanical (bracing) and biological (bisphosphonate) interventions. Thus targeting BMLs with novel treatments is a promising future strategy for OA.

Biological Considerations for Bone-Cartilage Crosstalk in Joint Disease

The clinical findings associating BMLs with joint disease are intriguing and compelling. In this section we will discuss the current understanding of microstructural, mechanical and biochemical properties at the osteochondral interface, this will help characterize and harness this new information towards new treatments and targets. First, if subchondral events such as BMLs can influence articular cartilage (patho)-physiology then diffusion/molecular-transport across the osteochondral interface is one mechanism by which this might occur. This kind of direct solute transport is not easily measured using standard histological tools, since it is not associated with observable microstructural changes. Another cross-talk mechanism may involve the local microvasculature. In other instances of inter-tissue crosstalk local this is an important method of communication. In this case, changes in neovasculature can be measured directly based on observed microstructural change. Finally, certain mechanical changes in the subchondral bone may induce a significant biological response if they occur in specific regions near the osteochondral interface. This point will be discussed more detail in the next section.

Before addressing these issues, a brief review of the transition zone between cartilage and bone will be useful (Figure 2). The deep articular (non-calcified) cartilage is separated from the upper border of zone of calcified cartilage by the tidemark. The tidemark has a pathophysiological role in OA as it appears ‘reactivated’ in many cases of advanced OA [10–12]. The zone of calcified cartilage then interfaces with the cortical plate at its lower border. Finally the cortical plate gives way to more porous subchondral trabecular bone, which incorporates regions of marrow [13–15]. Each of these tissues has unique physiological, morphological and mechanical characteristics and likely has an important role both mechanically and physiologically in joint disease [16–19].

The traditional view of the zone of calcified cartilage and the cortical plate is that they are impenetrable barriers for solute transport. However, more recent data suggest that numerous

canals and porosities exist that connect the two compartments [15, 20]. Interestingly in the tibia, these features are primarily located beneath the menisci. Some of these porosities appeared to penetrate into the marrow compartment [21]. A recent study using a rat model of knee PTOA showed that subchondral porosity co-localizes with the point of load application during ambulation [22]. These findings are consistent with the evolving view that the junction region is a complex dynamic interface, and suggests a potential route for molecular communication between the adjacent compartments.

Fluid flow across the interface, and associated molecular transport, increases with increasing cartilage erosion, subchondral bone plate thickness and vascularity [23]. Others have shown the dense subchondral vasculature in close proximity to the deep cartilage layer, and that micro-channels can penetrate the subchondral bone in disease, permitting communication between bone and cartilage [24]. Those studies suggested that more than half of the glucose, oxygen, and water requirements of cartilage are provided by perfusion from these subchondral vessels. Consistent with this idea, experimentally induced hypoxia was found to cause cell death in both the epiphyseal and deep articular cartilage zones [25]. Arkill et al. (2008) carried out studies to characterize permeability and molecular transport from the subchondral microcirculation, using an intact perfused joint to test the effects of static loading. Using the equine metacarpophalangeal joint as a model, fluorescein and rhodamine (approximately 400 Da), were introduced as tracers, and then followed throughout the joint by quantitative fluorescence microscopy. The interface was indeed permeable to both solutes, from both superficial and subchondral sides. The effective diffusivity of each solute was of 9×10^{-9} cm^2 s^{-1}, fivefold less than in uncalcified cartilage. Employing a similar strategy, Pan et al. (2009) showed that comparable tracer molecules (sodium fluorescein, 376 Da) could diffuse readily across the interface in mouse knees. These observations show the possibility of direct signaling between the subchondral and articulating compartments, at least for small molecules in animal models. The ability of solutes to traverse the subchondral barrier further supports the idea that cartilage and bone form a functional unit, both mechanically and biochemically, which may have a role in joint homeostasis and disease.

While it is clear that some molecules can traverse the bone-cartilage interface, it remains to be seen if factors that are relevant to joint pathogenesis are actually transported *in vivo*. Intra-articular delivery of recombinant lubricin was found to attenuate the onset of OA by positive feedback loop between articular cartilage and subchondral bone in a rat OVX model [26]. Treatment was found to be chondroprotective, and also effective in normalizing subchondral bone remodeling. The authors also suggest these changes in turn attenuated cartilage degradation by inhibition of vascular invasion based on reduced numbers of CD31 positive cells in calcified cartilage and angiography in subchondral bone.

The growth factor TGF-β is a central regulator of bone and cartilage homeostasis that likely plays a pivotal role in this system. Deregulation of TGF-β signaling in either cartilage or subchondral bone can drive the progression disease in a compartment-specific manner. For example, in work by the authors (TA), chondrocyte-intrinsic ablation of the canonical TGF-β effector Smad3 causes cartilage degeneration by suppressing collagen II and aggrecan synthesis while inducing MMP13 expression [27]. Therefore, insufficient TGF-β signaling

in articular cartilage exacerbates joint disease. On the other hand, excessive TGF-β signaling in subchondral bone also caused increased cartilage degeneration.

Transgenic overexpression of TGF-β in mesenchymal progenitors propels the progression of OA [28]. Administration of subchondral TGF-β inhibitors can mitigate the severity of cartilage degeneration. Beyond these mechanistic studies in mouse models the deregulation of TGF-β is apparent in humans, where TGF-β is present in increased amounts in OA bone [29] and synovial fluid [30]. Elevated levels of TGF-β mRNA have also been found in bone from end-stage OA human hip joints removed during joint replacement procedures [31]. Furthermore, osteoblasts that were isolated from similar samples showed increased TGF-β expression, and altered relationships with the expression of other cell regulatory molecules [32]. Additional research is needed to better understand the compartment-specific effects of TGF-β in bone and cartilage, how its function is corrupted in joint disease, and how it can be targeted therapeutically.

Physical cues resulting from abnormal mechanical stresses in joint disease are also important biological regulators. Changes in the mechanical or material environment may directly influence behavior in one or other compartment. This may in turn alter the dynamic relationship between the two. TGF-β signaling is mechanoregulated at multiple levels of the signaling cascade, from extracellular ligands to transcriptional control by Smads [33]. It is one of many factors that may participate in aberrant mechanobiologic crosstalk following joint injury. In a recent study, soluble mediators released by mechanically stimulated bone cells were assessed for their ability to induce catabolic activities in chondrocytes. Expression of matrix metalloproteinase 3 (MMP-3), MMP-13, collagen II, and aggrecan was measured. MMP-3 and MMP-13 were strongly induced and collagen II and aggrecan expression was inhibited. In parallel, differential secretome analysis showed that 10 proteins were up-regulated in stimulated bone cells. Among them, soluble 14-3-3ε (s14-3-3ε) dose-dependently induced the release of catabolic factors by chondrocytes. Addition of a 14-3-3ε blocking antibody greatly attenuated the CM-mediated induction of MMP activity. These results identify s14-3-3ε as a novel soluble mediator critical in the communication between subchondral bone and cartilage in OA, suggesting a potential target for future therapeutic or prognostic applications in OA. [34]

To link these findings back to BMLs in joint disease – there is a need to characterize BMLs in terms of other specific tissue characteristics. In a study buy one of the authors (DMF) BMLs were identified in tissues from human knee arthroplasty using two different MRI sequences termed ‘PDFS only’ or ‘PDFS + T1’ [35]. After scanning, multi-modal tissue analyses of the osteochondral interface were carried out including macroscopic grading, microCT, histology including OARSI scoring and histomorphometry. BMLs were detected in 74 % of tibiae, of which 59 % were designated BML 1 (detected only by PDFS) and 41 % were designated BML 2 (detected by both PDFS + T1). The presence of a BML was related to degeneration of the joint interface, particularly within the BML 2 category. When compared to controls (no BML) BML 2-containing joints were associated with reduced cartilage volume increased subchondral plate thickness as well as increased fibrosis and necrosis. For most measures, BML 1 was intermediate between No BML and BML 2. Thus,

this suggests MRI characteristics may enable identification of different BML phenotypes and help target approaches to treatment and prevention of OA.

Mechanical factors that may underlie BMLs and drive their communication with other joint tissues.

The MRI signal that defines BMLs may represent physical damage (microdamage), or a response to such damage in the subchondral bone [36–38]. While this is quite a common assertion, there are relatively few studies which directly analyzed subchondral bone microdamage. This is largely because its detection and measurement is not trivial, particular in the clinical setting, and thus confirmatory data is limited. Much of the bone microdamage characterization work carried out over the last decades was done in preclinical models. That work provided reproducible ways to identify various types of microdamage. Important mechanical and biological differences were shown among linear-microcracks, diffuse damage and trabecular microfracture [39].

Microdamage can occur in cortical and cancellous bone, and evokes measureable mechanical and biological consequences in each. From a mechanical perspective, microdamage can be generated by a single (monotonic) significant loading event, or by multiple (up to millions) cycles at lower magnitudes. Using engineering tools and calculations, it is possible to assess the amount of microdamage in bone, and then to calculate its overall effect on the structural tissue properties. Various studies have addressed this question, and each has arrived at a broadly similar conclusion; which is that very small amounts of tissue microdamage (1–2% damage volume fraction) can cause 50–60% reductions in strength upon subsequent mechanical loading [40–45]. From a biological perspective, bone microdamage also can have profound consequences. Early studies using the *in vivo* rat ulnar fatigue loading model, showed that mid-diaphyseal microdamage leads to intra-cortical remodeling which removes and replaces damaged bone [46]. The same group showed that microdamage causes apoptosis in nearby osteocytes which is the central event in initiating the osteoclast-mediated response [47] [48]. Later work carried out by one of the authors (ODK) went on to determine that inhibition of osteocyte apoptosis completely prevented remodeling and that the underlying molecular signaling was mediated by osteocyte-derived RANKL expression [49, 50]. These studies were carried out using the ulnar loading model, which generates microdamage at a cortical bone site. The way in which cancellous bone responds to microdamage *in vivo* is not well understood as there are only a few recently developed animal models in which microdamage is generated in trabecular bone *in vivo* [51, 52]. An important point to note in any discussion about microdamage is that location, or more specifically the type of tissue it resides in (cortical, cancellous or subchondral bone), is likely to be a crucial consideration in understanding the implications.

The most relevant bone compartment, in relation to OA, is likely to be the subchondral region. It should be noted that subchondral bone microdamage in OA has been investigated previously. Radin et al. carried out a series of studies to test the hypothesis that subchondral trabecular microfractures, and specifically their healing by micro-callus formation, was responsible for increased and damaging shear-stresses in overlying cartilage [53]. The

underlying mechanism that was proposed in that work was purely mechanical and ultimately proved to have limited applicability. More recent theories have a similar starting point, which is that subchondral microdamage occurs. Sokoloff et al, and Mori et al. both demonstrated the presence of microdamage in the subchondral plate [11, 12]. However the consequences of its presence are now thought to be strongly linked to biological repair responses, like those described above, rather than a direct mechanical mechanism *per se*.

Since clinical BMLs are typically seen in the subchondral trabecular bone compartment, it is instructive to discuss what is known about microdamage in this tissue type - and also the biological response it invokes. A recent series of studies by one of the authors (CJH) showed that both loading mode and microstructure influence microdamage behaviour in trabecular bone following a single overload [41, 54]. There was little effect of microarchitecture on the amount and distribution of microdamage caused by a single overload. In contrast, the use of more sensitive morphological methods has recently suggested that rod-like trabeculae are preferentially damaged during loading [40, 54, 55]. Furthermore, in a related study from the same group, microdamage was found to correlate with the number of rod-like trabeculae [56].

As discussed above, tissue microdamage is a well-recognized stimulus for bone resorption and remodeling. Another commonly held hypothesis is that resorption cavities generated by bone remodeling can act as stress concentrations. In this way, they promote the formation of further microdamage, forming a vicious cycle of damage-remodeling-damage. A recent detailed analysis of crack propagation in cancellous bone, however, showed that load-induced microdamage does not in fact form near resorption cavities but rather forms preferentially distant from resorption cavities [57]. The authors report that microdamage formation, while associated with tissue stress, appeared to be dominated tissue material properties. The authors point out that the heterogeneity of tissue damage enables cancellous bone to recover more deformation after an overload, thus making cancellous bone more tolerant of stress concentrations at strut surfaces. This also allows the structure to recover more deformation after failure and return to a closer approximation of its original shape. In the context of BMLs, these findings suggest that microdamage and microdamage induced bone remodeling that is commonly associated with BMLs may be influenced by cancellous bone mechanical properties, including tissue heterogeneity and resistance to crack formation and propagation.

Conclusions:

Mounting evidence supports the role of subchondral bone in OA development. The findings reviewed here provide a platform on which to continue this important area of research, where novel therapies will be crucial for improving OA diagnosis and treatment. Advances in radiological imaging have been crucial to this story, for example characterizatoin of BMLs by specific MRI sequences. In future additional knowledge may be gained from using multiple complementary imaging modalities. Thus, high resolution longitudinal MRI studies, together with HRPqCT and PET to examine BMLs over the course of joint disease progression would be extremely useful. Also standardized and/or automated measurement systems of subchondral BMLs will also be important – some of early versions of these have

already begun to emerge. Furthermore, expanding patient cohorts involved in such studies will also be crucial. Many studies focus on end-stage disease/joint replacement, which is understandable in terms of access to tissues etc. However capturing data from early stage disease from younger cohorts will add a significant extra dimension to this work. Finally, from a clinical perspective, robust and well-controlled clinical trials to test the efficacy of novel agents (such as bone-targeted anti-resorptives) should be carried out.

Future work on animal models will also shed new light on specific mechanisms of joint disease. Use of mouse transgenic/knock-out technologies will be key in defining mechanistic relationships between disease initiation and progression. Furthermore animal models could make it possible to study the specific pathophysiology of BMLs before overt joint degeneration. In particular, models in which mechanically induced BMLs could be created in subchondral bone with or without mechanical stimulus to overlying soft tissues would be particularly useful in understanding bone-cartilage crosstalk. Other general areas which will benefit from further attention in the future are the relationships between BMLs and pain, obesity and acute joint injury. The current state-of-the-art of BMLs in joint disease that is reviewed here demonstrates many exciting advances in the field and provides a platform for novel treatment strategies in the future.

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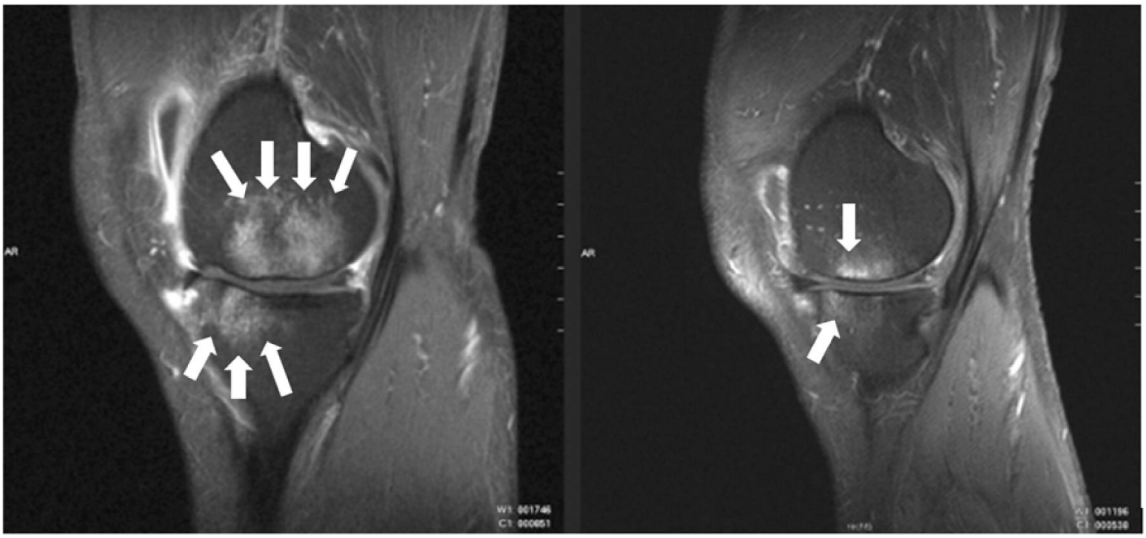

Figure 1:
MR images in the sagittal plane of a knee joint with Bone Marrow Lesions (BMLs) in the subchondral compartments of the distal femur and proximal tibia. These are the regions of diffuse white signal within the bone compartment, denoted by arrows.

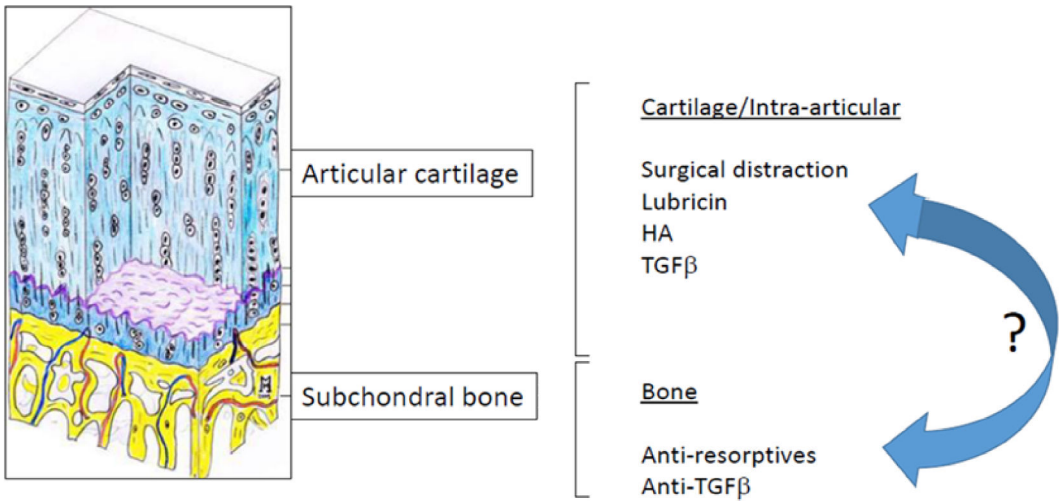

Figure 2:

The image shows articular cartilage overlaying sequentially the calcified cartilage layer, the subchondral bone plate and the subchondral trabecular bone. Potential treatments that might address the cartilage compartment, or the bone compartment, respectively, may also be protective of the other compartment, due to communication between the two. Thus, surgical distraction of the knee joint and HA treatment have been claimed to have efficacy for the cartilage clinically, and lubricin and TGF–β in animal models. Treatment of the bone compartment with anti-resorptives and anti-TGF-β at specific early time-points has been shown to have chondroprotective effects in animal models.

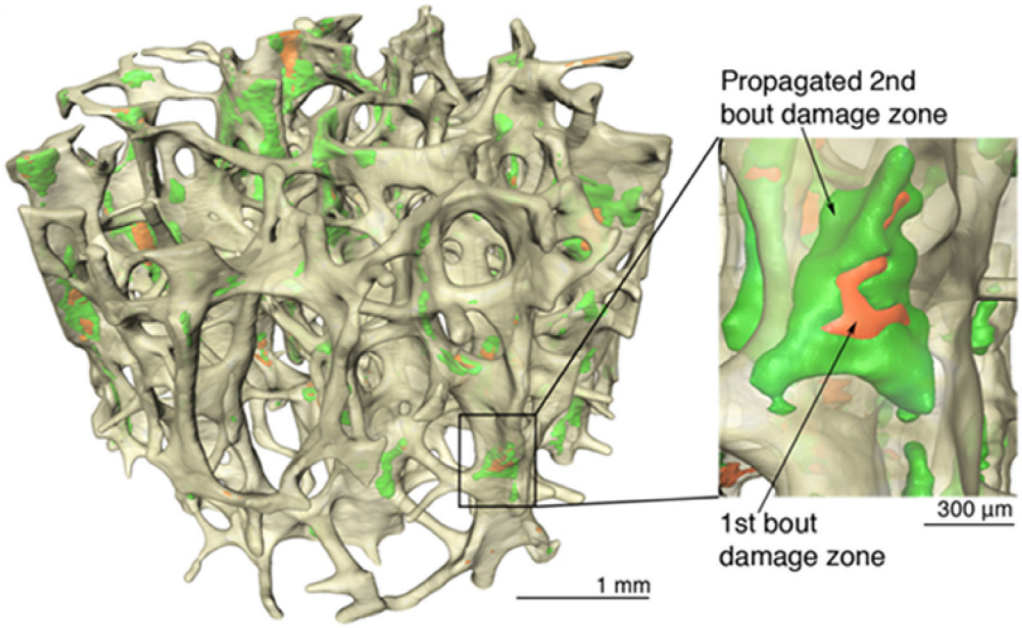

Figure 3:

Cyclic loading causes the initiation (orange) and propagation (green) of tissue microdamage in cancellous bone. Tissue material properties were associated with damage propagation. Microdamage and associated bone remodeling within a BML may therefore be influenced not only by applied mechanical loads but also by tissue material properties. From Torres et al. 2016 used with permission.