Is there a role for bone tissue in osteoarthritis?

Osteoarthritis (OA) is characterized by progressive articular cartilage loss, appositional new bone formation and sclerosis of the subchondral trabeculae and growth plate, formation of osteophytes, and an imbalance between loss of cartilage due to matrix degradation and an attempt to repair this matrix [1–3]. Synovitis is often observed and is considered to be secondary to the changes in hard tissues within the joint. In situ structural changes in subchondral bone during the course of OA can now be readily observed using imaging techniques. Indeed, increased subchondral bone activity, as judged by enhanced uptake of technetium-labeled diphosphonate, can predict cartilage loss [4], and cartilage lesions do not progress in the absence of significant subchondral activity. MRI revealed the presence of bone marrow lesions (BMLs) in OA patients, which increased in size gradually over time [5–7]. Using this technology, the presence of edema-like lesions in subchondral bone marrow and bone attrition were found to be strong indicators of bone turnover, as well as structural deterioration in knee OA. BMLs not only predict increases in knee cartilage loss in patients with knee pain, but even in patients without knee pain [5]. BMLs are characterized by sclerotic bone that is undermineralized [8]. Risks factors for OA in humans include age, gender, genetic predisposition, mechanical stress and/or joint trauma, and obesity [9], factors also affecting BMLs [5,6,8,10–13].

What is the importance of subchondral bone in OA?

Our comprehension of OA has been hampered by the nature of the disease with its slowly progressive and multifactorial nature, and its periods of active disease followed by remission. Therefore, our knowledge of the etiology, pathogenesis and progression of this disease remains incomplete. However, in recent years, our focus has evolved from a disease affecting only cartilage, with attempts to repair this loss or damaged cartilage, to one of a heterogeneous disease involving all the articular tissues including cartilage, subchondral bone, menisci and periarticular soft tissues such as the synovial membrane. Synovitis, although considered to be secondary to the alterations in other joint tissues, could also be a component of the early events leading to the clinical stage of the disease.

Changes in bone tissue in OA have long been considered secondary to cartilage degradation, yet it is now suggested that the modifications of the subchondral compartment is one of the causally most significant pathophysiological events occurring in cartilage. Indeed, subchondral bone alterations may actually precede cartilage changes as assessed in different animal models [14–20]. The remodeling of the OA subchondral bone is a key event in OA and, in addition to appositional new bone formation and sclerosis, we now know that phases of resorption are also important [21,22]. Moreover, imaging studies revealed that differences in the shape of the femoral head actually preceded manifestations of clinical OA [23]. Accumulating data from MRI now clearly indicate that two subgroups of patients can be observed, fast or slow progressors, in whom BMLs progress either rapidly or slowly [24–26]. Data from in vitro studies also indicate that subchondral bone tissue...
isolated from OA patients is not uniform [27–29]. Indeed, in vitro studies have shown that some features of human primary OA osteoblasts can discriminate two sub-groups of patients either presenting normal or high prostaglandin E2 levels [27,28] and that osteoblasts prepared from non-sclerosing and sclerosing areas of tibial plateaus of OA patients also show differentially altered features [30–32]. Moreover, indices of bone resorption can also discriminate patients with progressive knee OA from those who are nonprogressing OA patients [4,33]. This could be key evidence, since a study in a mouse model of OA recently described that inhibition of bone resorption reduced indices of OA in those mice showing high bone remodeling [34]. Evidence obtained using micro-computed tomography indicates an altered microarchitecture of the OA bone with trabeculae showing more plate-like structures than rod-like structures [35,36]. Such structures lead to increased bone stiffness.

What are the causes of abnormal subchondral bone remodeling in OA?

The progression of joint cartilage degeneration is associated with intensified remodeling of the subchondral bone and increased bone stiffness [37]. OA patients have high BMI, a better preserved bone mass [38–41], independent of body weight [42], and increased bone mineral density (BMD), suggesting that new bone synthesis exceeds degradation in OA, which could be viewed as a failed attempt at bone formation [43]. Studies have also revealed that OA bone tissue shows numerous microfractures [44–47]. Healing of trabecular microfractures in OA subchondral bone could generate a stiffer bone that is no longer an effective shock absorber [48,49]. This hypothesis, although attractive, was never demonstrated. However, recent evidence has indicated that OA bone tissue actually shows signs of increased microfractures compared with normal bone tissue and this was used as an indication that OA bone tissue may experience more fracture healing without reaching full maturity, a situation that would alter OA bone tissue composition and mechanical integrity [50]. Moreover, a very recent study indicated that excessive mechanical stress on isolated OA osteoblasts actually increase their capacity to alter chondrocytes in a co-culture system in vitro [51], implying that increased mechanical stress or increased stiffness of OA subchondral bone could alter the integrity of the overlying articular cartilage. In addition, subchondral bone stiffness may be part of a more generalized bone alteration, leading to increased apparent BMD or volume, and the association between osteophytes and femoral BMD indicates that a primary attribute of bone formation may underlie the pathophysiology of OA [52]. This also agrees with the recent hypothesis of a problem with growth of bone cells proposed by Aspden as opposed to a problem of decay [50]. IGF-I and -II, and TGF-β levels are higher in iliac crest bone biopsies of patients with OA [53]. Since the iliac crest is not a weight-bearing joint and is distant from any of them, this suggests that OA is a generalized bone metabolic dysfunction. However, stiffness and BMD are not uniform in OA bone [54–56]. The bone closest to the articular cartilage has the greatest effect on cartilage integrity, and variations in stiffness and BMD at this site in OA bone are probably causing more damage to cartilage than any of these parameters under normal conditions [57,58]. Increased osteoid volume is often more severe than cartilage changes in animal models of spontaneous OA [14–20], and the severity of cartilage fibration and loss generally exceeds bone changes only in advanced OA [14]. A recent study also provided contrasting data on the link between bone area and medial and lateral cartilage defect, whereas subchondral BMD was linked with medial defect but not cartilage loss, indicating that multiple mechanisms present in subchondral bone could lead to cartilage loss in older OA individuals [59].

The sum of these data seems to suggest that OA bone tissue is inappropriate and should show altered composition and/or features. Indeed, explants of the femoral head of OA patients at autopsy showed a lower mineralization of bone tissue than is normal [60–63]. Therefore, the apparent increase in BMD observed in OA patients may be due to an increase in material density, not an increase in mineral density. BMLs, consisting of edema-like lesions and cysts in subchondral bone, observed using MRI, are one of the hallmarks of knee OA [24,64]. BMLs are strong indicators of bone turnover and of progressive structural changes in knee OA patients. Felson et al. reported a strong correlation between bone marrow edema, the former description of BMLs, and pain in OA patients, but not with the severity of pain. In a longitudinal study, limb alignment and bone marrow edema were also shown to be related [65,66]. However, we must be cautious interpreting BMLs as they can be identified in patients without reported knee OA, whereas BMLs show a complex relationship with OA, obesity, dietary habits and bone mechanics [5,10,67–71]. Medial BMLs were mainly observed in OA patients with varus limbs, whereas lateral lesions were seen mostly in patients with valgus
Is there a role for bone tissue in osteoarthritis?

...
respond similarly to local leptin delivery. OA osteoblasts are also very sensitive to leptin, as we recently showed that it can alter the phenotype of these cells and their proliferation [102].

Could OA be considered as a systemic bone disorder? A number of data would support this notion. Indeed, OA patients show increases in BMD, yet analyses of their bone tissue show reduced bone mineral content and increased osteoid, in addition to alterations in subchondral bone microstructure. The progression of joint cartilage degeneration is associated with intensified remodeling of the subchondral bone and increased subchondral bone stiffness [37]. Alterations of bone formation and resorption indices have been described. Indeed, the group of Gevers and Dequeker was the first to demonstrate altered composition of bone tissue in OA with bone explants from non-weight-bearing areas. They reported elevated serum osteocalcin levels in women with hand OA, and elevated osteocalcin in cortical bone explants [108]. The levels of IGF-1, IGF-2 and TGF-β, were also found to be elevated in samples of iliac crest bone of patients with OA [53].

Inasmuch as OA is associated at a later stage with a thickening of subchondral bone, bone explants of the femoral head of OA patients at autopsy actually showed a low mineralization pattern compared with normal bone explants [61,63,109]. An increase in material density could explain the apparent increase in BMD in OA patients since there does not seem to be an increase in mineral density. Indeed, bone tissue mineralization in OA is lower than normal and even lower than in osteoporosis [110]. By contrast, the increase in material density is based on an increase in type I collagen production, which, combined with an increase in the ratio of type I collagen α1 to α2 chains in OA compared with normal tissue, would explain the undermineralization [72,74,111]. Indeed, a two- to threefold increase in the expression of COL1A1 chains of type I collagen, together with no variations in COL1A2 expression in OA osteoblasts, leads to an increase in the production of collagen type I collagen chains and this abnormal ratio. Together with the reduced number of cross-links in OA bone tissue [61], this could explain the reduction in bone mineralization. Other features of mature osteoblasts, such as increased levels of osteocalcin and alkaline phosphatase, have been reported for OA osteoblasts [50,112]. Therefore, both features of terminal differentiation and mineralization of OA osteoblasts are altered.

Besides modification of BMD, microdamage to bone tissues, such as microcracks and submicroscopic cracks, can contribute to loss of bone quality [113], a key factor for the progression of OA. Indeed, the accumulation of microdamages to bone is directly related to OA [114]. Since normal bone and articular cartilage are good shock absorbers [115,116], subchondral bone stiffening in OA tissue could increase trabecular bone strain in both the proximal tibial plateau and distal tibia [117-119]. In patients already showing compromised articular cartilage, this increased strain could then lead to subsequent cartilage lesions. Indeed, evidence suggests that increased stiffness leads to subchondral bone sclerosis in OA and not an increase in BMD [63].

Increased bone mass observed in OA individuals could be related to normal cell numbers producing more collagen, more cells producing similar amounts of extracellular matrix components or increased cell numbers producing more collagen. The exact mechanism(s) in place still remain poorly understood, yet evidence to date indicate that more cells are producing more collagen per cell [62,63,74]. Uncoupling of bone remodeling processes, bone formation and bone resorption could also explain this observation. The molecular mechanisms locally involved in the bone remodeling process include the coupling between osteoblasts and osteoclasts. The molecular triad receptor activator of nuclear factor-κB ligand (RANKL)/RANK/osteoprotegerin (OPG) emerged as playing essential roles not only in bone formation, but also in bone resorption. RANKL, a member of the TNF ligand family and produced by osteoblasts, binds to its specific receptor RANK on osteoclast precursors, promoting their differentiation and fusion into mature osteoclasts, and on mature osteoclasts to promote their activity. On the other hand, OPG acts as a decoy receptor for RANKL, preventing the recruitment, differentiation and fusion of osteoclasts. Bone remodeling is, thus, kept in equilibrium via the interplay of OPG and RANKL [120]. The ratio of OPG to RANKL in bone tissue, produced by osteoblasts, controls bone resorption under normal conditions. Studies using both ex vivo explants and in vitro osteoblasts have described modifications of the OPG:RANKL ratio in OA [121-125]. Of interest is the observation that this ratio was reduced in a subpopulation of OA patients, suggesting increased subchondral bone resorption, and increased in another subpopulation, favoring bone formation [124].

The control of osteogenesis in bone marrow appears to be regulated locally, at least in part, by Wnt agonists and antagonists produced by osteocytes [126,127]. Such antagonists include members...
of the DKK family (DKK1 and 2) [86,87,128] and sclerostin [129]. DKK1 is a master regulator of osteogenesis, and has opposite effects on early and late osteoblast development [86,87]. DKK2 controls terminal differentiation of osteoblasts and mineralization [128]. The Wnt signaling pathway may play a role in OA, but puzzling contradictory results have been published using animal models [89,90], whereas, in human studies, a potential role has been ascribed to DKK1 in advanced hip OA [85], and specific polymorphisms of the LRP5, LRP6 and FRZB (key receptors for Wnt signaling) have been described [150]. In addition, our own results indicated altered Wnt signaling in isolated OA osteoblasts and abnormal levels of DKK2 and sclerostin [131,132].

How can abnormal bone tissue features in OA after cartilage integrity?

The bone/cartilage cross-talk issue

In order for two tissues to exchange information or have an ongoing cross-talk, a route of communication must be present between them. Although the subchondral bone is richly vascularized, it was a long-held belief that the hyaline cartilage is not. This, however, is now challenged by histochemical studies demonstrating that the deep layer of hyaline cartilage is also vascularized. This implies that the hyaline cartilage can be nutritionally supplied via the subchondral bone as well as by the synovial fluid. Therefore, microvascular damage affecting the venous circulation in the bony tissue may cause alterations of chondrocyte function [133], but whether they are secondary to bony changes or the primary cause of bone changes in OA has not been investigated. A correlation between OA and cardiovascular disease risk factors exists [134–136], whereas the abnormal vascularization of OA tissues could initiate cartilage tissue damage [137]. Moreover, Conaghan et al. proposed that OA could be an atheromatous vascular disease [138]. Leptin increases arterial wall thickness, decreases vessel distensibility and elevates C-reactive protein levels [139], thereby contributing to abnormal vascular function in OA, a situation that would agree with the hypothesis of Conaghan et al. [138].

As the presence of the tidemark between articular cartilage and subchondral bone was believed impermeable, it was thought that chemical exchanges could not exist between the two tissues. However, cross-talk between cartilage and subchondral bone is now considered an integral part of the disease process [54,140,141]. Radin and Rose first suggested a possible role for subchondral bone in the initiation and progression of cartilage degeneration, since increases in bone mass and thickness might modify biomechanical properties that favor the appearance/progression of structural changes in the articular cartilage [49]. Indeed, the progressive structural changes experienced by the subchondral bone as the disease progresses are now considered to be part of the disease process [15,16,109,142,143]. In turn, these changes include biochemical pathways involved in both bone and cartilage tissue homeostasis and could contribute to cartilage degradation [27,30,31,53,61,144–147].

A number of studies have also reported that chondrocyte differentiation can be modified by factors secreted by osteoblasts [31,32,146,148,149]. Hence, locally produced cytokines/growth factors/eicosanoids could diffuse from subchondral bone tissue through the bone–cartilage interface and stimulate cartilage breakdown. Channels and fissures between cartilage and bone [46,47] could allow the diffusion of biological signals between the two compartments [150–152]. Microcracks have also been described in the calcified layer of aging articular cartilage [144,152], which could allow the transfer of humoral information from the subchondral bone region to the basal layer of cartilage. Pan et al. recently tested this hypothesis directly by measuring in situ sodium fluorescein (376 Da) diffusion from the subchondral bone region to the articular cartilage in mice, using a novel imaging method based on fluorescence loss induced by photo-bleaching [153]. Their results suggest that this long sought-after cross-talk between the two tissues exist, and that they form a functional unit with both mechanical and biochemical interactions. More importantly, a recent study also raised the possibility that mechanical constraints also influence the features of isolated osteoblasts. Indeed, applying a high-magnitude cyclic tensile stress of 15 kPa on isolated osteoblasts from porcine mandibular condyles modified their capacity to generate factor(s), which, in turn, disrupted chondrocytes in co-culture systems. These chondrocytes showed altered type II and type X collagen, aggrecan, and cartilage oligomeric matrix protein production, and increased matrix metalloproteinase-1, -3 and -13 genes, reminiscent of alterations observed in OA chondrocytes [51]. OA osteoblasts obtained from sclerotic and nonsclerotic areas of tibial plateaus were shown to have different features [27,30–32,111] and affect chondrocytes differently in
co-cultures [31,32,146,154]: this suggests that altered features of human OA osteoblasts could further change as mechanical pressure increases. Therefore, the progressive alteration of the bony tissue and articular chondrocytes in OA could be explained by both biomechanical and biological factors. This could then bring together the hypotheses of altered OA osteoblasts producing putative factor(s) affecting articular cartilage, disturbed mechanical forces and joint malalignment, creating these altered mechanical forces into a global concept of altered bone tissue in OA, leading to inadequate articular cartilage support and, ultimately, failure of the joint.

Future perspective
As an increasing amount of data uncover the role played by bone tissue in OA initiation and/or progression, efforts should be put forward to determine the key mechanisms involved in altered bone remodeling. Indeed, new therapies to treat OA should target both the articular cartilage and bone remodeling. Moreover, since recent studies have suggested a role of BMLs in the initiation/progression of OA, special care should be taken to determine the causes of these lesions. Most importantly, we need to know how these lesions relate to either pain, altered tissue integrity or altered bone biomechanics.

Financial & competing interests disclosure
The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Key factors involved in osteoarthritis
- Osteoarthritis (OA) is considered a whole-joint organ failure.
- OA involves modifications of the articular cartilage, the synovial membrane, the bone and subchondral bone tissues, and the bone marrow.
- Bone tissue changes in OA include increased bone mineral density, reduced bone mineral content, increased osteoid tissue; yet reduced mineralization, increased incidence of microfractures, and increased bone marrow lesions.
- OA incidence and progression are linked with bone tissue changes, including increased bone resorption and bone remodeling.
- A cross-talk exists between the articular cartilage and the subchondral bone, which permits chemical exchanges between the two tissues.

Future perspective
- OA therapies should target both the articular cartilage and bone remodeling, as further research uncovers the role played by bone tissue in OA initiation and/or progression, efforts should be made to determine the key mechanisms involved in altered bone remodeling.
- As recent studies also indicate a role of bone marrow lesions in the initiation/progression of OA, special care should be taken to determine the causes of these lesions.

Bibliography

Papers of special note have been highlighted as:
* of interest

Is there a role for bone tissue in osteoarthritis?


* Describes a striking new way of looking at the data available on OA pathophysiology and proposed a new hypothesis based on these data to understand how OA might be initiated.


* Builds on our comprehension of the role of a putative factor(s) derived from OA osteoblasts, and also how altered mechanical stress on these cells might contribute to increase their capacity to alter chondrocytes. Therefore, this study illustrates both an endogenous mechanism and a biomechanical stress contribute to OA pathology.


63 Li B, Aspden RM: Composition and mechanical properties of cancellous bone from the femoral head of patients with osteoporosis or osteoarthritis. J. Bone Miner. Res. 12, 641–651 (1997).


Is there a role for bone tissue in osteoarthritis?


102 Mutabaruka MS, Aoulad AM, Delalandre A, Lavigne M, Lajeunesse D: Local leptin production in osteoarthritic subchondral osteoblasts may be responsible for their abnormal phenotypic expression. *Arthritis Res. Ther.* 12, R20 (2010).


Lajeunesse

Is there a role for bone tissue in osteoarthritis?


131 Chan T, Couchourel D, Delalandre A, Lajeunesse D: Altered Wnt/β-catenin signaling in human osteoarthritic subchondral osteoblasts is due to alteredDickkopf-2 (Dkk2) and prostaglandin F, (PGF) levels. Osteoarthr. Cartil. 17(Suppl. 1), S38 (2009).


Is there a role for bone tissue in osteoarthritis?